21st Asian and Oceanian Myology Center Meeting

October 26-28, 2023 Shanghai · China

Program and Abstract Book

CONTENTS

WELCOME MESSAGE

Dear friends and colleagues,

We are pleased to invite you to attend the 21st Asian and Oceanian Myology Center (AOMC) Meeting to be held in Shanghai, China from 26-28 October 2023. This meeting is organised by the Asian Oceanian Myology Center (AOMC), the Shanghai Medical Association and the Hong Kong Society of Neuromuscular Disease (HKSAR), hosted by the Shanghai Medical Association and co-hosted by the Shanghai Stroke Association.

The congress venue is Hotel Golden Tulip Shanghai Rainbow, which is well-located and easy of access. We sincerely look forward to offering participants a flexible and convenient registration process.

The AOMC Annual Meeting was initiated in 2001, which is dedicated to provide academic communication platform, discuss clinical practices, promote consensus on guidelines, share cutting-edge knowledge, and explore the future research directions in the neuromuscular field.

This meeting will feature several thematic forums on muscular dystrophy, spinal muscular atrophy, congenital neuromuscular disorders, oculopharyngodistal myopathy, immune-mediated neuromuscular disorders, peripheral neuropathy and more.

We will invite Chinese and international experts in the field of neuromuscular disorders to give keynote lectures on the latest advances and hot topics in the aetiology, pathophysiology, diagnosis and treatment of neuromuscular disorders. The meeting will also feature excellent oral presentations, providing a good platform for communication between young and middle-aged neurologists. We welcome physicians, nurses, scientists, pharmaceutical company researchers and caregivers to actively participate and submit papers.

Shanghai, known as the "Pearl of the Orient", is a stunning coastal city with a rich history dating back over 1,000 years. Originally a fishing village and market town, Shanghai grew in importance in the 19th century due to both domestic and foreign trade and its favourable port location. We hope you will have a pleasant experience here, enjoying both the refreshing knowledge and the diverse cultural heritage.
We look forward to welcoming you to Shanghai!

Best regards,

Chair of AOMC 2023 Organizing Committee

Welcome

Organization

Asian Oceanian Myology Center (AOMC)
Shanghai Medical Association
The Hong Kong Society of Neuromuscular Disease (HKSAR)

Host

Shanghai Medical Association

Co-Host

Shanghai Stroke Association

Organizing Committee

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Chongbo Zhao (China)

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Yun Yuan (China)
Hui Xiong (China)
Ichizo Nishino (Japan)
Andrew J. Kornberg (Australia)
Satish Khadilkar (India)

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	Kum Thong Wong (Malaysia)
	Hui Xiong (China)
	Chuanzhu Yan (China)
	Yun Yuan (China)
	Chongbo Zhao (China)

Honorary Member and Advisory Board

Tadayuki Ishihara (Japan) , Byron A. Kakulas (Australia)
Ikuya Nonaka (Japan),Dingguo Shen (China)

AOMC 2023 Faculty

In alphabetical order by last name

Carsten BÖNNEMANN

USA

M.D.
Senior Investigator, Neuromuscular and Neurogenetic Disorders of Childhood Section, National Institute of Neurological Disorders and Stroke, NIH.
He has been elected to the American Association of Physicians (AAP) and is Co-Editor-in-Chief of the Journal of Neuromuscular Diseases (JND).

Bitao BU

China

Prof. and Director of Neuroimmunology and Neuromyopathy Division of Neurology Department, Tongji Hospital, Huazhong University of Science and Technology, Wuhan.Member of Chinese Medical Society, Chinese Immunology Society and American Society for Neurosciences.

Bingzhen CAO

China

Prof in neurology of the 960th Hospital of PLA.
The committee member of Chinese Society of Neuromuscular Disease, Chinese Society of Neuropathology, and vice-chairman of Shandong society of Neurology.

Jong-Hee CHAE

Korea

MD, PhD.
Professor, Department of Pediatrics, Division of Pediatric Neurology, Seoul National University College of Medicine, Seoul Korea.
Her research is currently focused on genetic muscular dystrophy, in developing diagnostic tools to detect its various genetic mutations using new technologies, running clinical trials of latest pharmacological therapy and gene therapy in selected patient groups.

Josiah CHAI

Singapore

MBBS, MRCP(UK), FRCP(Edin), FAMS(Neurology).
He is presently a Senior Consultant and Head of Department of Neurology in NNI (Tan Tock Seng Hospital campus). His special interest is in the evaluation and management of neuromuscular diseases, EMG and muscle histopathology.

Sophelia Hoi-Shan CHAN

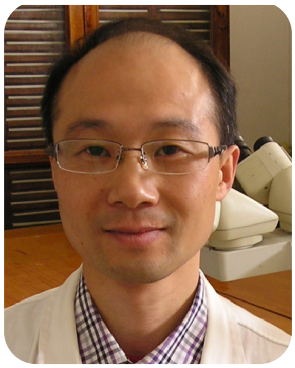
Hong Kong, SAR of China

MBBS (HK), MRCP (UK), MMedSc (HKU), FHKAM (Paed), FHKPaed (Specialist in Paed Neurology).
The Chief of the Paediatric Neurology Division and a Clinical Assistant Professor at the Department of Paediatrics and Adolescent Medicine at the University of Hong Kong's School of Clinical Medicine.

Ting CHANG

China

M.D., Ph.D. Professor and Vice-Chair, Department of Neurology, Tangdu Hospital, the Fourth Military Medical University.
Member, Chinese Neurological Association (Neuroimmunology Section)
Drafter of Chinese guidelines for the diagnosis and treatment of myasthenia gravis (2020).



Guoqian CHEN

China

Neurologist in the first affiliated hospital of Wenzhou Medical College.

AOMC 2023 Faculty

In alphabetical order by last name

Wanjin CHEN

China

Chief physician and Professor of the First Affiliated Hospital of Fujian Medical University

Martin CHEUNG

Hong Kong, SAR of China

BSc (CUHK); PhD (U of Nottingham).
Associate Professor, School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong.
Associate Director (Research and Innovation), School of Biomedical Sciences, The University of Hong Kong.

Liying CUI

China

Professor of Neurology, Peking Union Medical College Hospital.
Past president of Chinese Society of Neurology.
Coordinator of ALS cooperation group of Chinese Society of Neurology.
Honorary General Editor of Chinese Journal of Neurology.

Yuwei DA

China

Division Chief, Division of Neuromuscualr Disorders, Department of Neurology, Xuanwu Hospital, Chief Physician, Doctoral Advisor.
Member of the International Exchange Promotion Association of Chinese Healthcare- Neurology Branch.
Member of the Neuromuscular Disease Group of the Chinese Medical Association-Neurology Branch.
Member of the Expert Committee of the Chinese Medical Doctor ALS Association.

Charungthai DEJTHEVAPORN

Thailand

MD, PhD.
Associate Professor, Department of Clinical Epidemiology and Biostatistics, Mahidol University.
Education: Doctor of Medicine (2nd Calss), Faculty of Medicine Ramathibodi Hospital, Mahidol University.
Certification: Thai Board of Internal Medicine; Thai Board of Neurology; Thai Board of Family Medicine; Ph.D. in Clinical Epidemiology, Mahidol University.

Jihong DONG

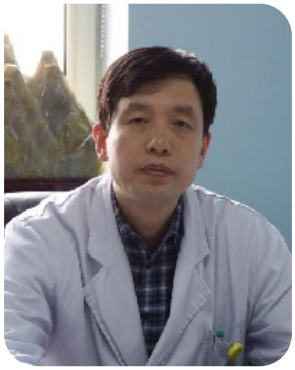
China

Professor, Doctor of Medicine, Deputy Chief Physician.
Head of Neuromuscular Disease Sub-specialty, Department of Neurology, Zhongshan Hospital, Fudan University.
Member of Neuroelectrophysiology Group and Neuromuscular Disease Group of Neurology Branch of Chinese Medical Association.
Member and Secretary of EEG and Neurophysiology Society of Shanghai Medical Association, etc.

Ailian DU

China

Professor and Chief Physician of Tongren Hospital, Shanghai Jiaotong University School of Medicine
Subject:Director of Neurology
Committee member of Chinese Society of Neurology Neuromuscular Disease Group



Honglin FENG

China

Director and Second-tier professor, Department of complicated neurology, the First Affiliated Hospital of Harbin Medical University.
Committee member of World Stroke Organisation (WSO).
Committee member of Amyotrophic lateral sclerosis collaboration Group, Chinese Medical Association Branch of Neurology.
Committee member of Peripheral neuropathy collaboration Group, Chinese Medical Association Branch of Neurology.
Committee member of Neurological rare diseases Specialty Committee of China Rare Disease Alliance.

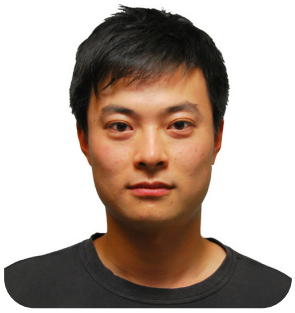
AOMC 2023 Faculty

In alphabetical order by last name

Sharon FUNG

Hong Kong, SAR of China

Consultant, Department of Paediatrics and Adolescent Medicine (P&AM), Kwong Wah Hospital.
The general and neurology team head in P &AM, Kwong Wah Hospital.



Yuan GAO

Hong Kong, SAR of China

MD, PhD.
A specialist in neurology and an associate consultant of Neurology in Queen Mary Hospital and honorary clinical assistant professor in Department of Medicine, The University of Hong Kong.
Dr. Gao is interested and specialised in Neuromuscular and Neurogenetic Disorders, and has recently been granted the first fellow in Genetics and Genomics (Medicine) under The Hong Kong College of Physicians.

Khean Jin GOH

Malaysia

Professor of Neurology at the University of Malaya, Kuala Lumpur, Malaysia.
His research interests are in clinical neurophysiology and neuromuscular diseases.
He is Executive Board Member of the Asian and Oceanian Myology Center (AOMC) and Associate Editor of the Neurology Asia journal.

Junhong GUO

China

Medical doctor, First hospital of Shanxi Medical University
Committee member: Neurology Branch of Chinese Medical Association, Neurology Branch of Neuromuscular disease Group of Chinese Medical Association, Neurology Branch of Chinese Medical Doctor Association, Neurology Branch of China Alliance of Rare Diseases

Yanlei HAO

China

Professor and Chief Physician, Director of the Neurology Department at Ningbo Taikang Hospital.
Committee member for the Neuro-Muscular Disease Group of the Chinese Medical Association's Neurology Branch.
Editorial board member for Chinese Journal of Neurology and Chinese Journal of Behavioral Medicine and Brain Science.
Member of the Cognitive Impairment Branch of the Chinese Society of Geriatrics
Chairman of the Neuro-Immunity Branch in the Shandong Neurological Society.

Daojun HONG

China

Professor in Neurology.
Director of Neurology Department, First Affiliated Hospital of Nanchang University.
Director of Rare Disease Center, First Affiliated Hospital of Nanchang University.

Jing HU

China

Dr. Hu graduated from Kagoshima University in Japan and is currently a Neurology professor at the Third Hospital of Hebei Medical University.

David HUTCHINSON

New Zealand

Dr Hutchinson served as Clinical Director of the Neurology Department of Auckland City Hospital from 2009-2016. He has received research grants from the New Zealand Neurological Foundation, and has served on this body's SAC. He has been secretary of the Neurological Association of New Zealand; and has served on the SAC for Neurology, a committee of the Royal Australasian College of Physicians which oversees training of neurologists in New Zealand. He has served on the Executive of the AOMC since 2009.

AOMC 2023 Faculty

In alphabetical order by last name

Luh Ari INDRAWATI

Indonesia

Medical staff, consultant neurologist for clinical neurophysiology, neuromuscular disease, and epilepsy in the Department of Neurology, Dr Cipto Mangunkusumo National Referral Hospital, Jakarta, Indonesia.
Lecturer of the Department of Neurology, Universitas Indonesia.
Secretary of clinical neurophysiology and neuromuscular diseases study group, Indonesian Neurology Association.

Haishan JIANG

China

Associate Chief Physician, Associate Professor, MD.
Deputy Director, Department of Neurology, Nanfang Hospital, Southern Medical University, Director of the subspecialty of Myopathy and peripheral neuropathy.
Member of the Neuromuscular Group of the Neurology Branch of the Chinese Medical Association, Standing member of the Neuroscience Committee of the Chinese Society of Research Hospitals,.

Yuh-Jyh JONG

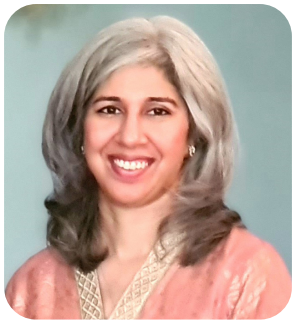
Taiwan, China

Chair Professor, Kaohsiung Medical University (KMU), National Yang Ming Chiao Tung University.
Visiting Staff, Departments of Pediatrics and Laboratory Medicine, KMU Hospital.
Taiwan Child Neurology Society (Honorary Director), Taiwan Human Genetics Society (Director), Formosan Medical Association (Executive Director), Chinese Foundation of Health (Director), National Health Research Institutes (NHRI) Board of Directors (Supervisor), Taiwan SMA Families (Executive Director), Asian Oceanian Myology Center (AOMC) (Executive Board Member).

Satish V. KHADIKAR

India

Current professional direction: Clinical and scientific research of peripheral neuropathy, neuromyopathy, and rare diseases of nervous system.



Sara KHAN

Pakistan

Associate professor of Neurology at the Aga Khan University hospital, Karachi.
Head of the section of neurology at AKUH and the Director of the Neurology residency Program and Director of the Neuromuscular Medicine Fellowship program.
Her research revolves around determining the prevalence, clinical phenotypes and genetic make up of neuromuscular disorders in the Pakistani population.

Dae-Seong KIM

Korea

MD, PhD.
Professor, Department of Neurology, Pusan National University School of Medicine
Korean Neurological Association (Member), Korean Society of Clinical Neurophysiology (Member), Korean Journal of Clinical Neurophysiology (President), Asian and Oceanian Myology Center (AOMC) (Executive board member), World Muscle Society (WMS) (Member).

Andrew J. KORNBERG

Australia

Prof Andrew Kornberg is a paediatric neurologist with broad clinical and research experience.
He completed formal Paediatric Neurology and Neuromuscular Fellowships in the United States working in St Louis, USA.
He has interests in metabolic disease in childhood and has been involved in the Consensus Statement formulation of treatment in Pompe disease.

Yung-Ting KUO

Taiwan, China

Director of Pediatric Neurology, Department of Pediatrics, Shuang Ho Hospital, Ministry of Health and Welfare, Taipei Medical University.
Associate Professor, Department of Pediatrics, School of Medicine, Taipei Medical University.
His research focus is on the pathogenesis of muscle atrophy caused by nerve damage and the study of relevant drugs or foods that can reverse the atrophy and maintain muscle function.

AOMC 2023 Faculty

In alphabetical order by last name

Jia LI

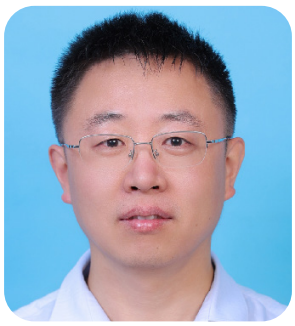
China

M.D.
Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

Pengfei LIN

China

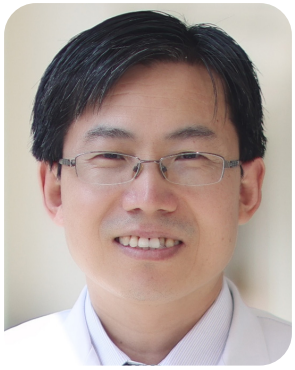
Associate Chief Physician in the Department of Neurology at Qilu Hospital, Shandong University.
He is also the Deputy Director of the Department of Neurology and a Clinical Associate Professor at Shandong University.



Gonglu LIU

China

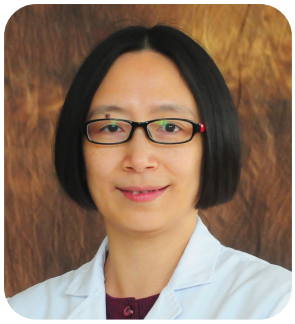
Associate director and associate Chief Physician, Department of Medical Genetics and Center for Rare Diseases, Second Affiliated Hospital, Zhejiang University School of Medicine.
Committee Member of the Myopathy Group, Neurology Branch, Chinese Medical Association.
Secretary of the Branch of Basic & Clinical Research in Neurology, Chinese Neuroscience Society.



Mingsheng LIU

China

Professor in neurology of Peking union Medical College Hospital.
Vice chairman of Chinese Society of Neuromuscular Disease, the vice chairman of Peripheral Neuropathy Collaboration Group of Chinese Society of Neurology, editorial board member of Clinical Neurophysiology Practice.
Focusing on clinical research of motor neuron diseases and peripheral neuropathy, including EMG and peripheral nerve ultrasound, clinical trial on ALS.



Jiahong LU

China

Chief Physician, Department of Neurology, Huashan Hospital affiliated to Fudan University.
Member of ALS collaboration group and PND collaboration group of Chinese Medical Association.
Committee member of Shanghai Rare Disease Prevention and Treatment Foundation.

Xinghua LUAN

China

Associate chief physician, Department of Neurology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine.
Member of the Neuromuscular Disease Group of the Neurology Branch of the SMA.
Member of the Neuromuscular Genetic Branch of the BNA.
Main research interests: neuromuscular disorders, neuropathy.

Haidong LV

China

Professor of Neurology at Jiaozuo People's Hospital, affiliated with Xinxiang Medical University.
The member of the Neuromuscular Group of the Neurology Branch of the Chinese Medical Association.

Mori-Yoshimura MADOKA

Japan

Chief Neurologist, Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Japan.
She works with patients with various neuromuscular diseases and has been engaged in clinical practice and clinical research in the area of neuromuscular diseases at the Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry since 2006.

AOMC 2023 Faculty

In alphabetical order by last name

Tahseen MOZAFFAR

USA

MD, FAAN
Dr. Tahseen Mozaffar is a Professor of Neurology and Pathology and Laboratory Medicine and the Director of the Division of Neuromuscular Disorders. He serves as chair of one of the biomedical committees and is the Associate Director for the Center for Translational Sciences Award (CTSA) at University of California, Irvine. He is the Principal Investigator for UCI-NEXT. He is also the Lead Investigator for a multicenter NIH/NIAMS funded Natural History Study in sIBM (INSPIRE-IBM).

Shahriar NAFISSI

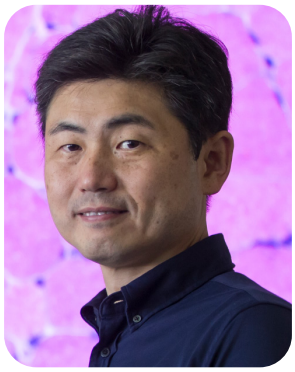
Iran

Professor of Neurology and Neuromuscular medicine at Tehran University of Medical Sciences.
He currently serves as the Dean of the Neuromuscular Research Center (NMRC) at Tehran University of Medical Sciences. Additionally, he is Editor-in-chief of Current Journal of Neurology, and also AOMC executive board member.
He was also a Neuromuscular Fellow at Montreal Neurological Hospital, McGill University in Montreal, Canada. His main areas of interest are immune-mediated neuromuscular disorders, motor neuron disease and storage myopathies.

Atchayaram NALINI

India

PrOF. DR. A. NALINI (MD, PHD). National institute of mental health and neuro sciences (an institute of national importance).
Dr Nalini is the Lead of NIMHANS Advanced Center for Neuromuscular Disorders. She leads the only Multidisciplinary Neuromuscular disorders clinic with more than 12000 registered cases. Has a large cohort of more than 2000 genetically confirmed muscle diseases. She is the Executive Board Member of the AOMC. Chairman of the “Neuromuscular disorders” of the National Consortium for Research and Development on Therapeutics for Rare Diseases and member of the Gene Therapy committee at Indian Council of Medical Research.



Ichizo NISHINO

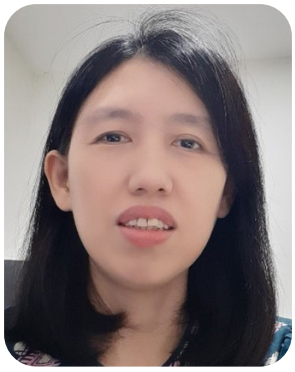
Japan

Director of Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP).
Current President of AOMC.

Fengnan NIU

China

M.D, Ph.D
Deputy chief physician, Department of Pathology, Nanjing Drum Tower Hospital.
A member of the 8th Committee of the Neurology Branch of the Chinese Medical Association, Neuro-muscular Diseases Group.



Ohnmar

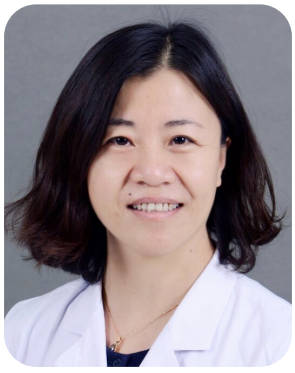
Myanmar

Associate Professor, Department of Neurology, Yangon General Hospital/University of Medicine 1, Yangon, Myanmar.
She is practicing as senior consultant Neurologist at Department of Neurology, Yangon General Hospital. She has published her review articles locally and research papers in local as well as in international journals. Presently, she is an academic secretary of Myanmar society for the study of pain, an executive board member of Asian Oceanian Myology Center (AOMC) and Southeast Asia therapeutic plasma exchange Consortium (SEATPEC), and also an active member of various international societies.

Shirley Yin-Yu PANG

Hong Kong, SAR of China

The University of Hong Kong | HKU · Department of Medicine
Hon. B.Sc., MBBS.



Min QIAN

China

Associate Professor in Neurology, Peking Union Medical College Hospital, Beijing, M.D.

AOMC 2023 Faculty

In alphabetical order by last name

Chao QUAN

China

Serves as Chief Physician, Professor, Doctoral Supervisor in the Department of Neurology, Huashan Hospital Affiliated to Fudan University, which is also the National Center for Neurological Disorders.
The member of the Neuroimmunology Branch of the Chinese Medical Association and the ICC Member of International Clinical Consortium for NMO.

Oranee SANMANEECHAI

Thailand

MD, Pediatric Neurology, EMG
Professor (Assistant) at Mahidol University, Thailand

Anne SCHÄNZER

Germany

Anne Schänzer is Professor of Neuropathology at the Institute of Neuropathology, Justus Liebig University of Giessen, Germany and is head of the diagnostic and research neuromuscular laboratory.
She is a member of the German reference centre for neuromuscular diseases and member of the associated research board of the German Muscle society.
Her research work involves immunological processes in neuromuscular disorder, metabolic myopathies (Pompe disease) and the cardio-skeletal link in muscular disorders.

Dingguo SHEN

China

Professor of Department of Neurology, Chinese PLA General Hospital.
Chairman of Chinese Society of Neuromuscular Disease, Chinese Medical Association (1989-2002).
Executive member of Asian & Oceanian Myology Center (2001-).
Advisor member of Chinese Society of Neuromuscular Disease.
Advisor member of Chinese Society of ALS.

Xinming SHEN

USA

Dr. Xin-Ming Shen currently serves as an associate professor of Neurology at Mayo Clinic, Rochester, Minnesota, USA.
Dr. Shen is a fellow of the American Academy of Neurology and the American Neurological Association. He also serves or served the academic community as member of the Research Careers Reimagined Course Planning Subcommittee of American Neurological Association, member of International Relations Committee of American Biophysical Society, member of Biopsy Subcommittee for Research at Mayo Clinic, and as section editor on neuromuscular diseases in two scholarly journals, and as scientific reviewer of numerous research funds and journals spanning both basic and clinical sciences.

Qiang SHI

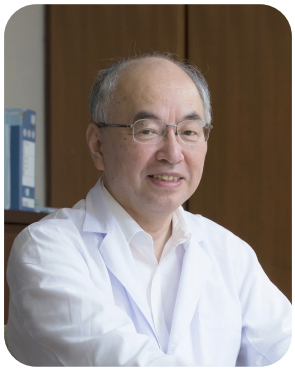
China

Chief Physician, Professor, and Supervisor of the Department of Neurology, PLA General Hospital.
He is a member of the Neuromuscular Disease Group of the Neurology Branch of the Chinese Medical Association and a member of the Youth Committee of the Neurology Branch of the Chinese Medical Association.

Xueqin SONG

China

Director of the department of Neurology at the Second Hospital of Hebei Medical University.
Deputy director of The Key Laboratory of Neurology, Ministry of Education.



Shin'ichi TAKEDA

Japan

Senior scientific advisor/Honorary director general, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP)
Visiting professor of Tokushima University.
Japan Muscle Society (former President), La Société Franco-Japonaise de Médecine (Directeur), American Society of Gene and Cell Therapy (Member), World Muscle Society (Member), Asian Oceanian Myology Center (Senior member of executive board).
Associate editor for reviews in J. Neuromuscular Diseases, Associate editor in American J. Pathology, Members of Board for Neuromuscular Disorders, Member of CINRG.

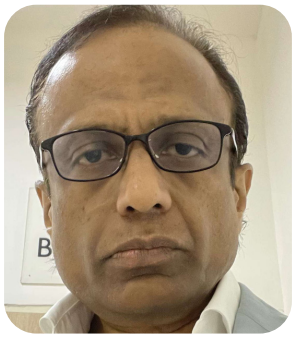
AOMC 2023 Faculty

In alphabetical order by last name

Song TAN

China

M.D., Ph.D.
Chief Physician, Department of Neurology, Sichuan Provincial People's Hospital.
Professor, Department of Clinical Medicine, Medical College, University of Electronic Science and Technology of China.
Deputy director, Rare Diseases Center of Sichuan Provincial People's Hospital.
Member of the Neuromyopathy Group of the Neurology Committee of the Chinese Medical Association.
Member of the Rare Disease Special Committee of the Chinese Hospital Association.



Umapathi THIRUGNANAM

Singapore

Sr Consultant neurologist with subspecialty interests in neuromuscular disease, neuro-ophthalmology and the practice of neurology in under-resourced regions.

Tatsushi TODA

Japan

Professor of Neurology, Graduate School of Medicine, The University of Tokyo.
Former President of Japanese Society of Neurology.
He has received Japanese Society of Neurology Award, Asahi Award, Award from Japanese Minister of Education, Culture, Sports, Science and Technology, Japan Medical Association Award, and Japan Academy Prize.

Andoni URTIZBEREA

France

MD, MSc.
Former scientific director of the European Neuromuscular Center (ENMC) and former medical director of AFM-Telethon.
Specialist in neuromuscular disorders, affiliated to the Institut de Myologie of Paris, France as a faculty.
Currently freelance consultant for pharma & patient organizations, medical writer and visiting professor.

Maggie WALTER

Germany

Associate Professor of Neurology at the Ludwig-Maximilians University of Munich. She is working at the Friedrich-Baur-Institute, the neuromuscular department of the LMU, in leading position.
She is coordinator of the German Muscular Dystrophy Network (MD-NET) and the German Charcot-Marie-Tooth Neuropathy Network (CMT-NET) since 2003 and 2016, and member of the executive committee of TREAT-NMD, an European Network of Excellence in the 6th EU frame program for translational research in neuromuscular diseases.

Yi WANG

China

President of Children's Hospital of Fudan University.
Chief physician; Tutor of doctorate candidate; Outstanding Academic Leaders in Shanghai. Vice-president of Chinese anti-epilepsy Association; president of Chinese anti-epilepsy Association; Member of ILAE; The leader of the Group of Rare Diseases of the Pediatric Society of Chinese Medical Association; The vice chairman of the Rare Diseases Committee of the Chinese Hospital Association:Standing member of Chinese Medical Association in Clinical Epidemiology and evidence-based medicine.

Zhiqiang WANG

China

Ph.D, Chief Physician, and Professor in Department of Neurology of the First Affiliated Hospital, Fujian Medical University.
Member of Muscular Dystrophy Committee, Chinese Society of Neurology.
Deputy Director of DMD/BMD Study Group, China Alliance of Rare Diseases.

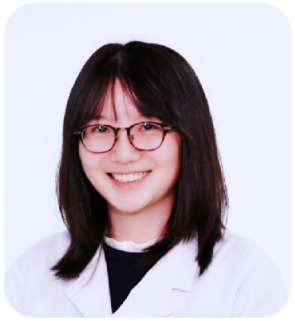
Zhaoxia WANG

China

Clinical neurologist in the Department of Neurology, Peking University First Hospital.

AOMC 2023 Faculty

In alphabetical order by last name



Xinmei WEN

China

MD, PhD.
Attending Physician, Department of Neurology, NCND, Xuanwu Hospital CCMU, Beijing, China.

Kum Thong WONG

Malaysia

MBBS, Mpath, FRCPath, MD, FaSc.
Honorary Professor in the University of Malaya and Adjunct Professor in the Monash University Malaysia.

Shiwen WU

China

Chief physician, Professor, Head of Subspecialty Group of neuromuscular disorders, Department of Neurology, Chinese PLA General Hospital.
Member of the TGDOC Publication Committee.
Chairman of China Dedicated Fund For Neuromuscular Disorders.
Vice chairman of the Neuroscience Committee of Chinese Research Hospital Association.

Jianying XI

China

Associated Professor, Department of Neurology Huashan Hospital, Fudan University.

Fei XIAO

China

Deputy director, Neurology department of the first affiliated hospital of Chongqing Medical University.
Member of the Neuromyology Group of the Neurology Branch of the Chinese Medical Association.

Xiao XIAO

China

Co-founder, Chairman and CSO of Belief BioMed.

Hui XIONG

China

Prof. and deputy director of department of Pediatrics and Rare Diseases Center, Peking University First Hospital.
Executive member of AOMC.
Standing committee member of Chinese society of Rare Diseases.
Vice president of the 18th Chinese Society of Pediatric Endocrinology and Metabolism and Vice Chair of the 17th Youth Committee of Chinese Society of Pediatrics.

Yanming XU

China

Chief Physician/Professor, Doctoral Supervisor, Department of Neurology, West China Hospital, Sichuan University.
Academic and Technical Leader of Sichuan Province.
Member of the Neuromuscular Disease Group of the Neurology Branch of the CMA.
Executive Committee Member of the PD Rehabilitation Professional Committee of the CRMA.
Member of the Neurology Special Committee of the Chinese Society of Integrated Traditional and Western Medicine.

AOMC 2023 Faculty

In alphabetical order by last name

Chuanzhu YAN

China

Vice president of Qilu Hospital and president of Qilu Hospital (Qingdao), Shandong University, PR.China.
Chair and professor of Neurology and Neuromuscular Center in Qilu Hospital of Shandong University.
President of Chinese Society of Neuromuscular Disorders.
Vice president of Chinese Society of Neurology and a board member of AOMC.

Xiaoli YAO

China

Chief Physician, Professor, Doctoral Supervisor, Director of NeurologyUnit I First:Affiliated Hospital, Sun. Yat-sen University.
Deputy head of Amyotrophic Lateral Sclerosis CollaborationGroup of Chinese Society of Neurology, Standing committeemember of Neuroloqical Rare Disease Committee of China Alliance foiRare Disease, Member of: Chinese Society of NeuromuscularDisease, Chairman of Neuroscience Committee of GuangdongHealth Management Association.

Sheng YAO

China

Professor of Neurology at the Sixth Medical Center of the General Hospital of the PLA.
Director of Neuromuscular and Genetics, Beijing Neurology Association.
Member of the Neuromuscular Disease Group of the Neurology Branch of the Chinese Medical Association.

Xuen YU

China

M.D.
Neurology chief physician, Associate professor
Head of department of neurology, hospital affiliated to neurological institute, Anhui University of Chinese Medicine.
Member of the Neuromuscular Disease Group of the Neurology Branch of the Chinese Medical Association.

Xuefan YU

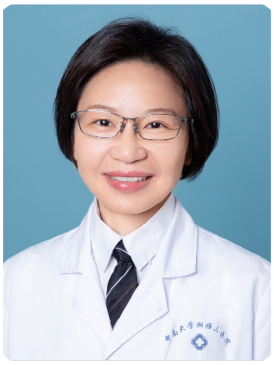
China

PhD, chief physician.
Department of Neurology and Neuroscience Center, the First Affiliated Hospital of Jilin University, Changchun.
Professor of the Difficult and Rare Diseases Center of the First Hospital of Jilin University.
Member of the Neuromuscular Group of the Neurology Branch of the Chinese Medical Association.
Member of the peripheral Neuropathy Cooperative Group of the Neurology Branch of the Chinese Medical Association.

Yun YUAN

China

Director of the Center for rare Diseases, Peking University first Hospital.
Vice Chairman of rare Diseases Branch of Chinese Medical Association.



Ruxu ZHANG

China

Chief Physician and Doctoral Supervisor at Xiangya Third Hospital, Central South.

Zaiqiang ZHANG

China

M.D,Ph.D, Professor of neurology.
Director, Neuromuscular Disease Center, Beijing Tiantan Hospital , Capital Medical University.
Vice-Chair, Neuromuscular Study Group, Neurology Branch of the Chinese Medical Association.

AOMC 2023 Faculty

In alphabetical order by last name

Cheng ZHANG

China

Prof in Neurology of the Affiliated First Hospital, Sun yat-sen University.

Chongbo ZHAO

China

Professor in Neurology.
Deputy director of Neurology Department, Huashan Hospital, Fudan University.
Executive board member of AOMC. Co-Chair of AOMC 2023 in China.

Zhe ZHAO

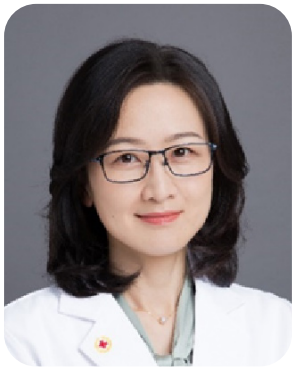
China

Deputy director, Neuromuscular Diseases Department of Hebei Medical University Third Hospital.
Member of the Neuromyology Group of the Neurology Branch of the Chinese Medical AssociationSociety

Yuying ZHAO

China

Prof of Neurology Dept,Qilu Hospital of Shandong University.
Vice chairman of Chinese Society of Neuropathologic Group, Secretary General of Rare Neurological Disease Committee,Chinese Alliance of Rare Diseases



Wenhua ZHU

China

MD, PhD
Associate Senior Doctor, Department of Neurology, Huashan Hospital, Fudan University.
Committee member, Committee of Neuromuscular Diseases, Chinese Society of Neurology, Chinese Medical Association.
Secretary, Committee of Neuromuscular disorders and Electrophysiology, Shanghai Society of Neurology, Shanghai Medical Association.

Meeting Agenda

Oct.25, Wednesday

Myasthenia Gravis Seminar

15:30-15:35	Opening	Chongbo ZHAO; Bitao BU
Session 1: Lecture Chair: Chongbo ZHAO; Bitao BU		
15:35-15:55	Out with the old in with the new —— The Biologics era of MG	Yuwei DA
15:55-16:15	From clinical trial to RWE	Min LIU
16:15-16:25	Panel discussion	Panelists: Wei WANG; Zhiguo LV; Jihong DONG
16:25-16:45	Efgartigimod in gMG: From global experience to Huashan practice	Sushan LUO
16:45-16:55	Discussion	Panelists: Xiaoli YAO; Xiaoping ZHAO; Ailian DU Shanshan YANG
Session 2: Case Sharing Chair: Bitao BU; Zaiqiang ZHANG		
16:55-17:10	Case sharing 1	Xu WANG
17:10-17:25	Case discussion	Panelists: Ruxu ZHANG; Zunbo LI; Jie ZHU Yanming XU
17:25-17:40	Case sharing 2	Qilong JIANG
17:40-17:50	Case discussion	Panelists: Xiaoling LI; Jianfeng WANG; Mingming MA; Song PANG
17:50-18:00	Closing	Chongbo ZHAO; Bitao BU

Meeting Agenda

Oct.26, Thursday

Time	Session and symposium	Speaker	Institute	Chair
08:30--09:00	Opening Ceremony	Ichizo NISHINO	President of AOMC, Japan	Chongbo ZHAO Sophelia HS CHAN
		Chuanzhu YAN	Qilu Hospital, China	
		Liying CUI	Peking Union Medical College Hospital, China	
		Jinglei WU	Shanghai Medical Association, China	
Muscular Dystrophy and Other Myopathies				
09:00--09:30	Recent advances of therapeutic approaches to Duchenne muscular dystrophy	Shin'ichi TAKEDA	National Center of Neurology and Psychiatry, Japan	Chuanzhu YAN
09:30--10:00	Limb-girdle muscular dystrophy	Satish KHADIKAR	Bombay Hospital & Medical Research Centre, India	Jiahong LU
10:00--10:30	Q & A and Tea Break			
10:30--11:00	GNE myopathy update	Ichizo NISHINO	National Center of Neurology and Psychiatry, Japan	Oranee SANMANEECHAI
11:00--11:30	Recent advances of alphadystroglycanopathy	Tatsushi TODA	The University of Toyko, Japan	Charungthai DEJTHEVAPORN
11:30--12:00	Recent Progress of Gene Therapy for Muscular Dystrophy	Yuh-Jyh JONG	Kaohsiung Medical University, Taiwan, China	Ruxu ZHANG
12:00--12:15	Q & A			
Lunch Symposium				
12:30--13:00	Landscape of CD19 targeting therapy in neuroimmunology	Chao QUAN	Huashan Hospital,Fudan University, China	Yanlei HAO
13:00--13:30	Common and uncommon manifestations of late-onset Pompe's disease	Wenhua ZHU	Huashan Hospital,Fudan University, China	Jing HU
13:30-14:30	Poster Presentation	GroupA: Ichizo NISHINO; Umapathin THIRUGNANAM; Honglin FENG; Qiang SHI; Haishan JIANG; Gonglu LIU		
		GroupB: Andrew KORNBERG; Ohnmar; Xuen YU; Guoqian CHEN; Xueqin SONG; Zhe ZHAO		

Meeting Agenda

Autoimmune-Mediated Neuromuscular Diseases				
14:30--15:00	Update of dermatomyositis	Andrew KORNBERG	The University of Melbourne, Australia	David HUTCHINSON
15:00--15:30	Inclusion body myositis	Tahseen MOZAFFAR	University of California, Irvine, United States	Junhong GUO
15:30--16:00	Understanding the principles of myopathies: the importance of muscle morphology	Anne SCHÄNZER	Institute of Neuropathology, Justus-Liebig-Universität Gießen,Germany	Song TAN
16:00--16:30	Q & A and Tea Break			
Challenges of NMD Care in Developing Countries				
16:30--17:00	Diagnosis and management of neuromuscular diseases in under resourced egions - a personal take	Umapathin THIRUGNANAM	National Neuroscience Institute, Singapore	Yung-ting KUO
17:00-17:30	The advances and challenges in the care and management of neuromuscular disorder in a developing country - Myanmar	Ohnmar	University of Medicine 1 Yangon, Myanmar	Dae-Seong KIM
17:30--17:45	Q & A			
Evening Symposium				
17:45--18:15	Exploration of standardized diagnostic and treatment for SMA	Yuying ZHAO	Qilu Hospital, China	Shiwen WU
18:30--21:30	Board meeting			

Meeting Agenda

Oct.27, Friday

Time	Session and symposium	Speaker	Institute	Chair
Rare Neuromuscular Disorders, Spinal Muscular Atrophy				
08:30--09:00	hTTR amyloid neuropathy in Malaysians	Khean Jin GOH	University of Malaya Medical Centre, Malaysia	Zaiqiang ZHANG
09:00--09:30	Recent advances of congenital myasthenic syndrome	Xinming SHEN	Mayo Clinic College of Medicine, United States	Bitao BU
09:30--10:00	Lipid storage myopathies	Shahriar NAFISSI	Tehran University of Medical Science, Iran	Mingshen LIU
10:00--10:30	Q & A and Tea Break			
10:30--11:00	Genotype mapping and treatment research for LAMA2-related muscular dystrophy	Hui XIONG	Peking University First Hospital, China	Sharon FUNG
11:00--11:30	SMA —the real world research in China	Yi WANG	Children's Hospital of Fudan University, China	Shirely PANG
11:30--12:00	Spinal muscular atrophy with treatment -The unmet needs	Sophelia HS CHAN	The University of Hong Kong, HKSAR, China	Josiah CHAI
12:00-12:15	Q & A			
Lunch Symposium				
12:30--13:00	Pioneering data with nusinersen from clinical trails to real-world evidence	Maggie WALTER	Ludwig-Maximilians-University of Munich, Germany	Xiaoli YAO
13:00--13:30	Landcape of complement inhibitor in treatment of gMG	Ting CHANG	Tangdu Hospital of Air Force Medical University,China	Fei XIAO
13:30-14:30	Poster Presentation	GroupC: Andoni URTIZBEREA; Yuh-Jyh JONG; Yanming XU; Fengnan LIU; Song TAN; Wenhua ZHU		
		GroupD: Carsten BÖNNEMANN; Shahriar NAFISSI; Xinghua LUAN; Jihong DONG; Min QIAN; Ailian DU		

Meeting Agenda

Solved the Unsolved Neuromuscular Disorders				
14:30--15:00	Identification of novel disease-causing genes and conceptual treatment of neuromuscular diseases	Wanjin CHEN	The First Affiliated Hospital of Fujian Medical University, China	Sara KHAN
15:00--15:30	Diagnosis of difficult-to-diagnose NMDs	Jong Hee CHAE	Seoul National University College of Medicine, South Korea	Zhiqiang WANG
15:30-16:00	Genetic Therapies for Neuromuscular Diseases: Opportunities and Challenges	Carsten BÖNNEMANN	National Institute of Neurological Disorders and Stroke, National Institute of Health, United States	Yuwei DA
16:00--16:30	Q & A and Tea Break			
Oculopharyngodistal myopathy				
16:30--17:00	The Discovery of OPDM Genes	Zhaoxia WANG	Peking University First Hospital, China	Cheng ZHANG
17:00--17:30	Shifting Horizons of OPDM: Expanding the Clinical Landscape	Jianying XI	Huashan Hospital,Fudan University, China	Andoni URTIZBEREA
17:30--18:00	From Pathology to Pathogenesis NOTCH2NLC-related OPDM,	Daojun HONG	The First Affiliated Hospital of Nanchang University, China	Xuefan YU
18:00--18:20	Q & A			

Meeting Agenda

Oct.28, Saturday

Time	Session and symposium	Speaker	Institute	Chair
NMD Research Bench to Bedside				
08:30--09:00	Role of DLC1 Isoform 1 in Spinal Muscular Atrophy Pathogenesis and Treatment	Martin CHEUNG	The University of Hong Kong, HKSAR, China	Haidong LV
09:00--09:30	Gene therapy for DMD (TBC)	Xiao XIAO	Belief Biomed, China	Luh Ari INDRAWATI
09:30--10:00	LGMDR7: From Phenotypes to Genotypes and Research on Potential Gene Therapy	Pengfei LIN	Shandong University, China	Yuan GAO
10:00--10:30	Q & A and Tea Break			
Clinical Pathological Conference				
10:30--11:00	Case 1	Kum Thong WONG	University of Malaya, Malaysia	Discussants: Ichizo NISHINO Jong Hee CHAE Josiah CHAI Mori-Yoshimura MADOKA Wenhua ZHU Chuanzhu YAN Bingzhen CAO Sheng YAO
11:00--11:30	Case 2	Atchayaram NALINI	National Institute of Mental Health and Neuro Sciences, India	
11:30--12:00	Case 3	Jia LI	Peking Union Medical College Hospital, China	
12:00--12:30	Case 4	Xinmei WEN	Xuanwu Hospital, Capital Medical University, China	
Award and Closing ceremony				
12:30--13:00	Youth Scholarship Award Ceremony	Ichizo NISHINO; Sophelia HS CHAN; Chongbo ZHAO		
	Closing Remarks	Chongbo ZHAO		

General Information for Delegates

Date: October 26-28, 2023

Venue: Golden Tulip Shanghai Rainbow

Address: 2000, Yan An Road (W), Shanghai 200051, China

Tel: +86 21 6275 3388

Fax: +86 21 6275 7244

Web: https://AOMC2023.sciconf.cn

Important Dates

08:00-18:00, October 26, 2023

Registration

Location: 2F, Golden Tulip Shanghai Rainbow

08:30-09:00, October 26, 2023

Opening Ceremony

Location: Tulip Ballroom,2F, Golden Tulip Shanghai Rainbow

On-site registration

On-site registration will be open on 08:00-18:00, October 26, 2023.

Congress Registration Fees:

Registration Types	Regular Fees
Regular Participants (Chinese)	1200RMB
Regular Participants (International)	150USD
Graduate Students & Residents	600RMB/75USD

Payment: Cash / Credit Card

General Information for Delegates

Delegates Identification

Name badge is the only identification of all delegates.
According to the regulation of the Venue, you are kindly requested to wear your badge during all the session of the congress.

Meals

Lunch and Refreshment will be provided at the conference.
You may redeem the lunch coupon for the lunch in the Indicated dining area.

Simultaneous Interpretation

Chinese-English simultaneous interpretation will be provided in main conference hall. Please pay the deposit or mortgage your passport to get the headphone equipment at the entrance if you are in need, and return it promptly at the end of meeting.

Speakers and Moderators

1.Speakers are strongly advised to submit your presentation file (USB disc) to the conference staff at least 2 hours before your presentation begins.
2.Please pay attention to the date and time and get good preparation for your presentation. Please be aware of and strictly control your presentation time.
3.As the moderator of the conference, please strictly control the process of your hosting session and make sure each presentation duration time will not be exceeded than 3 minutes.

Others

1.Please turn your mobile phone to silent/vibration mode when you are in the conference room to minimize disruption to the forum proceedings.
2.Please do not leave any personal possessions in the conference room overnight as the conference room may be used for other functions. You should also carry your valuables with you at all times since we cannot be held responsible for any loss.

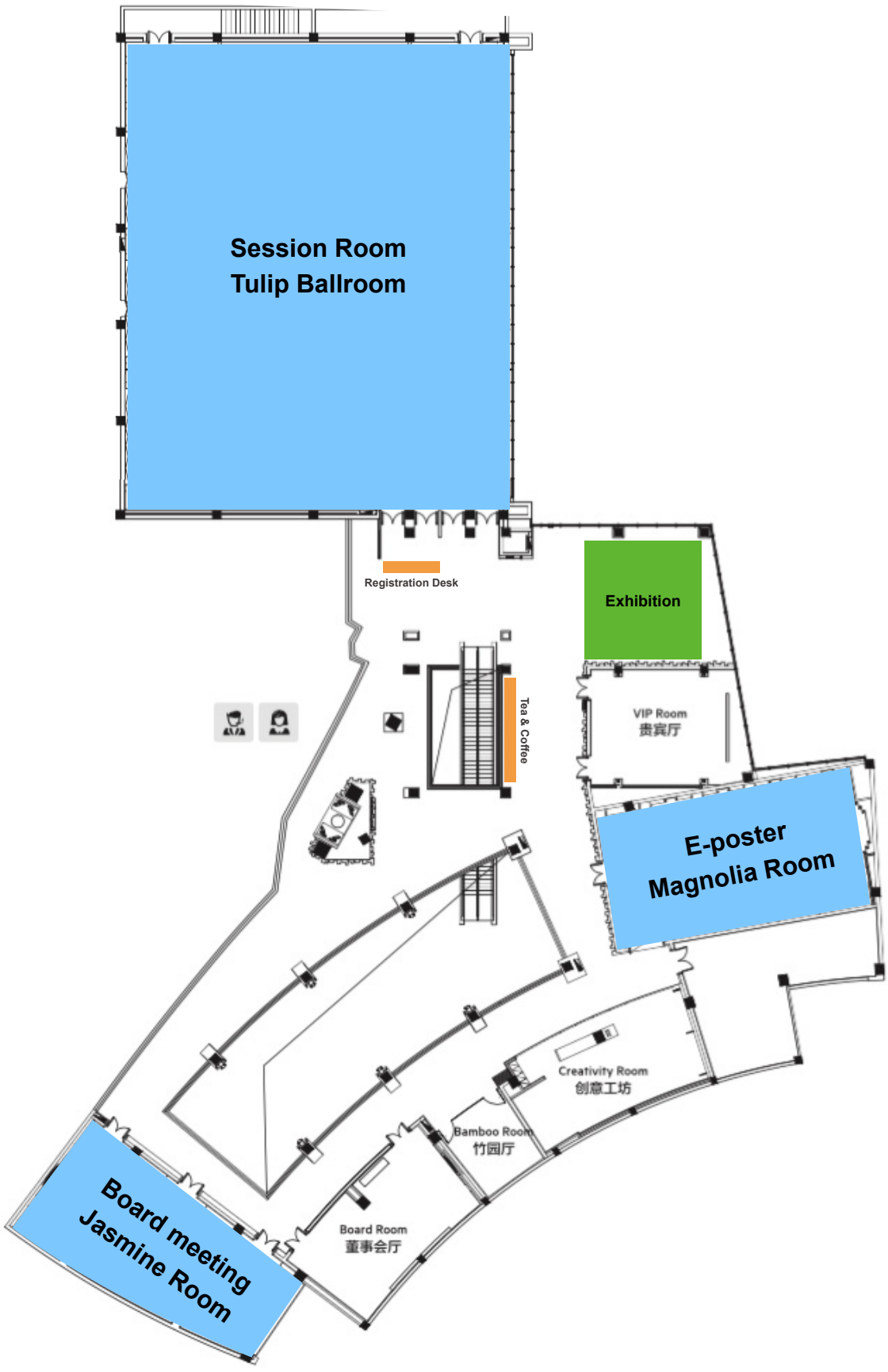
General Information for Delegates

Transportation info.

From Pudong International Airport (PVG) to Golden Tulip Shanghai Rainbow
(50km, about 60 minutes drive)

From Hongqiao International Airport (SHA) to Golden Tulip Shanghai Rainbow
(7.5km, about 20 minutes drive)

Floor Plan


Session Room
Tulip Ballroom
Registration Desk
Exhibition
Tea & Coffee
VIP Room
贵宾厅
E-poster
Magnolia Room
Creativity Room
创意工坊
Bamboo Room
竹园厅
Board Room
董事会厅
Board meeting
Jasmine Room

e-Poster Abstract

Genotype-Phenotype Correlations within autosomal recessive limb-girdle muscular dystrophy-23

Xiuli Huang[1],Dandan Tan[1],Zaiqiang Zhang[2],Lin Ge[1],Jieyu Liu[1],Juan Ding[1],Haipo Yang[1],Cuijie Wei[1],Xingzhi Chang[1],Yun Yuan[1],Chuanzhu Yan[3],Hui Xiong[1]

1. Peking University First Hospital
2. Beijing Tiantan Hospital, Capital Medical University
3. Qilu Hospital, Cheeloo College of Medicine, Shandong University

Introduction

Autosomal recessive limb-girdle muscular dystrophy-23(LGMD R23) due to mutations in the *LAMA2* gene,which encodes laminin a2,is extremely rare. The detailed clinical phenotypes and genetic information associated with LGMD R23 were unknown.

Methods

LGMD R23 patients were collected: (1) 19 patients followed up in Peking University First Hospital from June 2013 to December 2022. (2) Reviewed the cases reported in the literature.

Results

A total of 52 patients were included. The onset age range from young children to elderly people. The onset symptom in 11.5% of patients were epilepsy. The MRI of thigh muscle showed that fatty infiltration predominantly affecting adductor magnus. The merosin was partial reduced or normal. Peripheral nervous system involvement was found in 41.7% of patients. Cognitive impairment were found in 13.5% of patients.

A total of 68 pathogenic variants were detected. Missense variants were the most common. The high-frequency pathogenic variants in Chinese patients were c.437C>A(p.S146Y). Exon 4 and exon 5 of *LAMA2* were the high-frequency variation location. The pathogenic variants were mostly located in the LN domain, followed by the EGF-like domain and the G-like domain.

In Chinese patients with epilepsy, the frequency of missense variants in exon 4 was 50%, while the frequency of that was 7.7 % in patients without epilepsy. In other racial patients with epilepsy, the frequency of missense variants in exon 5 was 26%, while no missense variants in exon 5 was detected in patients without seizures. There was a statistical difference.

Conclusions

LGMD R23 is rare, but has characteristic. Mild or moderate high CK with white matter abnormalities, epilepsy and electrophysiological changes of peripheral nerve involvement are common. The missense variants of exon 4 and exon 5 are the high-frequency pathogenic variants in patients with LGMD R23-related epilepsy. This study further improved the diagnosis capability of LGMD R23 and provided a theoretical basis for long-term management of these patients.

Fat-fraction quantification using 3-point Dixon technique in Duchenne muscular dystrophy and its correlation with clinical progression

Nalini Atchayaram
National Institute of Mental Health and Neurosciences

Background: Quantitative magnetic resonance image(MRI) using 3-point Dixon MRI to measure muscle fat fraction(FF) is more precise and reliable than visual fat fraction methods for longitudinal follow-ups in Duchenne muscular dystrophy(DMD). This study aims to detect any correlation between a one-time FF estimation using MRI 3-point Dixon technique as a biomarker of clinical phenotype and also of disease severity at 1 year. Also tried to identify characteristic pattern of disease distribution.

Methods: 10 boys with genetically confirmed DMD were serially evaluated.. Muscle FF obtained for different compartments of thigh muscles(quadriceps, adductors and hamstrings). Age, body mass index(BMI), muscle strength assessment, MRC sum score, North Star Ambulatory Assessment(NSAA), timed functional assessment(6 minute walk test, 6MWT) were evaluated at baseline. Follow up clinical data at 6 months and 1 year could be obtained for 9 patients. Pearson's correlation used to assess relationships between FF and clinical assessments.

Results: highest mean MFF found in quadriceps(mean, 26.26%±10.91 SD). Mean FF in adductors and hamstrings were 10.83%±9.32 SD and 11.17%±9.20 SD respectively. Quadriceps FF had a very strong negative correlation with MRC sum score at baseline(10 patients, r=-0.804, p=0.005), at 6 months (9 patients, r=-821, p=0.007) and at 1 year (9 patients, r=-0.862, p=0.003). Quadriceps FF also had a strong negative correlation($p<0.05$) with 6MWT at all 3 time points. Quadriceps FF correlated with NSAA and was significant at 6 months and 1 year follow-up($p<0.005$).

Conclusion: We could quantify differential fatty replacement in different muscle groups in thigh. Quadriceps muscles had highest FF which significantly correlated with MRC sum score, 6MWT and NSAA score at baseline and 6 months and 1 year follow-up. Muscle FF may prove clinically useful in monitoring muscle changes as a result of the disease process and in predicting treatment outcomes in DMD.

Uniparental disomy for chromosome 1 with POMGNT1 splice-site variant causes muscle-eye-brain disease

Yidan Liu,Dandan Tan,Danyu Song,Yanbin Fan,Xiaona Fu,Lin Ge,Hui Xiong
Peking University First Hospital

POMGNT1, encoding protein O-mannose beta-1,2-N-acetylglucosaminyltransferase 1, is one of the genes responsible for dystroglycanopathy (DGP), which includes multiple phenotypes such as muscle-eye-brain disease (MEB), congenital muscular dystrophy (CMD) with intellectual disability, and limb-girdle muscular dystrophy (LGMD). Here, we report a case of MEB that is the result of a homozygous variant of POMGNT1 that is revealed through uniparental disomy (UPD). An 8-month-old boy was admitted with mental and motor retardation, hypotonia, esotropia, early onset severe myopia, and structural brain abnormalities. A panel testing of genetic myopathy-related genes was used to identify a homozygous c.636C>T (p.Phe212Phe) variant in exon 7 of POMGNT1 in the patient, a heterozygous c.636C>T variant in the father, and the wild type in the mother. Quantitative polymerase chain reaction (q-PCR) revealed no abnormal copy numbers in exon 7. Trio-based whole-exome sequencing (trio-WES) revealed a possible paternal UPD on chromosome 1 of the patient. Chromosomal microarray analysis (CMA) revealed a 120,451 kb loss of heterozygosity (LOH) on 1p36.33-p11.2, encompassing POMGNT1, and a 99,319 kb LOH on 1q21.2-q44, which indicated UPD. Moreover, RNA sequencing (RNA-seq) verified that the c.636C>T variant was a splice-site variant, leading to skipping of exon 7 (p.Asp179Valfs*23). In conclusion, to the best of our knowledge, we present the first case of MEB caused by UPD, providing valuable insights into the genetic mechanisms underlying this condition.

Prevalence Of Adeno-Associated Virus-9 Neutralizing Antibody In Chinese Patients With Duchenne Muscular Dystrophy

Cuijie Wei,Dongliang Li,Meng Zhang,Yanping Zhao,Yidan Liu,Yanbin Fan,Lu Wang,Jieyu Liu,Xingzhi Chang,Yuwu Jiang,Hui Xiong
Peking University First Hospital

Objective: The delivery of a mini-dystrophin gene to skeletal muscles using recombinant adeno-associated virus serotype 9 (AAV9) holds great potential as a gene therapy for Duchenne muscular dystrophy (DMD). However, the presence of neutralizing antibodies (NAbs) against AAV may impede the effectiveness of gene transduction. This study aimed to evaluate the prevalence of anti-AAV9 NAbs in Chinese patients with DMD.

Methods: A total of one hundred male patients with DMD were included in this study, and demographic and clinical data were collected. A blood specimen was obtained from each participant for the purpose of evaluating the existence of anti-AAV9 neutralizing antibodies through a cell-based functional assay conducted at a centralized laboratory. A NAb titer exceeding 1:4 was considered positive. The positivity rates of anti-AAV9 NAb were compared among different subgroups.

Results: The median age of this DMD cohort was 8 years old, ranging from 3 to 15 years old. 42% of patients tested positive for anti-AAV9 NAb. Notably, all samples from patients under 4 years old tested negative, and the positivity rates of anti-AAV9 NAb differed significantly across the three age subgroups (<4 years old, ≥4 years old and <12 years old, and ≥12 years old, $\chi2=7.221$, $P=0.023$). Further investigation into the living environment revealed a higher positivity rate of anti-AAV9 NAb in rural patients compared to urban patients ($\chi2=3.923$, $P=0.048$). Moreover, the prevalence in patients from different cities/provinces varied greatly ($\chi2=16.550$, $P=0.003$). There was no statistically significant difference in the positivity rate of NAb among subgroups of patients with different motor functions (ambulatory or non-ambulatory) and different treatment strategies (taking or not taking glucocorticoid).

Conclusion: In Chinese DMD patients, the prevalence of anti-AAV9 NAb was found to reach 42%. Moreover, these antibodies exhibited an upward trend across age groups and revealed notable regional discrepancies.

A rare complex structural variation in the dystrophin gene - combination of a novel intragenic inversion and a reciprocal translocation t(X;1)(p21.2;p13.3)

Yaye Wang[1],Xinmei Wen[1],Li Di[1],Yun Li[1],Shu Zhang[1],Qi Wen[1],Jingsi Wang[1],Nairong Xie[1],Haoran Liu[1],Yuting Jiang[1],Jianying Duo[1],Yue Huang[1],Yan Lu[1],Min Wang[1],Min Xu[1],Hai Chen[1],Wenjia Zhu[1],-Lingtao Zhan[2],Shirang Pan[2],Yuwei Da[1]

1. Xuanwu Hospital, Capital Medical University

2. Grandomics Biosciences, Beijing, 100176, China

Introduction Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder caused by pathogenic variants in the dystrophin (*DMD*) gene. While multiplex ligation probe amplification and next-generation sequencing are commonly used for DMD diagnosis, they have limitations in detecting deep intronic variants or larger genomic rearrangements. This study aims to present a case of a Chinese family with a complex structural variant in the *DMD* gene, thereby deepening our understanding of the genetic profile of DMD.

Methods We described the clinical data, imaging, and pathological staining of a case in a non-consanguineous Chinese family. A rare complex structural variant in the *DMD* gene was revealed via long-read whole-genome sequencing (LRS).

Results The proband, a 10-year-old boy, and his mother, with clinical signs of pseudohypertrophic muscular dystrophy, elevated levels of creatine kinase, and intellectual disability. Muscle biopsy from the boy showed dystrophin deficiency. However, routine molecular techniques failed to detect abnormalities in the *DMD* gene. Dystrophin mRNA transcripts analysis revealed an absence of exons 59 to 79 (NM_004006.3). Ultimately, the proband underwent LRS using Oxford Nanopore technology, which identified a novel 77134bp intragenic inversion that encompasses *DMD* exons 63 to 67. Additionally, a balanced reciprocal translocation located at chr1:116084053 (gene-free region) and chrX:31208712 (intron 67 of the *DMD* gene) were detected respectively. Breakpoints were validated using Sanger sequencing. Unfortunately, the proband's mother passed away due to heart failure before genetic verification could be conducted.

Conclusion Our study was the first to present a Chinese family with both chromosomal inversion and balanced translocation in the *DMD* gene by LRS, broadening the genetic profile of dystrophinopathy. LRS might be an informative tool when no pathogenic variant of DMD is discovered through conventional molecular diagnostic techniques.

The Clinical Features and TCAP Mutation Spectrum in a Chinese Cohort of Patients with Limb-girdle Muscular Dystrophy R7

Xiaoqing Lv[1],Feng Lin[3],Wenjing Wu[1],Hui Wang[4],Yuebei Luo[5],Zhiqiang Wang[3],Chuanzhu Yan[2],He Lv[4],Sushan Luo[6],Pengfei Lin[2]

1. Qilu Hospital of Shandong University, Cheeloo College of Medicine, Shandong University
2. Qilu Hospital of Shandong University
3. The First Affiliated Hospital of Fujian Medical University
4. Peking University First Hospita
5. Xiangya Hospital, Central South University
6. Huashan hospital, Shanghai Medical College, Fudan University

Limb-girdle muscular dystrophy R7 (LGMDR7) is an autosomal recessive hereditary muscular dystrophy caused by mutations in titin-cap (TCAP). Here, we summarized the clinical characteristics and TCAP mutations in a Chinese cohort of 30 patients with LGMDR7. The onset age of Chinese patients was 19.89 ± 6.70 years old, which is later than European and South Asian patients ($p<0.05$). Clinically speaking, 20.0% of patients presented with predominant distal weakness, and 73.3% of patients presented with predominant pelvic girdle weakness. Radiological study revealed semitendinosus and magnus adductor were severely involved in Chinese LGMDR7 patients. Rectus femoris, vastus lateralis, vastus intermedius, soleus and tibialis anterior were moderately to severely involved. The most prevalent mutation in this cohort is c.26_33dupAGGTGTCG, while c.165dupG and c.110+5G>A are unique in Chinese population as two of the common mutations. Besides, variant c.26_33dupAGGGTGTCG might be a founder mutation in Asian patients. Internal nuclei, lobulated fibers, and scattered rimmed vacuoles were typical morphological changes in Chinese LGMDR7 patients. This is the largest LGMDR7 cohort in the Chinese population and in the world. This article also expands the clinical, pathological, mutational, and radiological spectrum of patients with LGMDR7 in China and in the world.

The association of handgrip strength with all-cause and cardiovascular mortality: results from the NHANES database prospective cohort study

Lijiao Xiong,Zhaohao Zeng,Tingfeng Liao,Xiaohao Wang,Xinyu Wang,Guangyan Yang,Yanchun Li,Lixing Li,Jing Zhu,Pengfei Zhao,Shu Yang *,Lin Kang *,Zhen Liang *
The Second Clinical Medical College, Jinan University (Shenzhen People's Hospital)

Objection: To explore the association between handgrip strength (HGS) with all-cause and cardiovascular disease (CVD) mortality in US adults.
Method: We analyzed data from the National Health and Nutrition Examination Survey (NHANES) prospective cohort study (2011-2014) with 10,470 participants. We performed cox regression analysis, Kaplan-Meier survival curves, fitted curves, ROC curves, and propensity score-matched analysis (PSM) with inverse probability of treatment weighting regression analysis to assess the relationship between HGS and all-cause and CVD mortality.
Results: The low HGSs (men<37.4 Kg, women<24 Kg), was found to be associated with higher all-cause and CVD mortality in a reverse J-shaped curve (P<0.05). Adjusting for multiple covariates including age, BMI, race, education level, marriage status, smoking and alcohol use, and various comorbidities, the hazard ratio (HR) for all-cause mortality in the lowest HGS quintile 1(Q1) was 3.45 (2.14-5.58) for men and 3.3 (1.88-5.79) for women. For CVD mortality, the HR was 2.99 (1.07-8.37) for men and 10.35 (2.29-46.78) for women. The area under the curve (AUC) for HGS alone as a predictor of all-cause mortality was 0.791 (0.768-0.814) for men and 0.780 (0.752-0.807) for women (P<0.05), while the AUC for HGS and age was 0.851 (0.830-0.871) for men and 0.848 (0.826-0.869) for women (P<0.05). For cardiovascular-specific mortality, the AUC for HGS alone was 0.785 (95% CI 0.738-0.833) for men and 0.821 (95% CI 0.777-0.865) for women (P<0.05), while the AUC for HGS and age as predictors of all-cause mortality was 0.853 (0.861-0.891) for men and 0.859 (0.821-0.896) for women (P<0.05).The HGS Q1 (men <37.4 kg and women <24 kg) was matched separately for PSM. After univariate, multivariate cox regression models, PSM, IPTW, SMRW, PA, and OW analyses, women had 2.37-3.12 and 2.92-5.12 HRs with low HGS for all-cause and CVD mortality, while men had 2.21-2.82 and 2.33-2.85 for all-cause and CVD mortality, respectively. (p < 0.05).
Conclusion: The adults with low grip strength (men <37.4 kg and women <24 kg) had a significantly higher risk of all-cause and CVD mortality. Low grip strength was also an independent risk factor and a predictor for all-cause and CVD mortality.

Development and validation of nomograms for the prediction model of sarcopenia in middle-aged and older adults from four countries

Lijiao Xiong[1],Hongjuan Fang[2],Tingfeng Liao[1],Zhaohao Zeng[1],Guangyan Yang[1],Xiaohao Wang[1],Xinyu Wang[1],Lan Li[1],Ying Zhao[1],Meng Xue[1],Ping Xu[1],Shu Yang*[1],Lin Kang*[1],Zhen Liang*[1]

1. the Second Clinical Medical College, Jinan University (Shenzhen People's Hospital), Shenzhen, China

2. Department of Endocrinology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China

Objective: This study aimed to establish and validate nomograms that predict the risk of sarcopenia in community-dwelling middle-aged and older adults.

Methods: A total of 6 datasets with 9579 individuals were collected from China, India, Polish, and Thailand. The 70% of 8740 patients from the China Health and Retirement Longitudinal Study (CHARLS) were used to establish a training cohort, and the remaining 30% were assigned to the validation cohort. The 839 patients from th other 5 datasets were used for external validation. logistic regression combined with the least absolute shrinkage and selection operator (LASSO) analysis were performed to screen the independent predictors. The risk factors included age, gender, BMI, and handgrip strength for sarcopenia were identified, area under the curve (AUC) was used to evaluate the model discrimination ability.

Results: Two risk-prediction nomogram models for sarcopenia were developed and validated. The nomogram model A consists only age, gender, and BMI, whereas the nomogram model B covers age, gender, BMI, and handgrip strength. The training group's AUC values for models A and B were 0.975 (95%CI 0.972-0.978) and 0.977 (95%CI 0.974-0.981). The AUC of nomograms A and B in the internal validation dataset were 0.977 (95%CI 0.972-0.982) and 0.978 (95%CI 0.973-0.983). The AUC of nomogram A in the five external validation datasets were 0.956 (95%CI 0.933-0.980), 0.902 (95%CI 0.847-0.957), 0.910 (95%CI 0.847-0.947), 0.913 (95%CI 0.868-0.957), and 0.898 (95%CI 0.834-0.963) respectively. The AUC of nomogram B in the five external validation datasets were 0.955 (95%CI 0.932-0.979), 0.956 (95%CI 0.925-0.986), 0.975 (95%CI 0.945-1.000), and 0.964 (95%CI 0.939-0.989) and 0.947 (95%CI 0.903-0.991) in turn.

Conclusions: The model built in this study offer an easy-to-use and economical measure to assess the risk of sarcopenia in middle-aged and older adults. Both nomogram model A and B have strong predictive ability with excellent accuracy, not only in community-dwelling residents but also in patients with multiple comorbidities.

The Relationship among Sarcopenia and Mortality in Chinese community-dwelling adults: A 7 years Cohort Study with propensity score matching

Lijiao Xiong,Tingfeng Liao,Zhaohao Zeng,Shuojia Wang,Guangyan Yang,Xiaohao Wang,Xinyu Wang,Jing Zhu,Pengfei Zhao,Yanchun Li,Lixing Li,Lin Kang*,Shu Yang*,Zhen Liang*
the Second Clinical Medical College, Jinan University (Shenzhen People's Hospital), Shenzhen, China

Background: Sarcopenia is a common age-related condition characterized by loss of muscle mass, strength, and function. It has been associated with a range of negative outcomes, including mortality. However, there is limited information on the mortality risk associated with sarcopenia in the Chinese population. This study aimed to assess the 7-year mortality risk of sarcopenia in a community-based population in China.
Methods: The study analyzed data from the China Health and Retirement Longitudinal Study (CHARLS), which collected population demographics, chronic disease status, and mortality data from community-dwelling individuals between 2011 and 2018. Sarcopenia was diagnosed using the Asian Working Group for Sarcopenia (AWGS) 2019 diagnostic criteria. The association between sarcopenia and mortality risk was assessed using logistic regression analysis, Kaplan-Meier survival curves, and propensity score-matched analysis with inverse probability of treatment weighting analysis.
Results: The study included 9,006 participants, of which 45.9% were male and 54.1% were female. Among them, 3,892 had no sarcopenia, 3,570 had possible sarcopenia, 1,125 had sarcopenia, and 419 had severe sarcopenia. Over 7 years of follow-up, there were 871 deaths, including 147 without sarcopenia, 395 with possible sarcopenia, 196 with sarcopenia, and 133 with severe sarcopenia. The Kaplan-Meier survival curves showed that sarcopenia and severe sarcopenia had a higher risk of 7-year mortality. The logistic regression analysis showed that the risk factors for 7-year mortality were sarcopenia, severe sarcopenia, age, diabetes, hypertension, cancer, stroke, lung disease, and memory-related diseases. Protective factors were female, married, and divorced. Compared to no sarcopenia, the odds ratios (ORs) of sarcopenia for 7-year mortality were 5.37 (95% CI 4.29-6.74) and 1.41 (95% CI 1.06-1.87) after adjusting for confounding variables ($P<0.05$). The ORs of severe sarcopenia were 11.85 (95% CI 9.1-15.42) and 2.11 (95% CI 1.51-2.95) after adjusting for confounding variables. Propensity score-matched analysis and inverse probability of treatment weighting analysis confirmed these findings. The adjust ORs for sarcopenia and 7-year mortality were 2.94 (95% CI, 1.6–5.39) in the 45–60 age group, 1.72 (95% CI, 1.11–2.68) in the 60–80 age group, and 5.03 (95% CI, 0.48–52.65) in the ≥80 age group. The ORs for severe sarcopenia and 7-year mortality were 6.92 (95% CI, 1.95–24.5) in the 45–60 age group, 2.59 (95% CI, 1.61–4.17) in the 60–80 age group, and 12.52 (95% CI, 1.18–133.18) in the ≥80 age group.
Conclusion: Sarcopenia is associated with a higher 7-year mortality risk in the Chinese community population, particularly in older age groups. Clinicians and policymakers should consider interventions to prevent and manage sarcopenia as part of efforts to reduce mortality in older adults.

Association of Handgrip Strength with Hip Fracture in Community-dwelling middle-aged and older adults: A 4-year Longitudinal Study

Tianting Guo[1],Lijiao Xiong#[2],Zhihua Huang[4],Xiaoan Zhang*[1],Jianwen Mo*[3]

1. Department of Orthopedics, Ganzhou Hospital of Guangdong Provincial People's Hospital (Ganzhou Municipal Hospital), Ganzhou 341000, Jiangxi province, China

2. Department of Geriatrics, The Second Clinical Medical College, Jinan University (Shenzhen People's Hospital), Shenzhen518000, Guangdong province, China.

3. The First Affiliated Hospital of Gannan Medical University, Ganzhou 341000, Jiangxi province, China

4. Gannan Medical University, Ganzhou 341000, Jiangxi province, China.

Background: Hip fracture and falls are significant health concerns among middle-aged and older adults. This longitudinal study aimed to investigate the association between Handgrip strength (HGS) and the risk of hip fracture and falls over a 4-year period in individuals aged 45 years and above.

Methods: This study included 10,092 participants(4,471 men and 5,621 women) aged 45 years and above from the China Health and Retirement Longitudinal Study (CHARLS). Incidents of hip fractures and falls were recorded during a 4-year follow-up, along with various demographic and clinical factors. Participants were categorized into five groups based on their HGS quintiles. Logistic regression models were employed to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) to assess the relationship between HGS and hip fracture/fall risk.

Results: During the 4-year follow-up period, 223 cases of hip fracture (2.2%) and 1,831 cases of falls (18.1%) were documented. Notably, higher HGS demonstrated a strong inverse association with the risk of hip fracture in both males and females (P<0.05). In comparison to the lowest HGS quintile, the adjusted odds ratios (ORs) for hip fracture were 0.46 (0.27-0.78) for the total population, 0.4 (0.19-0.81) for males and 0.48 (0.23-0.98) for females in the highest HGS quintile. Furthermore, a profound and statistically significant negative correlation between HGS and falls was detected (P<0.05). The adjusted ORs for falls in the highest HGS quintile, compared to the lowest quintile, were 0.62 (0.51-0.76) in the overall population, 0.59 (0.44-0.78) in males, and 0.78 (0.62-0.99) in females.

Conclusions: Our findings highlight the significant inverse association between HGS and the risk of hip fracture and falls in both males and females aged 45 years and above. Assessing handgrip strength may serve as a valuable tool for predicting fracture and fall risk.

Clinical, muscle pathology and molecular genetic analysis of myofibrillar myopathy 3 associated with MYOT gene mutation

Guiguan Yang,Xiaoqing L,Wei Li,Tingjun Dai,Dandan Zhao,Chuanzhu Yan,Pengfei Lin
Qilu Hospital of Shandong University

Introduction: To analyze the clinical phenotypic characteristics, muscle pathology, genetic mutations and related proteins of myofibrillar myopathy 3 caused by mutation in MYOT gene,and a literature review and summary of this disease were also conducted.

Methods: A retrospective analysis of the clinical phenotypic characteristics,muscle pathology and genetic test results of a patient with myofibrillar myopathy 3 caused by mutation in MYOT gene diagnosed in Qilu Hospital of Shandong University.Whole exon sequencing was applied to conduct high-throughput screening of pathogenic genes in patient.After finding candidate pathogenic mutation, Sanger sequencing was applied to verify the mutation sites in patient and family members. Meanwhile, functional verification was carried out on the mutation sites found in MYOT gene, and the relevant literature was reviewed.

Results: The patient was a 47-year-old woman with weakness in her lower limbs for 8 years. Electromyography showed myogenic changes.The muscle pathology suggests that there is deposition of abnormal substances and rimmed vacuoles within some muscle fibers.Gene testing showed that the patient was a carrier of the MYOT gene c.170C>T (p.Thr57Ile) heterozygous mutation, and her son and daughter also carried the same mutation at the same site.The son of the patient has an elevated creatine kinase (CK) level and spontaneous potential are occasionally observed on electromyography, while the daughter has no abnormalities.Two younger brothers did not carry the mutation.Protein functional studies suggested that the mutation of MYOT gene c.170C>T mutation can lead to the change of partial spatial structure of myotilin, and the abnormal aggregation of p62 protein and myotilin was involved in the pathogenesis of the disease.Literature review revealed that c.170C>T (p.Thr57Ile) mutation has only been reported in foreign populations.This is the first detailed report on the clinical phenotype, muscle pathology and gene function of MYOT-related myofibrillar myopathy type 3 in China.

Conclusion: The clinical manifestations of myofibrillar myopathy type 3 caused by MYOT gene mutation are heterogeneous, mainly manifested as muscle weakness in the distal or proximal extremities.The electrophysiological manifestations were myogenic lesions. The main manifestations of muscle pathology were abnormal deposition of related proteins in some muscle fibers and rimmed vacuoles. Accurate diagnosis of the disease mainly depends on gene detection. The co-localization of p62 protein and myotilin protein provides a new idea for the diagnosis and molecular mechanism research of the disease.

Correlation between Neurophysiological Indicators and the Prognosis in Amyotrophic Lateral Sclerosis

Feng Xiao,Jie Yang,Kai Chen,Jiaying Bai,Chunyan Zhu,Song Tan
Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China

Introduction: Neuro-electrophysiological examination not only has high sensitivity for early clinical identification of amyotrophic lateral sclerosis (ALS), but also plays an important role in monitoring the disease progression. This study aimed to explore the relationship between neuro-electrophysiological indicators and the prognosis of ALS.

Methods: Neuro-electrophysiological parameters of median, ulnar, common peroneal, tibial and superficial peroneal nerve were collected, including nerve conduction velocity, terminal motor latency, amplitude, negative wave area, duration. Patients were followed up by telephone and the primary outcome event was death or tracheotomy positive-pressure ventilation. Binary Logistic regression was used to analyze the relationship between neuro-electrophysiological parameters and disease progression rate. Gender, site of onset, age of onset, and revised ALS functional score being used as covariates, Cox proportional hazards analysis and Kaplan-Meier survival curve were used for survival analysis.

Results: A total of 114 patients were included in this study. The results of binary Logistics regression analysis showed that the larger of compound muscle action potential (CMAP) amplitude and CMAP negative wave area of the median, ulnar and tibial nerve, the disease progression is the slower($P<0.05$). Multivariate Cox regression analysis showed that the smaller the CMAP amplitude, CMAP negative wave area, neurophysiological index of the median nerve and CMAP negative wave area of the ulnar nerve, have caused higher the risk of death ($P<0.05$). Univariate analysis showed that in ALS patients with lower limb onset, smaller the CMAP negative wave area of the common peroneal nerve had the shorter survival time than those in larger area ($P=0.011$).

Conclusion: The CMAP negative wave area of the median, ulnar and the common peroneal nerve, and SNAP negative wave area of the ulnar nerve may be used as an electrophysiological index to predict the prognosis of ALS.

Clinical presentation a patient with JAG2-related muscular dystrophy

Narges Karimi[1],Nafissi Shahriar[2]
1. Mazandaran University of Medical Sciences
2. Tehran University of Medical sciences

Introduction: JAG2 is an autosomal recessive form of muscular dystrophy located on chromosomal region 14q32.33. The disorder is characterized by progressive muscle weakness that mainly affects the lower limbs, leading to difficulty walking or loss of movement.
Case presentation: A 32-year-old male patient presented with progressive proximal upper and lower limb weakness since the age of 8 years. Parents are second cousins. The first symptoms were frequent falls, difficulty climbing stairs, and difficulty running. 10 years after the onset of symptoms, he presented with axial and proximal motor weakness in four limbs. He has pseudohypertrophy of the calf muscles. There are no joint contractures, facial weakness, or oculomotor disturbances. Cardiac evaluation is normal. The paraclinical examinations show a CK level of 765 and myopathic features on the EMG. A muscle biopsy performed at the age of 18-revealed wide variation in fiber size, internalized nuclei, and moderate to severe myopathic atrophy. An increase in endomysial connective tissues associated with severe adipose replacement was observed, all of which were initially suspected to be Becker muscular dystrophy. Immunohistochemically study of sarcolemma showed mild patchy labeling of dystrophin, dysferlin, and gamma dystroglycan. A muscle MRI reveals a severe fatty involution in the muscles of the hamstring and soleus. The first genetic analyzes relate to GAA, FKRP, DYSF, CALP, SGCA, SGCD, SGCB, ANO5, and TCAP genes were normal. A whole exome analysis reveals the presence of a homozygous variant of uncertain significance JAG2 gene (c.1135G>A, p.Gly379Arg).
Conclusion: Muscular dystrophy associated with the JAG2 (Protein jagged-2) gene shows progressive muscle weakness, which is more prominent in the proximal lower limb and axial muscles.

The Value of Serum Creatinine in Dystrophinopathy

liang wang[1],Min Xu[2],Dawei Liu[1],Yingyin Liang[1],Pinning Feng[1],Huan Li[1],Yuling Zhu[1],Ruojie He[1],Jinfu Lin[1],Huili Zhang[3],Ziyu Liao[1],Menglong Chen[1],Yiming Sun[1],Juan Yang[4],Lulu Xiao[5],Cheng Zhang[1]

1. The First Affiliated Hospital, Sun Yat Sen University
2. The Second Affiliated Hospital of Guangzhou Medical University
3. Guangzhou First People's Hospital
4. Zhujiang Hospital, Southern Medical University,
5. Nanfang Hospital, Southern Medical University

Introduction: Dystrophinopathy is a common neuromuscular disorder, including two main phenotypes, Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD). Biomarkers for distinguishing phenotypes and monitoring disease progression are urgently needed. We assessed the value of the serum creatinine (SCRN) level for a biomarker in dystrophinopathy.

Methods: We enrolled hundreds of male dystrophinopathy patients and non-dystrophinopathy controls for the assessment. Patients' basic information, phenotypes, motor function, muscle imaging and histology were evaluated. The correlations between these parameters and SCRN levels were studied, and determined changes in SCRN levels with maturation between different phenotypes.

Results: SCRN levels correlated with motor function, as well as with muscle fatty infiltration and dystrophin levels. SCRN levels increased with maturation in control; it slowly increased with maturation in patients with BMD but decreased generally with maturation in patients with DMD. This difference in SCRN levels between phenotypes could be used for distinguishing phenotypes in the early stage of the disease, and the area under the curve (AUC) was more than 0.8.

Conclusion: These results indicated that the SCRN level is helpful for distinguishing phenotypes as well as a valuable biomarker for monitoring disease progression in dystrophinopathy.

Generation of induced pluripotent stem cell lines from patients with Duchenne muscular dystrophy

liang wang,Huan Li,Zhong Pei,Cheng Zhang
The First Affiliated Hospital, Sun Yat Sen University

Introduction: Duchenne muscular dystrophy (DMD) is a common hereditary neuromuscular disorder characterized by progressive muscle wasting and weakness. The induced pluripotent stem cell (iPSC) is a good cell model for investigating the pathogenesis and therapeutics of disease. In this study, we successfully generated the iPSCs of DMD for scientific researches.
Methods: We enrolled three patients with DMD for the study, whose mutations covered large deletion, large duplication, and nonsense mutation, respectively. Their urine or blood were collected, and the purified cells in the samples were used for reprogramming.
Results: The iPSC lines showed typical iPSC morphology and normal karyotypes (diploid 46, XY). Short tandem repeat (STR) analysis confirmed that the iPSC lines were derived from the patients, and mutation analysis showed the consistency between cell lines and the donors. The characteristics of iPSC lines were also confirmed by the expression of relevant markers (OCT4, NANOG, and SOX2) and the trilineage differentiation potentials.
Conclusion: We generated three DMD iPSC lines successfully, which can serve as a model for studying the pathogenesis and therapeutics of DMD.

Duchene Muscular Dystrophy (DMD) patients living in high altitude areas walk independently for 2 years longer than those living on the plains, results of a retrospective analysis in Nepal.

Rohit Kumar Pokharel
Institute of Medicine, Tribhuvan University

Introduction: DMD is a progressive muscular wasting genetic disease. Early loss-of-ambulation (LOA) and death at a young age are inevitable in DMD. Definite treatment of DMD is not available yet. In sports, high-altitude training is popular to improve athletic performance.

Method: We investigated the influence of altitude on DMD in relation to age at LOA. Ninety-one patients living in different elevations of Nepal were divided into <200m (plain), 200-700m (intermediate), 700-1000m (middle), and >1000m (high) groups, and the age at LOA was recorded from the MDF-Nepal data base.

Results: The median age at LOA for each group increased with elevation, and the median LOA age in the >1000m group was significantly higher than that in the <200m group by about 2 years (median ± SD; 11.20 ± 2.78 Vs 9.62 ± 2.02, $p<0.005$).

Discussion: This indicated a longer period of independent walking for DMD patients living in high altitude areas.

Myotonic Dystrophy Type 1: Genetic and Clinical Features of a Multicenter Chinese Cohort

Huahua Zhong[1],Li Zeng[2],Song Tan[2],Xuefan Yu[3],Qing Ke[4],Jihong Dong[5],Yan Chen[6],Lijun Luo[7],Xueli Chang[8],Junhong Guo[8],Yiqi Wang[4],Hui Xiong[9],Rongrong Liu[10],Changxia Liu[11],Jibao Wu[12],Jie Lin[1],Jianying Xi[1],ua Zhu[1],Chongbo Zhao[1],Jiahong Lu[1],Sushan Lo[1]

1. Huashan Hospital
2. Department of Neurology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China
3. Department of Neurology and Neuroscience Center, the First Affiliated Hospital of Jilin University, Changchun, Jilin, China
4. Department of Neurology, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
5. Department of Neurology, Zhongshan Hospital Fudan University, Shanghai, China
6. Department of Neurology, Tongji Hospital, Tongji University, Shanghai, China
7. Department of Neurology, Wuhan No.1 Hospital, Huazhong University of Science and Technology, Wuhan, China
8. Department of Neurology, the First Hospital of Shanxi Medical University, Shanxi, China.
9. Department of Pediatrics, Peking University First Hospital, Beijing, China
10. Department of Neurology, Shaoxing Second Hospital, Shaoxing, China
11. Department of Neurology, Yancheng First People's Hospital, Yancheng, China
12. Department of Neurology, Chenzhou First People's Hospital, China

Introduction: As the most common subtype of muscular dystrophy worldwide, there is a lack of systematic reporting on myotonic dystrophy type I (DM1) in the Chinese population. This study aims to analyze the genetic and clinical characteristics of Chinese patients with classical DM1.

Methods: Based on the multicenter collaboration of the Pan-Yangtze River Delta Alliance for Neuromuscular Disorders, peripheral blood samples were collected from 211 DM1 patients who were clinically, electrophysiologically, and genetically diagnosed from November 2019 to April 2023. Dynamic mutation of the DMPK trinucleotide was analyzed using flanking-PCR. Additionally, clinical characteristics of 64 DM1 patients from disease onset to follow-up were retrospectively collected. These clinical features included myotonia, cognitive impairment, tumor, metabolism, daily sleep and diet, medication history, as well as cataract surgery, wheelchair use, cardiac pacemaker implantation, and the use of gastric tubes and respirators. The Epworth Sleepiness Scale and Fatigue Severity Scale were used to quantify the severity of daytime sleepiness and fatigue in patients.

Results: Among the 211 DM1 patients with CTG dynamic mutations, the mean CTG repeat length was 511.3, with a range of 92 to 1945 repeats. There were 124 male patients (age 40.9 ± 12.9, CTG repeat 454.6 ± 248.4) and 84 female patients (age 42.0 ± 11.2, CTG repeat 511.3 ± 358.8).

Among the 64 DM1 patients with complete clinical data (age 41.0 ± 12.0), although female patients had a higher mean CTG repeat length than male patients (507.5 > 431.3, n = 27:37), survival analysis showed that the age of onset in male patients was significantly earlier than in female patients (4.8 years earlier, p=0.03). Myotonia (85.9%), fatigue (73.4%), and daytime sleepiness (70.3%) were the most common clinical features in DM1 patients. Among them, 14.1% of patients underwent cataract surgery, 7.8% used wheelchairs, 4.7% used respirators, and 1.6% required gastric tubes. Additionally, 4.7% of patients had tumors, 17.2% had diabetes, 23.4% had respiratory difficulties, 28.1% occasionally experienced insomnia, 43.8% experienced swallowing cough, and 25% had cognitive impairment (mainly memory decline). In terms of medication, 51.6% of patients took mexiletine, and 26.6% took coenzyme Q10. The CTG repeat length itself and the patient's condition showed no apparent correlation with the instability of dynamic mutations. However, patients with an earlier age of onset exhibited more severe clinical features.

Conclusion: Through a multicenter analysis of Chinese DM1 patients, this study summarizes the genetic and clinical characteristics of Chinese patients with classical DM1.

Aberrant mRNA processing caused by splicing mutations in TTN-related neuromuscular disorders

Guangyu Wang,Xiaoqing Lv,Pengfei Lin
Qilu Hospital of Shandong University

Mutations in the TTN gene have been reported to be responsible for a range of neuromuscular disorders, including recessive distal myopathy and congenital myopathy (CM). Only fifive splicing mutations have been identifified to induce aberrant mRNA splicing in TTN-related neuromuscular disorders. In our study, we described detailed clinical characteristics, muscle pathology and genetic analysis of two probands with TTN-related autosomal recessive neuromuscular disorders. Besides, we identifified two novel intronic mutations, c.107377+1 G > C in intron 362 and c.19994-2 A > G in intron 68, in the two probands. Through cDNA analysis, we revealed the c.107377+1 G > C mutation induced retention of the entire intron 362, and the c.19994-2 A > G mutation triggered skipping of the first 11 bp of exon 69. Our study broadens the aberrant splicing spectrum of neuromuscular disorders caused by splicing mutations in the TTN gene.

Aberrant splicing caused by three distinct intronic mutations in CAPN3 related autosomal recessive limb-girdle muscular dystrophy-1

Guangyu Wang,Wenjing Wu,Pengfei Lin
Qilu Hospital of Shandong University

Autosomal recessive limb-girdle muscular dystrophy-1 (LGMDR1) is the most common subtype of autosomal recessive limb-girdle muscular dystrophy caused by biallelic mutations in the CAPN3 gene. Hundreds of mutations have been identified in LGMDR1 patients, and some studies have demonstrated aberrant splicing as a pathogenic mechanism in LGMDR1 patients carrying intronic mutations. Here, we describe three LGMDR1 probands carrying three distinct splicing mutations, namely, c.2185-14T>G in intron 20, c.1193+30G>A in intron 9, and c.1194-9 A>G in intron 9 of the CAPN3 gene. The c.2185-14T>G and c.1193+30G>A mutations were reported here for the first time. Through RNA analysis, we found that these three mutations induced aberrant CAPN3 mRNA splicing. The c.1193+30G>A mutation led to retention of the first 31 bp of intron 9, and the c.1194-9A>G mutation led to retention of the last 8 bp of intron 9 (Fig. 2H). Notably, the c.2185-14T>G mutation occurred in the polypyrimidine tract of intron 20 and caused the pseudoexonization of all of intron 20. Western blotting showed reduced expression of both the 94-kDa and 60-kDa calpain 3 bands in the two probands. Our study broadens the spectrum of aberrant CAPN3 mRNA splicing caused by intronic mutations.

The correlation between the expanded CTG repeats in DMPK gene and muscle strength of different muscle groups in Myotonic dystrophy type 1

Yuean Yang[1],Sushan Luo[2],Yi Wu[1],Chongbo Zhao[2]
1. Huashan Hospital
2. Department of Neurology, Huashan Hospital

Introduction: Myotonic dystrophy type 1 (DM1) is an autosomal dominant multisystem disease characterized by progressive muscle weakness, muscle atrophy, and myotonia, with multiorgan or systemic involvement of the eye, heart, respiratory system, and endocrine system. The disease is more prevalent in Western European and North American populations, and rarer in Asian and African populations. According to the literature, more than 49 CTG repeats in the DM1 protein kinase (DMPK) gene cause DM1. In DM1, it has been shown that there is a correlation between the length of the CTG expansion and disease severity. However, the assessment of muscle strength in each specific group of limb and trunk skeletal muscles has not been well studied. The aim of this study was to investigate the muscle strength performance of different groups in patients with DM1 and the correlation between the expanded CTG repeats in the DMPK gene and muscle strength.

Methods: The study subjects were collected from 40 patients with genetically confirmed DM1 who attended the outpatient clinic of Huashan Hospital from March 2019 to November 2022. The size of CTG repeat on DMPK was detected by polymerase chain reaction (PCR) and capillary electrophoresis. Each patient was clinically assessed by the same physical therapist. The muscle strength of the upper and lower extremities, trunk, and neck was assessed by manual muscle testing(MMT). The muscle strength was categorized into grades of 0-5, with higher grades showing greater muscle strength. The correlation between the expanded CTG repeats and muscle strength of different muscle groups was analyzed after correcting for age and gender.

Results: Forty patients, aged 19-60 years old, with a mean age of 38 years old, including 20 males and 20 females. All patients had varying degrees of muscle weakness in different muscle groups, including trunk flexors (87.2%), neck flexors (94.6%), anterior shoulder flexors, shoulder abductors (72.5%), shoulder external rotators (80%), elbow extensors (71. 1%), wrist palmar flexors (76.9%), wrist dorsal extensors (85%), finger flexors (86.5%), finger extensors (94.6%), finger abductors (94.4%), finger adductors (94.6%) and ankle plantar flexors (78.8%) showed a higher percentage of decreased muscle strength. After correcting for age and gender, the analysis showed that the number of CTG repetitions and the strength of the anterior shoulder flexors (r=-0.395, p=0.017), posterior shoulder extensors (r=-0.361, p=0.033), hip flexors (r=-0.473, p=0.004), hip extensors (r=-0.434, p=0.008), hip abductors (r=-0.346, p=0.039), knee flexors (r=-0.335, p=0.046), knee extensors (r=-0.398, p=0. 016), ankle plantarflexors (r=-0.371, P=0.048) and trunk flexors (r=-0.475, P=0.004) showed a significant low negative correlation with muscle strength performance; a

significant low negative correlation was found for trunk extensors (r=-0.583, P=0.001) and posterior cervical extensors (r=-0.531, P=0.001) there was a significant moderate negative correlation with muscle strength.

Conclusion: In addition to muscle weakness in the fingers and wrists, most DM1 patients had reduced muscle strength in the shoulder muscles, trunk flexors, neck flexors and ankle plantar flexors. These findings reveal the selective involvement in different muscle domains in DM1 and further inform the longitudinal monitoring of the axial muscles and potential pulmonary functions.

Phenotypic Heterogeneity of MEGF10 Variants: a Case Report of Respiratory Difficulty and Nocturnal Awakening in Patients with MEGF10-associated myopathy

Kexin Jiao, MD[1,2,3,*], Bochen Zhu, MD[1,2,3,*], Ning Zhu, MD, PhD[4], Xingyu ia, MD[1,2,3,] Lingchun Liu, MD[5],Mingshi Gao, MD6,Nachuan Cheng, MD[1,2,3], Ningning Wang, MD[1,2,3], Sushan Luo, MD,PhD[1,2,3],Jianying Xi, MD, PhD[1,2,3], Wenhua Zhu,MD, PhD [1,2,3], Shengging Li,MD[4], Chongbo Zhao, MD, PhD [1,2,3]

1.Department of Neurology, Huashan Hospital, Fudan University, Shanghai, China

2.National Center for Neurological Disorders (NCND), Shanghai, China

3.Huashan Rare Disease Center, Shanghai Medical College, Huashan Hospital, Fudan University, Shanghai, China

4.Department of Respiratory and Critical Care Medicine, Huashan Hospital, Fudan University, Shanghai, China.

5.Department of Neurology, The First People's Hospital of Yunnan Province, Yunnan, China

6.Department of Pathology, Huashan Hospital, Fudan University, Shanghai, China*These authors contribute equally to this paper.

Objective: Mutations in the multiple epidermal growth factor-like domains 10 (MEGF10: NM_032446.2) gene are known to cause early-onset myopathy characterized by areflexia, respiratory distress, and dysphagia (EMARDD: OMIM 614399), and a milder phenotype of minicore myopathy. This study details an unusual case of myopathy related to compound heterozygous mutations in the MEGF10 gene.

Methods: We accrued clinical, laboratory, and muscle pathology data from a patient with MEGF10-associated myopathy, who initially presented with recurrent nocturnal awakenings, at Huashan Hospital, affiliated with Fudan University, in January 2023. Whole exome sequencing was conducted on the patient's peripheral blood sample.

Results: The 29-year-old male patient described a year-long history of "chest tightness and shortness of breath," with episodes of nocturnal awakenings recurring for the past two weeks. The symptoms began in early 2021 and were exacerbated by physical activity, but without clear progression or remission. Starting January 2022, recurrent nocturnal awakenings occurred without obvious triggers, coupled with morning fatigue, though daytime mental state remained normal. He occasionally experienced cough and sputum, but the severity of chest tightness and fatigue remained unchanged. Laboratory findings indicated elevated white blood cells count of 15.46*10^9 and neutrophils at 76.7%, with a whole blood CRP of 3.61mg/L. Blood gas analysis revealed a carbon dioxide partial pressure of 57.8mmHg and an oxygen partial pressure of 64.2mmHg. A chest CT scan showed inflammation in the right upper and left lung lobes, with localized atelectasis in the right middle lobe. Despite symptom-di-

rected supportive treatment with ceftriaxone, levofloxacin, and other antibiotics, no significant improvement was observed. Recurrent hypoxemia during the hospital stay necessitated non-invasive ventilation. The patient noted suboptimal physical performance since childhood. Physical examination revealed a lean face, high-arched palate, and stiff spine. Muscle pathology showed marked variation in muscle fiber size, hypertrophic and splitting fibers, swirling fibers, moderate nuclear internal migration, endomysial fibrosis, rimmed vacuoles, and a small number of abnormal deposits. GAA enzyme activity was within the normal range. Whole exome sequencing identified compound heterozygous mutations in the MEGF10 gene: c.1A>T(p.Met1?) and c.2087G>T(p.Gly696Val).

Conclusion: MEGF10-associated myopathy displays considerable clinical heterogeneity, easily mistaken for late-onset Pompe disease, thereby underscoring the importance of careful differential diagnosis.

A case of Ullrich congenital muscular dystrophy caused by a new variant of COL6A3 gene

Jiongbo Zhao,Qianqian Qu,Wenhao Cui,Shiyao Li,Jiaxuan Wang,Cong Hu,Haidong Lyu
Jiaozuo People's Hospital, Xinxiang Medical University, Jiaozuo, Henan 454002, China

Objective To summarize the clinical, muscle MRI and pathological data of a patient with Ullrich congenital muscular dystrophy (UCMD) due to a COL6A3 gene variant, as well as the **results** of genetic testing, and to discuss the clinical and molecular genetic features of UCMD due to a COL6A3 gene variant.

Methods Detailed clinical, muscle MRI and muscle pathology data of a patient with UCMD were collected, and genetic variants were detected in preexisting patients and family members by next-generation sequencing technology and discussed in the context of relevant literature.

Results A 13-year-old male was admitted to the Department of Neurology of Jiaozuo People's Hospital in September 2022 because of weakness of both lower limbs aggravated for 10 years and weakness of both upper limbs for 3 years .The child was born normally .When he was 3 years old, he was found by his parents to run slowly and fall easily. Running at the age of 5 was obviously not as laborious as standing up after squatting for children of the same age. Three years ago, the lower limbs were unable to rise after squatting, difficult to rise up the stairs, easily to fall. After that, the weakness of both upper limbs gradually appeared, holding irrelevant, and the weight of both upper limbs was distal weakness, and the weight of both lower limbs was proximal weakness. Physical examination: development and intelligence were normal, and no cerebral nerve abnormalities were observed. Cervical flexor strength grade 3, tendon reflexes of both upper limbs (+), proximal muscle strength grade 4, distal muscle strength grade 3-4, tendon reflexes of both lower limbs (-), proximal muscle strength grade 2-3, distal muscle strength grade 3-4. The quadriceps muscles of both lower limbs were obviously atrophied, the gastrocnemius and tibialis anterior muscles were mildly atrophied, the proximal muscles of both upper limbs were not obviously atrophied, and the arches of the feet were high bilaterally.Bilateral arch height Serum CK 681U/L, LDH 239U/L. Electromyography showed that some of the examined muscles showed myogenic damage. Muscle MRI suggested that the lesion mainly involved the gluteus, thigh and calf anterior and posterior muscle groups, with predominantly myasthenia and steatosis, with unremarkable muscle tissue edema.Muscle biopsy pathology showed myofibers of markedly unequal sizes, with small round atrophic fibers and compensatory hypertrophic muscle fibers seen, showing pathological changes of myotonic dystrophy. Genetic testing revealed a c.6248G>A missense mutation in the COL6A3 gene, and family lines were verified for co-segregation.

Conclusion Ullrich congenital muscular dystrophy due to the COL6A3 gene is a rare autosomal recessive or dominantly inherited myopathy characterized by progressively worsening limb weakness and high clinical heterogeneity. Genetic testing is important for confirming the diagnosis of this disease, and the c.6248G>A point mutation we reported further extends the spectrum of mutations in the COL6A3 gene.

Nocturnal respiratory management of a collagen VI-related myopathy patient: a case report

Danyu Song,Yi Chen,Yanbin Fan,Leping Ye,Hui Xiong
Peking University First Hospital

Objective: Collagen VI-related myopathy is an inherited muscle disease caused by mutations in the genes encoding collagen VI, COL6A1, COL6A2, and COL6A3. We are aimed to report a case with collagen VI-related myopathy and summarize the experience of nocturnal respiratory management.
Methods: We collected clinical data of a patient with collagen VI-related myopathy and nocturnal respiratory insufficiency, including age of onset, motor development, recognizable symptoms, multi-channel sleep monitor test results, pulmonary function, genetic results, echocardiography, electrocardiogram and holter findings.
Results: The patient was an 8-year-old girl. Symptoms such as muscle weakness and hypotonia were present at neonatal period. She had a delay in motor development since birth. She was able to lift head at 7 months and sit without support at 1 year. She has been unable to stand alone until now. Four months ago, the patient had chest distress and dyspnea, occasionally with cough. Physical examination revealed that facial skin and skin of the extensor side of the limbs was excessively keratinized. Heart, lung, and abdominal examination showed no abnormality. Neurological examination showed muscle weakness with striking joints (elbow, knee and ankle joint) laxity and contractures. Muscle strength of limbs was between III- level and IV- level with predominantly proximal muscle weakness. Bilateral tendon reflexes were not elicited. Pathological signs were negative. Auxiliary examination: genetic examination revealed c.850G>A (p.G1y284Arg) in COL6A1 gene, a novel reported pathogenic variant. Chest X-ray showed no obvious problem. Pulmonary function showed mild restrictive ventilatory dysfunction. Bronchodilatation test was negative. Multi-channel sleep monitor showed average blood oxygen saturation during sleep was 98% with minimum value 87%. The minimum value was related to respiratory events. There were some respiratory disturbances and hypoxia events during sleep. Apnea-hypopnea index during sleep was 4.8 times/hr, mostly accompanied by blood oxygen drop. The number of blood oxygen saturation drop >3% per hour was 4.2 times. There were some respiratory rhythm instability during sleep, mostly not accompanied by obvious blood oxygen drop. Echocardiography, electrocardiogram and holter showed no abnormality. Although this patient had mild restrictive ventilatory dysfunction and mild hypoxia events, her symtoms were obvious with somnipathy. So, noninvasive bi-level positive airway pressure ventilation was used to help her breath with ST mode (parameters were IPAP 8cmH20, EPAP 4cmH20, backup frequency 14, and tidal volume 200-300ml) when sleeping at night. With the help of ventilator, patient's chest distress significantly improved without dyspnea and somnipathy.
Conclusions: This collagen VI-related myopathy patient showed severe respiratory symptoms with mild restrictive ventilatory affecting her sleeping. Noninvasive ventilation can help relieving symptoms and improving sleep quality and avoid nocturnal respiratory failure. We should pay more attention to nocturnal respiratory management of collagen VI-related myopathy patients.

Cardioembolic stroke in a Chinese young patient with Emery-Dreifuss muscular dystrophy

Yanbin Fan[1],Shan Li[3],Han Xie[3],Qianqian Xia[3],Yanan Zhang[3],Cuijie Wei[3],Jing Zhou[2],Xueqin Liu[3],Qingyou Zhang[3],Zhaoxia Wang[1],Xin Zhang[3],Xingzhi Chang[3],Hui Xiong[3]

1. Peking University First Hospital
2. Department of Cardiovascular Medicine, Peking University First Hospital
3. Department of Neurology, Peking University First Hospital

Background This study analyzed the diagnosis and treatment of cardiogenic stroke in a patient with autosomal dominant Emery-Dreifuss muscular dystrophy (EDMD) caused by missense variation of LMNA gene.

Methods Clinical data of the patient were collected, and electrocardiogram, especially 24-hour holter electrocardiogram, echocardiography, head MRI, MRV, MRS and other examinations were completed to determine the location and nature of the lesions.

Results The patient was a 12-year-old school-age female child with muscle weakness, delayed motor development, and abnormal gait from childhood. Genetic testing at the age of 1 year revealed de novo heterozygous mutations in LMNA genes (c.116A>G, p.Asn39Ser), and was diagnosed as autosomal dominant EDMD. Two days before admission to our hospital, there was no obvious cause of non-ejection vomiting. One day before admission, there was numbness around the mouth and in the left hand in the morning, and then there was increased weakness in the left upper limb, accompanied by decreased sense of touch and pain in the left upper limb, accompanied by headache and paroxysmal increase. During the period, there was one convulsion, manifested as loss of consciousness, left Angle of mouth, and shaking of limbs, which lasted for 2-3 minutes. Physical examination: Lethargy, awakenable, left frontal striae shallow, left nasolabial groove shallow, right-sided mouth Angle, left eye closure weakness, left cheek and drum weakness, tongue extension left, unable to turn over, right upper limb muscle strength proximal IV, distal IV, left upper limb proximal III, distal II, both lower limb muscle strength IV, left upper limb shallow and deep sensory abnormalities, pathological signs negative, Meningeal irritation is not cooperative. Blood biochemistry and BNP were normal, hypersensitive troponin I was slightly elevated; No significant abnormalities were found in coagulation items. The number of nucleated cells in CSF was 19/mm3, multiple nucleated cells were 17/mm3, and the CSF biochemistry was normal. The 24-hour holter electrocardiogram showed third degree atrioventricular block and junction arrhythmia. Echocardiography showed enlarged heart, pulmonary hypertension (moderate), small regurgitation of the pulmonary valve and small regurgitation of the tricuspid valve. Head MRI showed multiple abnormal signals in left frontal lobe, right frontal lobe, basal ganglia, right radiative crown and corpus callosum. Head MRV showed that the local development of the straight sinus was not clear, and small defects could be filled in the left sigmoid sinus cavity. MRS Showed reduced NAA peaks in

the right basal ganglia and left frontal lesions, and inverted Lac double peaks were seen. The overall consideration was acute ischemic stroke caused by cardiac embolism. He was admitted to the hospital for cranial pressure reduction with mannitol and hyperosmolar sodium, dexamethasone anti-inflammatory, aspirin antiplatelet, dapheparin anticoagulation, fluid restriction, diuretic and nutritional myocardial therapy, improved implantation of single-cavity implanted cardioverter defibrillator (ICD), postoperative oral warfarin anticoagulation, captopril, hydrochlorothiazide, spironolactone to improve myocardial remodeling, and sodium fructose diphosphate and coenzyme Q10 nutritional myocardial therapy. At present, the child was conscious, the bilateral frontal striae and nasolabial groove were basically symmetrical, the extended tongue was centered, and the muscle strength of the left upper limb was grade III, which was better than before. Heart rate 60 beats/min, the pacing rhythm; Reexamination echocardiography showed that the left atrial left ventricular diameter was lower than before, EF64%.

Conclusion Patients with EDMD may have early cardiac involvement, manifested as heart failure and various cardiac conduction disorders, and are at risk of cardiac arrest, cardiogenic stroke and sudden death. Regular electrocardiogram and echocardiography should be performed, and pacemaker implantation should be performed if necessary.

Nutritional status of Chinese cohort of pediatric patients with spinal muscular atrophy

Shuang Li[1],Ying Wu[2],Yanbin Fan[1],Yidan Liu[1],Cuijie Wei[1],Hui Xiong[1]
Peking University First Hospital

Introduction: The nutritional problems were becoming more and more prominent in pediatirc patients with spinal muscular atrophy(SMA) . The purpose of this study was to evaluate the nutritional status of single-center SMA children in China.

Methods: Clinical data including the body weight,length, body mass index (BMI),weight for height(WHZ), potassium,sodium, calcium,total cholesterol(TC),triglycerides(TG), the levels of serum 25-hydroxy Vitamin D (25-OHD) of SMA patients from October 2019 to June 2023 were collected and analyzed. We used the Z-score (standard deviation) to analyze the BMI and WHZ.

Results: A total 58 pediatric patients with SMA (11 SMA I,28 SMA II, and 19 SMA III) with ages ranging from 12 months old to 16 years old were included. Nearly 32.8% of SMA patients showed nutritional problems. Malnutrition was observed in 36.3% (4/11) of SMA I patients, 32.2% (9/28) of SMA II patients and 36.6% (6/19) of SMA III patients; overweight was found in 7.1% (2/28) of SMA II patients and 15.8% (3/19) of SMA III patients. The 25-OHD deficiency was observed in 7.1% (2/28) of SMA II patients, 21.1% (4/29) of SMA III patients. The was found in 9.1%(1/11) of SMA I patients, 25% (5/20) of SMA II patients and 23.1% (3/13) of SMA III patients. TG was found elevated in 45.5%(5/11)of SMA I,42.9%(12/28)pf SMAII， 31.6%(6/19)of SMA III. TC was elevated in 36.3%(4/11) of SMA I,4.3%(4/28)of SAM I,15.8%(3/19)of SMA III. Electrolyte and fasting blood glucose were within normal range for age.

Discussion: This study showed that malnutrition was commom in SMA I patients, 25-OHD deficiency or insufficiency was frequent for the three types of SMA. Dyslipidemia is particularly prominent in SMA I patients.Dietary adjustment and increasing nutrient intake are very important for SMA patients.

Conclusion: In this study, we demonstrated the nutrition situations in a Chinese cohort of pediatric patients with SMA.

Clinical, Genotypic, and Muscle MRI characteristics in Limb-Girdle Muscular Dystrophy R7 from a Thai neuromuscular center

Jakkrit Amornvit[1,2],Tanitnun Paprad[3],Worawan Sirichana[4],Chupong Ittiwut[6],Rungnapa Ittiwut[6],Kanya Suphapeetiporn[6],Nath Pasutharnchat[2],Numphung Numkarunarunrote[5]

1. King Chulalongkorn Memorial Hospital, The Thai Red Cross Society
2. Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
3. Division of Neurology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
4. Division of Pulmonary and Critical Care Medicine, Department of Medicine, Faculty of Medicine Chulalongkorn University Bangkok Thailand
5. Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.
6. Excellence Center for Genomics and Precision Medicine, King Chulalongkorn Memorial Hospital, the Thai Red Cross Society, Bangkok, Thailand.

Introduction: Limb-girdle muscular dystrophy R7 (LGMDR7), a rare autosomal recessive form of limb-girdle muscular dystrophy, caused by mutations in the TCAP gene. The underlying genetic variations and their correlation with clinical manifestations need further exploration.

Methods: Five patients from three unrelated families with TCAP mutations were retrospectively identified at the Neuromuscular Center at King Chulalongkorn Memorial Hospital. Demographic, clinical, laboratory, and muscle MRI data were collected and analyzed.

Results: We report a mild phenotype associated with asymptomatic/paucisymptomatic hyperCKemia in a family and the classic LGMD phenotype in two unrelated patients. A novel mutation, c.136_137del, was identified in a compound heterozygous state with c.26_33dup in the family with the mild phenotype. Muscle MRI of our four patients revealed consistent sparing of the sartorius and illiopsoas muscle across all patients.

Conclusion: The study identified a novel TCAP gene variant and muscle MRI patterns, expanding our understanding of LGMDR7's genetic and phenotypic diversity. These findings could help refine the diagnostic, management, and treatment approaches for LGMDR7. Further research is warranted to understand the disease's progression and natural history.

Quantification of muscle fat fraction by iterative decomposition of water and fat with echo asymmetry and least-squares estimation quantitation sequence (IDEAL IQ) in Duchenne muscular dystrophy

Yanyu Lu,Liang Yin,Zhaoxia Wang,Jiangxi Xiao,Yun Yuan,Zhiying Xie
Peking University First Hospital

Introduction: Despite the widespread use of quantification of muscle fat fraction with magnetic resonance imaging (MRI) to track disease progression in muscle disorders, it is still unclear how the disease progress temporally and spatially.

Methods: We conducted a cross-sectional and observational study design, including 133 boys with DMD and 41 control subjects and acquired IDEAL-IQ sequence fat fraction (FF) of twelve muscles in pelvis and thigh. In 18 patients with neuromuscular diseases, we performed muscle biopsies in vastus lateralis. Motor function was assessed by timed function tests and ambulatory status by North Star Ambulatory Assessment (NSAA). We correlated the FF to the fat percentage measured on biopsies of the corresponding muscles, as well as to the motor function tests. We also evaluate the spatial distribution of fat replacement within these muscles and the model the disease trajectory.

Results: First, there was a significant positive correlation between MRI and FF value measured by pathology (ρ=0.967). The Bland-Altman plot shows that the differences were within the 95% consistency limit. There was a moderate correlation between the mean FF of gluteus maximus and timed function tests ($r = 0.527$-0.567, $p < 0.001$), and NSAA ($r = -0.731$, $p < 0.001$). By selecting 5 non-consecutive slices, we evaluate the FF on MRI for 12 thigh muscles from origin to insertion, we observed different patterns of fat replacement within each of the muscles. Furthermore, MRI FF increased with DMD disease duration, with the progression time constants differing markedly across muscles. The average age at half maximal muscle involvement (μ) occurred earliest in adductor magnus(9.1) and latest in gracilis(18.8).

Conclusions: We showed a strong correlation of FF on MRI and on muscle biopsy for diseased muscles, as well as moderate correlation with motor function tests. Pelvis and thigh muscles with DMD show a distinct and inhomogeneous fat replacement pattern, both temporally and spatially.

Genetic and clinical characterization of facioscapulo-humeral muscular dystrophy type 1 in Hong Kong

Shirley Pang,Michael Yu,Yuan Gao,Anna Kwong,Patrick Law,Khan Hire,Stephen Cheng,Godfrey Chan,Sophelia Chan
The University of Hong Kong

Background: Facioscapulohumeral Muscular Dystrophy (FSHD) is the third most prevalent hereditary muscular dystrophy worldwide. Currently, FSHD1 genetic testing is not publicly funded in Hong Kong (HK), resulting in significant obstacles to diagnosis and management. This study aims to characterize FSHD1 patients in HK.

Methods: Subjects with suggestive symptoms of FSHD were recruited from neurology clinics between March 2021 and July 2022. D4Z4 unit number was determined using molecular combing (MC) or Southern blot (SC) techniques.Genetically confirmed FSHD1 patients were invited to complete a self-reported survey and undergo assessment for FSHD clinical score.

Results: Eighty-three subjects suspected of having FSHD joined the study; 61 were diagnosed with FSHD1 (56 by MC , 5 by SC). The mean ages of symptom onset and diagnosis were 22.5 years and 47.0 years respectively. Nine (22.5%) of the 40 affected families involved two generations, and one (2.5%) involved three. Shoulder weakness was the most frequently reported symptom (83.0%,n=44). Fourteen patients (26.4%) required wheelchair (age: 5-70 years; D4Z4 repeat units: 2-6), and two required ventilation support. D4Z4 repeat unit showed a high positive correlation with age starting wheelchair use ($r=0.742, p<0.01, n=14$), a moderate positive correlation with the age of disease onset ($r=0.426, p<0.001, n=53$) and a moderate inverse correlation with FSHD clinical score ($r=-0.591, p<0.001, n=44$).

Conclusion: FSHD1 is common in Hong Kong. The lack of publicly funded genetic testing in Hong Kong has resulted in significant diagnostic delay of more than 20 years from symptom onset in most patients. While the onset and severity of the disease are correlated with D4Z4 repeat size, other as yet unknown factors likely play a modifying role as we have observed intrafamilial variability among patients with the same repeat unit. This requires further studies to identify possible therapeutic targets for disease modification.

Clinical, pathological, and genetic characterization in a large Chinese cohort with female dystrophinopathy

Chang Liu[1],Jiajian Ma[2],Yanyu Lu[1],Yunlong Lu[1],Jiahui Mai[3],Li Bai[1],Yikang Wang[1],Yilei Zheng[1],Meng Yu[1],Yiming Zheng[1],Jianwen Deng[1],Lingchao Meng[1],Zhaoxia Wang[1],Yun Yuan[1],Zhiying Xie[1]

1. Peking University First Hospital
2. The Chinese University of Hong Kong (Shenzhen)
3. Shenzhen Children's Hospital

Introduction: We aimed to investigate the clinical, pathological, and genetic characteristics of Chinese female dystrophinopathy and to identify possible correlations among them.

Methods: One hundred forty genetically and/or pathologically confirmed female DMD variant carriers were enrolled, including 104 asymptomatic carriers and 36 symptomatic carriers. Twenty of 36 symptomatic and 16 of 104 asymptomatic carriers were sporadic with no family history. Muscle pathological analysis was performed in 53 carriers and X chromosome inactivation (XCI) analysis in 19 carriers.

Results: In asymptomatic carriers, the median age was 35.0 (range 2.0–58.0) years, and the serum creatine kinase (CK) level was 131 (range 60–15,745) IU/L. The median age, age of onset, and CK level of symptomatic carriers were 15.5 (range 1.8–62.0) years, 6.3 (range 1.0–54.0) years, and 6,659 (range 337–58,340) IU/L, respectively. Four female carriers with X-autosome translocation presented with a Duchenne muscular dystrophy (DMD) phenotype. Skewed XCI was present in 70.0% of symptomatic carriers. Compared to Becker muscular dystrophy (BMD)-like carriers, DMD-like carriers were more likely to have an early onset age, rapidly progressive muscle weakness, delayed walking, elevated CK levels, severe reduction of dystrophin, and skewed XCI.

Conclusion: Our study reports the largest series of symptomatic female DMD carriers and suggests that delayed walking, elevated CK levels, severe reduction of dystrophin, X-autosome translocation, and skewed XCI pattern are associated with a severe phenotype in female dystrophinopathy.

Clinical, Morphological and Genetic Studies of a Cohort of Hong Kong Chinese Patients with Novel Pathogenic FLNC Nonsense Mutation

Yuan Gao[1],Ronnie Siu Lun Ho[2],Kam Ho Lee[3],Felix Chi Kin Wong[4],Ching Wan Lam[4],Shirley Yin Yu Pang[1]

1. Queen Mary Hospital
2. Division of Anatomical Pathology, Department of Pathology, Queen Mary Hospital, The University of Hong Kong
3. Department of Radiology, Queen Mary Hospital, The University of Hong Kong
4. Division of Chemical Pathology, Department of Pathology, Queen Mary Hospital, The University of Hong Kong

Introduction:

Myofibrillar myopathy type 5 (MFM5) is a rare hereditary myopathy caused by a heterozygous mutation in the *FLNC* gene. The main clinical features are adult-onset progressive skeletal muscle weakness and respiratory failure in advanced disease stages. In this study, we characterized the clinical, radiological, and pathological features of a cohort of Hong Kong Chinese MFM5 patients carrying a heterozygous *FLNC* c.8129G>T (p.Trp2710Ter) pathogenic nonsense variant.

Methods:

Forty patients from five families carrying the same heterozygous *FLNC* c.8129G>T (p.Trp2710Ter) pathogenic variant were included. Clinical features, MRI muscle patterns, and muscle histopathology were described.

Results:

In our cohort, 16 (40%) patients were men and 24 (60%) were women. The mean age of symptom onset is 49.3 years. The presenting symptoms are weakness (40, 100%), wasting (17, 42.5%), dyspnea (10, 25%), palpitation (9, 22.5%) and paresthesia (2, 5%). Eight patients died of respiratory failure at the mean age of 64 years during follow-up. MRI thigh revealed a characteristic pattern of fatty infiltration of adductors, semitendinosus, and biceps femoris, while semitendinosus was relatively spared even at advanced disease stages. Muscle histopathology showed cytoplasmic rimmed vacuoles, abnormal inclusions with desmin and dystrophin staining, reduction of oxidative enzyme activity by light microscopy, and marked smearing of Z-lines and extensive myofibrillar disruption with abnormal mitochondria by electron microscopy.

Conclusions: his represents the largest Chinese MFM5 cohort carrying a heterozygous *FLNC* c.8129G>A nonsense mutation. The clinical features, MRI pattern, and muscle histopathology were characteristic. This disease is highly penetrant, has high mortality by way of respiratory failure, and is currently without a cure. Further studies to elucidate the pathogenic mechanisms by which mutant Filamin-C causes myopathy will be useful to explore potential therapeutic strategies.

FHL1 gene mutation related late-onset reducing body myopathy in a Chinese family

Wenhao Cui

Jiaozuo People's Hospital of Henan Province

Objective: To summarize the characteristics of clinical, muscle pathology and gene mutation of the proband in a family with late-onset reducing body myopathy caused by FHL1 gene mutation, in order to improve clinicians' understanding of this disorder.

Methods: The clinical, muscle pathology and muscle MRI imaging data of the proband from a family diagnosed as reducing body myopathy in Jiaozuo People's Hospital in December 2021 were collected. Genetic tests and pedigree verification were conducted on the proband and his son.

Results: The proband was a 59-year-old female with progressive, asymmetrical limb weakness and muscular atrophy. Her mother, sister and brother had similar symptoms. Electromyography showed myogenic combined with neurogenic damage. Muscle MRI indicated that the lesion mainly involved the posterior muscles of the thigh and calf, as well as the gluteus maximus. The muscle pathology showed eosinophilic granular inclusion bodies and rimmed vacuoles in the muscle fibers of the lesion. The structure of myofibrils was disordered and abnormal protein deposition was observed. The gene sequencing showed the human four and a half LIM domain 1 (FHL1) gene p.C150S heterozygous variation.

Conclusion: Late-onset reducing body myopathy is characterized by progressive asymmetric proximal limb muscle weakness, partially involving distal limb muscles and gluteus maximus. Muscle pathology shows the characteristic pathological changes of many kinds of myofibrillar myopathies. FHL1 gene mutation is an important basis for diagnosis.

Alternatively spliced exons skipping caused by splicing mutation in NEB nemaline myopathy: Case Series Study and literature review

XiaoJing Wei,Jing Miao,Hui Sun,Ye Han,Ruike Jin,Zhenwei Ma,Wei Sun,Xuefan Yu
The First Affiliated Hospital of Jilin University

Introduction: Nemaline myopathy (NM) is a hereditary heterogeneous myopathy, which is named by the presence of rod or nemaline bodies inside muscle fibers. The clinical features of NM include weakness predominantly involving facial, axial, and distal limb muscles. Nebulin gene contains 183 exons, of which 42 exons (63–66, 143–144 and 167–177) are alternatively spliced in the middle of the gene.

Methods: We report four patients who harbored the nebulin (NEB) variant in the intron 144 of the NEB with proximal and distal muscle weaknesses.

Results: We found a distinct pattern on muscle imaging characterized by prominent involvement of the gluteus maximus and medius, adductor magnus, biceps femoris long head, semimembranosus and vasti. Lower legs showed a severe fatty infiltration, prominently affecting gastrocnemius and soleus muscle. This pattern was consistent in all the 4 patients. The severity of muscle involvement was significantly correlated with age. Trio-based whole-exome sequencing (trio-WES) and WES revealed an intronic splicing variant of c.21522+3A > G shared by four unrelated Chinese patients with NM. Furthermore, reverse transcription polymerase chain reaction (RT-PCR) revealed the splicing variant c.21522+3A > G construct contained a new aberrant transcript that caused skipping of complete exon 144.

Conclusion: The identification of c.21522+3A > G establishes a link between splicing mutation and the alternatively spliced exons variant of NM, which broadens the clinical and the mutational spectrum of the known NEB variants. Muscle MRI at the thigh level showed that patients can be distinguished from other NEB nemaline myopathy based on the trefoil with single fruit sign.

A case of congenital myopathy with tremor and literature review

Ying Zhao,Chuanzhu Yan,Kunqian Ji
Qilu Hospital, Cheeloo College of Medicine, Shandong University

Objective: To summarize and discuss the clinical manifestations and muscle pathology of congenital myopathy with tremor and to improve clinicians' understanding of the disease.
Methods: A family of congenital myopathy with tremor was reported. Enzyme histochemical staining and immunohistochemical staining were performed on the muscle tissues of the patient, and the expression level of sMyBP-C and mitochondrial DNA copy number were detected. The literatures of congenital myopathy with tremor reported previously were reviewed and summarized.
Results: The proband is a middle-aged male, whose clinical symptoms occurred from childhood, mainly manifested as irregular muscle vibration of the limbs and exercise intolerance, with mild proximal limb muscle weakness. Muscle biopsy showed mild myogenic damage with abnormal mitochondrial changes, and gene detection showed that MYBPC1 gene c.788T>G heterozygous mutation. Further detection showed that the expression level of sMyBP-C was significantly reduced, and the number of mitochondrial DNA copies was increased in the patient. The diagnosis of congenital myopathy with tremor was clear, and the symptoms did not progress during long-term follow-up. We summarize the clinical characteristics of 15 patients from 7 families in this case and previous reports. Tremor is a prominent clinical manifestation, combined with mild to moderate muscle weakness, which could be accompanied with varying degrees of hypotonia, exercise intolerance and skeletal joint malformation. Electromyography and muscle biopsy indicate myogenic damage, and the symptoms have no progress or chronic progress.
Conclusion: This case is the first family of congenital myopathy with tremor in China. For early-onset tremor of unknown reason with muscle weakness, hypotonia, and skeletal joint malformation, it is necessary to consider the possibility of congenital myopathy with tremor, and to further perform electromyography, muscle biopsy, and gene detection for a clear diagnosis. Muscle ultrasound is beneficial for detecting abnormal contraction patterns such as muscle vibration.

Intra-familial variability in patients with dominant RYR1 variations: analysis of 10 families

Xingzhi Chang,Cuijie Wei,Jieyu Liu,Yanbin Fan,Hui Xiong
Peking University First Hospital

Introduction: Pathogenic variation in RYR1 is the most common cause of congenital myopathy. Clinical heterogeneity was noted between patients with RYR1-related myopathies, both in dominant and recessive inheritance. While phenotype variance among family members with the same variation was not fully understood.

Method: Clinical, muscle pathologic and gene test data were collected and analyzed.

Results: 64 patients were identified with dominant RYR1 variations from 10 families, patients scattered in at least three generations in 8 families. In 5 large families, there was at least 5 members involved, with 25 patients in the largest family. The clinical spectrum was highly variable among family members. Hereditary anticipation appeared in 7 families, as probands had earlier onset and more severe manifestation than their parents, and the motor ability of child usually worse than that of their parents. Ten missense pathogenic variations were identified, two out of them in exons 95, one in exon 100, one in exon 101, and six in exon 102. All located in Pore forming and PVSD domains.

Discussion: Intra-family clinical diversity of RYR1 were observed in large families, and hereditary anticipation phenomenon was noticed with unknown mechanism. Modifying gene may exist encoding a protein nearing Pore forming domain of RyR1.

Cognitive impairment characteristics and brain structure and functional network in myotonic dystrophy type 1

Jiaying Bai,Li Zeng,Kai Chen,Feng Xiao,Chunyan Zhu,Song Tan
Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China

Introduction: Cognitive impairment has a substantial influence on the quality of life and social functioning of patients with Myotonic dystrophy type 1 (DM1). This study aims to improve the understanding of the characteristics of DM1 cognitive impairment and brain structure and functional network by studying the cognitive impairment of DM1.

Methods: Comprehensive neuropsychological measures, resting-state functional magnetic resonance imaging, and diffusion tensor imaging (DTI) were conducted on 12 DM1 patients' clinical features. The domain and degree of cognitive impairment, changes in brain structure and function, and the association between the foregoing outcomes were investigated in individuals with DM1.

Results: The cognitive function scores of DM1 group differed considerably from those of healthy control group, and the impaired attention was the most prominent. All 12 DM1 patients had lower MoCA scores, and 9 of them had lower MMSE scores. Multiple cognitive function scores were related to functional activity scores ($P < 0.05$). Compared with the healthy control group, the network connection between the Default Mode Network (DMN) and the Task Positive Network (TPN)in the DM1 group was abnormally enhanced or weakened. DTI revealed a symmetrical reduction in FA in several white matter tracts in DM1 patients. The correlation study of cognitive function and DTI data revealed that cognitive impairment was highly linked with alterations in white matter microstructure.

Conclusion: DM1 affects various cognitive areas, most notably attention. MoCA detects DM1 cognitive impairment more easily than MMSE. Functional activity is significantly impacted by cognitive impairment. The changes in the DMN-TPN connection in different DM1 individuals were varied. Cognitive impairment in several domains of DM1 was linked to alterations in white matter microstructure in various areas.

Exon skipping caused by splicing mutation in TNNT1 nemaline myopathy

Guangyu Wang,Chuanzhu Yan,Pengfei Lin
Qilu Hospital of Shandong University

The TNNT1 gene encoding the slow skeletal muscle TnT has been identifified as a causative gene for nemaline myopathy. TNNT1 nemaline myopathy is mainly characterized by neonatal-onset muscle weakness, pectus carinatum and respiratory insuffificiency. Herein, we report on a Chinese girl with TNNT1 nemaline myopathy with mild clinical phenotypes without thoracic deformities or decreased respiratory function. Muscle biopsy showed moderate to marked type 1 fifiber atrophy and nemaline rods. Next_x0002_generation sequencing identifified the compound heterozygous c. 587dupA (p. D196Efs*41) and c. 387+5G>A mutations in the TNNT1 gene according to the transcript NM_003283.4. RNA sequencing revealed complete exon 9 skipping caused by the c. 387+5G>A mutation. Through quantitative PCR, we found that both the truncation c. 587dupA (p. D196Efs*41) and the splicing c. 387+5G>A mutations triggered nonsense-mediated mRNA decay (NMD). Western blotting showed the residual amount of the truncated TNNT1 protein by deletion of exon 9, which may ameliorate the disease to some extent.

Deletion of exon 6-9 of the ISPD gene is an ancestral mutation in the Chinese patients with dystroglycanopathy

Jihang Luo,Yidan Liu,Danyu Song,Yanbin Fan,Hui Xiong
Peking University First Hospital

OBJECTIVE: The ISPD gene (OMIM: 614631) CDP-L-ribitol pyrophosphorylase A(CRPPA), is one of the causative genes in dystroglycanopathy (DGP). The phenotype of ISPD-associated DGP varies from myo-oculo-encephalopathy (MEB) in severe patients to congenital muscular dystrophy with or without mental retardation (CMD-MR/CMD) in intermediate patients and limb-girdle muscular dystrophy (LGMD) in mild patients only. In this paper, we report four cases of DGP due to compound heterozygous variants of the ISPD gene, from which exon 6-9 deletions was found to be an ancestral mutation in the Chinese Han nationality.

METHODS: We summarized the clinical features of four patients with DGP due to ISPD gene variants, and performed breakpoint analysis and haplotype analysis of exon 6-9 deletions in the ISPD gene by whole-genome sequencing of the family.

RESULTS: (1) Clinical features: The four patients included two cases of MEB, one case of CMD-MR and one case of LGMD. The patients with MEB and CMD-MR were intellectual and motor underdeveloped since childhood and showed cerebellar hypoplasia on head MRI. Two of the patients with MEB had eye symptoms such as internal strabismus and retinitis pigmentosa. The patient with LGMD had abnormal gait and normal mental development. Two of the four patients had muscle biopsies indicating myotonic dystrophy. (2) Genetic analysis: We sequenced the whole genome of the four patients and found that the four patients were compound heterozygous variants of the ISPD gene, all carrying exon 6-9 deletions. A breakpoint position analysis of exon 6-9 deletions revealed consistent breakpoint positions in the four patients. Haplotype analysis using 16 tag SNP loci linked to ISPD revealed consistent SNP loci in these four patients, and the haplotype was not present in the 15 randomly selected control samples.

CONCLUSIONS: This paper summarizes the clinical features of four children with DGP due to ISPD gene variants and confirms that the deletion of exon 6-9 of the ISPD gene is an ancestral mutation in the Chinese Han nationality by whole-genome sequencing of the family.

A case of congenital muscular dystrophy with intellectual impairment caused by POMGNT2 gene variation

Jihang Luo,Danyu Song,Yidan Liu,Yun Yuan,Jing Liu,Hui Xiong
Peking University First Hospital

OBJECTIVE: The POMGNT2 gene (OMIM: 614828) encodes N-acetyl-glucosamine mannosyltransferase 2, one of the causative genes of dystroglycanopathy (DGP), which adds β1,4-linked GlcNAc to O-mannose (Man) residues to obtain core M3-type sugars. The POMGNT2-associated DGP phenotype varies in severity, with heavy patients presenting with Walker-Warburg syndrome or myo-oculo-encephalopathy (MEB) whereas light patients presenting only with limb-girdle muscular dystrophy (LGMD). In this paper, we report a case of congenital muscular dystrophy with mental retardation (CMD with MR) caused by a compound heterozygous variant of the POMGNT2 gene.

METHODS: We analyzed and summarized the clinical features of a patient with CMD with MR due to POMGNT2 gene variant and verified the deletion of the α-DG glycan chain in the child by immunofluorescence.

Results: A 4 years and 6 months old boy, attended our paediatric outpatient clinic at 1 year 4 months for "motor development delay" and was followed up several times. The child has had intellectual and motor underdeveloped since childhood, had an erect head at 8 months old, sitting alone at 1 year old but unable to stand now. He is able to express single meaningful words, cannot express long sentences but understand simple commands. The parents are not consanguineous, the boy was first birth, and there was no asphyxia after birth, without family history of neurogenetic disorders. Physical examination: bilateral gastrocnemius fullness, bilateral knee and ankle contractures, low muscle tone in all four limbs, muscle strength decreased, proximal writings, bilateral upper limb muscle strength proximal grade IV- and distal grade IV, bilateral lower limb muscle strength proximal grade III+ and distal grade IV-, bilateral knee tendon reflexes not elicited, negative pathological signs. Ancillary tests: creatine kinase (CK) 12000-13825 IU/L. Muscle biopsy suggested muscle fibers were hypertrophy, atrophy, necrosis and regeneration consistent with myotonic dystrophy-like changes, and immunofluorescence staining suggested alpha-DG glycan chain deficiency. The head MRI suggested cerebellar hypoplasia and abnormal signals in the white matter of the brain. Genetic testing for hereditary myopathy genes revealed compound heterozygous variants c.328C>T (p.Arg110Trp) and c.437C>T (p.Pro146Leu) in the POMGNT2 gene, which were derived from the parents, respectively.

CONCLUSION: This paper summarizes the clinical features of a child with CMD with MR due to POMGNT2 gene variant, and verifies the α-DG glycan chain deletion by immunofluorescence staining, further enhancing the understanding of POMGNT2 gene-associated DGP disease.

Clinical phenotype spectrum in two Chinese families with rippling muscle disease-2 caused by CAV-3 c.80G>A

Yu Shen,Yanyan Yu,Dandan Tang,Min Zhu,Daojun Hong
The First Affiliated Hospital of Nanchang University

BACKGROUND AND OBJECTIVES: Rippling muscle disease-2 (RMD2) is a rare benign myotonic myopathy caused by pathogenic variants in caveolin-3 (CAV-3) gene, characterized by highly irritable muscles, transient localized muscle bulges and ripple-like contractions. The variant CAV-3 c.80G>A is high frequent, while still lacking systematic understanding of the related phenotype variations. In this study, we aimed to identify clinical phenotype spectrum of the RMD2 patients.

MATERIALS AND METHODS: Clinical data including medical history, physical examination and ancillary examinations were collected and analyzed from the patients with RMD2 in two Chinese families. CAV-3 mutation analysis was performed by next-generation sequencing and Sanger sequencing. The expression changes of CAV3 protein were analyzed by immunohistochemistry and Western blotting. In addition, we performed literature review of all previously reported RMD2 patients and focused on patients with CAV-3 c.80G>A.

RESULTS: A total of 12 patients with RMD2 were clinically diagnosed in two family. All patients presented with childhood-onset exercise intolerance, muscle stiffness and myalgia after exercise. Percussion-induced rapid muscle contraction was observed in all patients. Serum creatine kinase was mildly to moderately elevated. Electromyography revealed myotonic potential bursts and neurogenic damage in distal limb muscles in Patient 1, and myogenic damage in Patient 2. Muscle magnetic resonance imaging suggested normal presence in Patient 1 and mild muscle atrophy in Patient 2. Muscle pathology showed non-specific myopathy-like changes in Patient 2. A heterozygous variant c.80G>A (p.Arg27Gln) in the CAV3 gene was identified in all patients with RMD2. Immunohistochemical and Western blotting analysis revealed reduced expression of CAV3 protein in muscle tissue of Patient 2.

CONCLUSION: This study demonstrated the clinical, electromyographical, and pathological features of RMD2 patients in two large Chinese families and literatures, providing better understandings of the clinical phenotype variations of RMD2 associated with CAV3 c.80G>A.

CLCN1-related myotonia congenita in Chinese population

Yuting He,Daojun Hong
2.Institute of Neurology, the First Affiliated Hospital of Nanchang University, Nanchang, China

Background: Myotonia congenita (MC) is a rare hereditary muscle disease caused by pathogenic variants in the CLCN1 gene, and characterized by delayed relaxation of skeletal muscle. There are significant diversities in the phenotype spectrum of MC, and the clinical phenotype of Chinese MC patients is still relatively unclear.
Methods: Patients suspected as MC were genetically identified by whole exome sequencing in our clinic from 2019 to 2022. The clinical and genetic data were retrospectively collected and analyzed. The clinical and genetic data of Chinese MC patients reported from June 2004 to December 2022 were summarized.
Results: A total of 10 MC patients were identified. The average age of onset was 13.1± 2.4 (ranging 9.0-16.0) years old. The initial symptoms were difficulty in walking or running (8/10), and difficulty climbing stairs (2/10). Muscle rigidity involved in lower limbs in all patients, along with upper limbs in 9 of them. Warm-up phenomenon and muscle balls were found in all patients. The common inducing factors of myotonia were cold temperature (5/10) and emotional stress (3/10). Myotonic potential was detected in 9 patients (9/9) by the electromyogram. Thirteen genetic variants including 6 novel variants were found in the CLCN1 gene. Ninety-seven Chinese MC patients including our 10 patients were re-analyzed and re-summarized from reported literature. A total of 144 pathogenic or likely pathogenic variants in the CLCN1 gene were identified from 51 patients with autosomal dominant inheritance and 46 patients with autosomal recessive inheritance. The hot-spot mutation regions were exons 8, 12 and 19 for autosomal dominant inheritance, and exons 8, 12 and 15 for autosomal recessive inheritance.
Conclusion: The clinical characteristics of Chinese MC patients were typical, while with earlier onset age. A total of 6 novel mutations and high-frequency mutation regions in CLCN1 gene were found. This study provided better understandings of clinical and genetic characteristics of Chinese MC patients, and supported more information for treatment of MC.

Sporadic Inclusion Body Myositis in a Thai Population: A Case Series

Thanawan Tiraweerakhajorn,Jakkrit Amornvit,Nath Pasutharnchat
Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn Universit

Introductions: Sporadic Inclusion Body Myositis (sIBM) is considered uncommon in Thailand compared to the global prevalence, resulting in limited information in Thai patients. The study described sIBM in a Thai cohort with an aim to increase awareness of sIBM in Thailand.

Methods: In this retrospective study, all patients diagnosed with sIBM based on ENMC 2011 criteria who had received treatment at the neuromuscular unit, at King Chulalongkorn Memorial hospital in Thailand between 2013 and 2022 were recruited. Demographic data, clinical presentation, electromyogram, histopathology, muscle MRI, and treatment outcomes were revealed.

Results: Among 72 patients diagnosed with immune-mediated myopathies, seven (9.7%) were identified as sIBM, accounting for 15.9% (7 out of 44) of patients aged >45 years. Five (71.4%) were female. Four were classified as clinically defined sIBM and three were classified as probable sIBM. Median age at diagnosis was 67 years [IQR: 64-69]. Median time from symptom onset to diagnosis was 3 years [IQR: 2.5-6.5]. All patients exhibited asymmetrical weakness in the finger flexors and/or quadriceps, with three developing dysphagia. One exhibited nocturnal hypoventilation requiring non-invasive ventilation. One had anal sphincter muscle weakness. Mean CK level was 691.29 u/L [Mean ±SD: 352.15–1030.43]. Six patients (86%) tested positive for Anti CN-1A antibodies, two (29%) for Anti Ro-52; one of these was associated with Sjögren's syndrome. Electromyogram showed irritable myopathy in all. Histopathological, and muscle MRI studies were consistent with previous findings. Follow-up duration spanned 2-6 years. Treatments included intravenous immunoglobulin, corticosteroids and immunosuppressants. Only one experienced temporary and partial improvement.

Conclusion: This study has provided insights into the clinical characteristics, diagnosis, and management of sIBM in a Thai population. It revealed a distinctive epidemiological pattern.

Clinical and genetic characteristics of 8 Chinese patients with ACTA 1 congenital myopathy

Tsui Hang Sharon FUNG[1],Hoi Shan Sophelia CHAN[2]
1. Kwong Wah Hospital

Abstract

ACTA1 mutations account for 20% of patients with congenital myopathies and are associated with variable clinical and histopathological features. Here we describe the clinical, genetic and muscle biopsy findings in 8 Chinese patients with ACTA1 myopathies. Clinical/ genetic characteristics: All cases presented since birth with hypotonia, absent/ reduced reflexes, limb and facial weakness. Among the 8, 4 including a pair of twins, had severe phenotypes required tube feeding and invasive ventilation since birth. 3 of them died early, one at 46 day, the other 2 at 6month old. The remaining 1 survived with tracheostomy and gastrostomy with limited walking since 5.5 years old. Another three patients (2 siblings and their father, aged currently 3year 10months, 22 months and 40 years old) had typical congenital phenotype. Despite gastrostomies and OSA on NIV in infancy, they showed constant motor and clinical improvement and walked since 18 month old to ~4 year-old. The father remained well ambulatory with mild muscle weakness. The last patient had milder phenotype with arthrogryposis multiplex congenita and delay motor milestones but no major feeding problems nor respiratory problems requiring ventilatory support. She walked at 24 month-old. Laboratory/genetic findings: CK levels are all normal. Muscle biopsies done in 4 of them showed intracytoplasmic rods in 1, mild myopathic changes with type 1 predominance in another and cytoplasmic bodies without rods in the pair of twins. All ACTA 1 mutations are heterozygous autosomal dominant and 'de novo' except in the siblings with typical congenital type. The ACTA1 mutations are c.1001 C>G (p.Pro334Arg), c.547G>A (p.Ala183Thr) and c.282C>A (p.Asn94Lys) (the twin pair), c.143G>C (p.Gly48Ala) (the family of 3) and c.874G>A (p.Arg292Gly) (mild congenital one).

Conclusions: The clinical phenotype of ACTA 1 myopathy is highly variable from early death to constant improvement in early childhood and stable mild congenital myopathy.

A different pattern of clinical, muscle pathology and brain MRI findings in MELAS with mt-ND variants

Kunqian Ji,Yuying Zhao,Chuanzhu Yan
Research Institute of Neuromuscular and Neurodegenerative Diseases, Qilu Hospital, Shandong University

Objective: To explore the clinical characteristics of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) caused by mitochondrial DNA encoded complex I subunit (mt-ND) variants.

Methods: In this retrospective study, the clinical, myopathological and brain MRI features of patients with MELAS caused by mt-ND variants (MELAS-mtND) were collected and compared with those of MELAS patients carrying the m.3243A>G variant (MELAS-A3243G). Result: A total of 18 MELAS-mtND patients (female: 7; median age: 24.5 years) represented 15.9% (n = 113) of all patients with MELAS caused by mtDNA variants in our neuromuscular center from January 2012 to June 2022. In this MELAS-mtND cohort, the two most common variants were m.10191 T>C (4/18, 22.2%) and m.13513 G>A (3/18, 16.7%). The most frequent symptoms were seizures (14/18, 77.8%) and muscle weakness (11/18, 61.1%). Compared with 87 MELAS-A3243G patients, MELAS-mtND patients were significantly more likely to have a variant that was absent in blood cells (40% vs. 1.4%). Furthermore, MELAS-mtND patients had a significantly lower MDC score (7.8±2.7 vs. 9.8±1.9); less hearing loss (27.8% vs 54.0%), diabetes (11.1% vs. 37.9%), and migraine (33.3% vs. 62.1%); shorter stature (males≤165 cm; females≤155 cm; 23.1% vs. 60.8%) and higher body mass index (20.4±2.5 vs. 17.8±2.7). MELAS-mtND patients had significantly more normal muscle pathology (31.3% vs. 4.1%) and, fewer RRFs/RBFs (62.5% vs. 91.9%), COX-deficient fibers/blue fibers (25.0% vs. 85.1%) and SSVs (50.0% vs. 81.1%). Moreover, brain MRI evaluated at the first stroke-like episode showed significantly more small cortical lesions in MELAS-mtND patients (66.7% vs. 12.2%). Interpretation: Our results suggested that MELAS-mtND patients have distinct clinical, myopathological and brain MRI features compared with MELAS-A3243G patients.

Queuine alleviates mitochondrial dysfunction caused by a novel MELAS associated mt-tRNAHis variant

Yan Lin,Kunqian Ji,Jiayin Wang,Yuying Zhao,Chuanzhu Yan
Qilu Hospital of Shandong University

Mitochondrial tRNA (mt-tRNA) genes are well-established hotspots for pathogenic variants associated with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Despite this, mt-tRNAHis variants, which are relatively infrequent, present unique challenges in understanding their role in disease development. Current therapeutic strategies for MELAS are limited, underscoring the necessity for expanded research in this field. In response, our study utilized a comprehensive approach, incorporating genetic and histopathological analyses, molecular dynamics simulations, and a set of mitochondrial function assays to elucidate the molecular pathomechanisms of a novel mt-tRNAHis variant. Additionally, cybrid cell lines were employed to assess the therapeutic potential of queuine in mitigating the mitochondrial dysfunction induced by this variant. We detail the clinical and genetic attributes of an 18-year-old MELAS patient harboring the novel m.12143T>C variant. Our data illustrate how this variant reduces the steady-state level of mt-tRNAHis, causing a decrease in tRNA transcription, disruption of the queuosine (Q) modification of mt-tRNAHis, and hindering the synthesis of mitochondria-associated proteins, thus compromising mitochondrial function. Notably, our in vitro studies revealed that queuine supplementation could counteract the deleterious effects of the m.12143T>C variant on mitochondrial translation and respiration. Cumulatively, our study offers valuable insights into the pathogenic mechanism of the m.12143T>C variant and highlights the potential of queuine supplementation as a therapeutic intervention for patients harboring this variant.

Primary limb-girdle mitochondrial myopathy has distinct clinicopathologic features compared with other mitochondrial myopathy subtypes

Yan Lin,Kunqian Ji,Yuying Zhao,Chuanzhu Yan
Qilu Hospital of Shandong University

Background and Objectives: Primary limb-girdle mitochondrial myopathy (PLMM) is an under-recognized mitochondrial disorder primarily affecting skeletal muscles, with its phenotypic, genotypic features, and long-term prognosis poorly understood.
Methods: In this observational cohort study at a national diagnostic center for mitochondrial disease, we enrolled 47 PLMM patients from 643 mitochondrial disease cases followed up at Qilu Hospital between January 1, 2000, and January 1, 2021. The study compared the PLMM cohort's clinical, pathological, and genotypic features with those of chronic progressive external ophthalmoplegia (CPEO) and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) cases, while also exploring the role of GDF15 in PLMM pathogenesis.
Results: PLMM patients presented with a higher prevalence of muscle weakness (95.7%) and exercise intolerance (72.3%), but less multisystem involvement compared to CPEO and MELAS cases. Many patients also exhibited subclinical peripheral neuropathy. Muscle biopsies revealed that COX-positive ragged-red fibers (RRFs) were a typical pathological feature in PLMM patients. Genetic analysis identified mtDNA point mutations (59.6%) and single (12.8%) or multiple (4.2%) mtDNA deletions in the majority of PLMM patients. Serum GDF15 levels, a biomarker of mitochondrial myopathy, were significantly elevated in PLMM patients, strongly correlating with the presence of RRFs and muscle pathology severity. In the follow-up, 76.1% of PLMM patients experienced improvement or stabilization after treatment.
Conclusion: Our study highlights the unique characteristics of a large PLMM cohort, supporting its classification as a distinct mitochondrial disease subtype. These findings carry significant implications for the clinical diagnosis and management of PLMM patients, contributing to better patient outcomes.

HyperCKemia: an early sign of childhood-onset neutral lipid storage disease with myopathy

Xiaona Fu[1],Xinying Yang[1],Xiaofei Wang[1],Bingjing Jia[1],Wenna Ma[1],Hui Xiong[2],Fang Fang[1],Xiaotun Ren[1],Junlan Lv[1]

1. Beijing Children's Hospital, Capital Medical University
2. Peking University First Hospital, Beijing, China

Introduction: Neutral lipid-storage disease with myopathy (NLSDM) is an autosomal recessive neuromuscular disorder caused by mutations in PNPLA2, with an average age of onset at 30 years. However, limited information is available regarding childhood-onset NLSDM.

Methods: In this study, we investigated three previously unreported patients with childhood-onset NLSDM and conducted a comprehensive review of the literature, including eight childhood-onset and 82 adult-onset NLSDM patients.

Results: In the childhood-onset cohort, initial presentation in 10 out of 11 patients was asymptomatic or paucisymptomatic hyperCKemia. Follow-up evaluations revealed the onset of limb muscle weakness in five out of 11 childhood-onset patients. In the adult-onset cohort, 95.1% (78/82) of patients presented with limb muscle weakness. Cardiac involvement was observed in six out of 11 childhood-onset patients, while hepatomegaly was noted in three out of 11 patients. Serum creatine kinase levels were significantly elevated in childhood-onset patients and mildly to moderately elevated in adult-onset patients. Cytoplasmic lipid droplets were detected in leukocytes or myocytes through peripheral blood smears or muscle biopsies.

Conclusion: Our findings indicate that NLSDM can manifest in childhood with asymptomatic or paucisymptomatic hyperCKemia prior to the onset of muscle weakness. The presence of lipid droplets in leukocytes (known as Jordan's anomaly) assists in the diagnosis and confirmation of pathogenic PNPLA2 variants with uncertain significance. Nevertheless, no clear genotype-phenotype correlations were identified among NLSDM patients.

Insights into the mechanisms of telbivudine-induced myopathy associated with mitochondrial dysfunction

Wenfei Yu[1,2],Zhuxvn Li[3],Wenjing Wu[1],Dandan Zhao[1],Chuanzhu Yan[1],Pengfei Lin[1]
1. Qilu hospital of Shandong university
2. University of Health and Rehabilitation Sciences
3. Shandong University Cheeloo College of Medicine

Background: As a nucleotide analogue (NA), telbivudine was widely used in the treatment for chronic hepatitis B (CHB) by interfering with reverse transcriptase of hepatitis B virus. However, the use of NAs for hepatitis B treatment has been accompanied by numerous reports highlighting the occurrence of neuromyopathy, particularly in the case of telbivudine. This study aimed to investigate the underlying mechanisms responsible for telbivudine-induced myopathy.

Methods: We performed histopathological studies on muscle biopsy specimens obtained from three patients diagnosed with telbivudine-induced myopathy. Additionally, we established animal and cell models of telbivudine-induced myopathy using C57BL/6 mice and C2C12 cells, respectively. We evaluated the impact of telbivudine on mitochondrial DNA (mtDNA) replication, expression and activity of mitochondrial complexes, oxidative stress levels, and mitochondrial respiratory function.

Results: Our findings revealed that telbivudine significantly reduced mtDNA copy number and caused increase of oxidative stress. Expression of mitochondrial complex I and IV was obviously inhibited by telbivudine. Moreover, telbivudine treatment impaired the function of the mitochondrial oxidative phosphorylation respiratory chain. Pathological staining of muscle sections exhibited a prominent feature: an increase in ragged red fibers, indicating the accumulation of abnormal mitochondria in atrophic muscle fibers.

Conclusions: In conclusion, our study provides compelling evidence suggesting that telbivudine-induced myopathy is associated with mitochondrial toxicity and impaired energy metabolism. The observed muscle pathology, depletion of mtDNA, elevation of oxidative stress and altered mitochondrial function support the hypothesis that telbivudine disrupts mitochondrial homeostasis, ultimately leading to muscle damage. Perhaps this is also a common mechanism for NAs to cause neuromyopathy.

A novel mutation in the glycoside hydrolase-like domain of PHKA1 associated to glycogen storage disease type IXd

Xiaoqing Lv[1],Wenjing Wu[1],Wei Li[2],Dandan Zhao[2],Chuanzhu Yan[2],Pengfei Lin[2]

1. Qilu Hospital of Shandong University, Cheeloo College of Medicine, Shandong University
2. Qilu Hospital of Shandong University

Glycogen storage disease type IXd (GSD IXd) is an inherited disorder resulting from mutations in PHKA1, which encodes the α subunit of phosphorylase b kinase in skeletal muscle. In this investigation, we have identified a missense mutation within the glycoside hydrolase-like (GHL) domain of PHKA1 in a patient. This mutation has been shown to cause a reduction in enzymatic activity. Additionally, a comprehensive analysis of clinical characteristics and muscle pathology was performed on the affected patients. By examining previously documented cases, we have discovered that the GHL domain may serve as a prominent region for missense variants in individuals affected by GSD IXd. This finding elucidates that the GHL domain plays a critical role in maintaining the enzymatic activity of phosphorylase b kinase. In addition, the observations made in this study contribute to the expanding understanding of the clinical and genetic manifestations associated with PHKA1 mutations in GSD IXd.

Characteristics of Iranian Neutral Lipid Storage Disease with Myopathy: Report of Nine Cases

Mahtab Ramezani[1],Hamed Shahriari[1],Farzad Fatehi[1],Yalda Nilipour[2],Ali Asghar Okhovat[1],Ariana Kariminejad[4],Leila Aghaghazvini[3],Shahriar Nafissi[1]

1. Neuromuscular Fellowship, Tehran University of Medical Sciences
2. Pathology Department, Shahid Beheshti University of Medical Sciences
3. Radiology Department, Tehran University of Medical Sciences
4. Chief Genetic Counselor Kariminejad Najmabadi Pathology and Genetic Center

The rare disorder known as Neutral Lipid Storage Disease with Myopathy (NLSDM) presents with a variety of clinical manifestations, including myopathy, cardiac dysfunction, and other organ complications. Early diagnosis is crucial due to the increased risk of cardiomyopathy. We describe the clinical, histopathological, muscle imaging, and genetic findings of nine NLSDM patients. Proximal weakness and asymmetric involvement may suggest lipid storage myopathy. While skeletal muscle weakness was the main manifestation in our patients, one case presented only with hyperCKemia. Additionally, three patients had fertility issues, two suffered from diabetes mellitus, and one had hypothyroidism. Muscle histopathology revealed lipid depositions (LDs) and rimmed vacuoles (RVs), prompting peripheral blood smears (PBS) to detect Jordan Anomalies. All muscle biopsies and PBS showed LDs, RVs, and Jordan Anomaly. Identifying PNPLA2 gene mutations is important for diagnosing NLSDM; our cases showed some novel mutations. This study highlights the importance of early diagnosis and comprehensive evaluation in managing NLSDM patients.

Efficacy and Safety of Avalglucosidase Alfa in Participants With Late-Onset Pompe Disease After 145 Weeks' Treatment: Phase 3 COMET Trial

Benedikt Schoser[1],Priya S. Kishnani[2],Hani Kushlaf[3],Shafeeq Ladha[4],Tahseen Mozaffar[5],Volker Straub[6],Antonio Toscano[7],Ans T. van der Ploeg[8],Paula R. Clemens[9],John W. Day[10],Sergey Illarioshkin[11],Mark Roberts[12],Shahram Attarian[13],Gerson Carvalho[14],Sevim Erdem-Özdamar[15],Ozlem Goker-Alpan[16],Anna Kostera-Pruszczyk[17],Kristina An Haack[18],Olivier Huynh-Ba[18],Swathi Tammireddy[19],Nathan Thibault[19],Tianyue Zhou[19],Jordi Díaz-Manera[6],Mazen M. Dimachkie[20]

1. LMU Klinikum München
2. Division of Medical Genetics, Department of Pediatrics, Duke University Medical Centerr, Durham, NC, USA
3. Department of Neurology & Rehabilitation Medicine and Department of Pathology & Laboratory Medicine, University of Cincinnati, Cincinnati, OH, USA
4. Gregory W. Fulton ALS and Neuromuscular Center, Barrow Neurological Institute, Phoenix, AZ, USA
5. Department of Neurology, University of California, Irvine, Orange, CA, USA
6. John Walton Muscular Dystrophy Research Centre, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK
7. Department of Clinical and Experimental Medicine, Reference Center for Rare Neuromuscular Disorders, University of Messina, Messina, Italy
8. Center for Lysosomal and Metabolic Diseases, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
9. Department of Neurology, University of Pittsburgh, and Department of Veterans Affairs Medical Center, Pittsburgh, PA, USA
10. Departments of Neurology and Pediatrics, Stanford University, Stanford, CA, USA
11. Research Center of Neurology, Moscow, Russia
12. Salford Royal NHS Foundation Trust, Salford, UK
13. Referral Centre for Neuromuscular Diseases and ALS, Hôpital La Timone, Marseille, France
14. Instituto Chronos de Apoio à Pesquisa, Brasília, DF, Brazil
15. Department of Neurology, Hacettepe University Faculty of Medicine, Ankara, Turkey
16. Lysosomal and Rare Disorders Research and Treatment Center (LDRTC), Fairfax, VA, USA
17. Department of Neurology, Medical University of Warsaw, Warsaw, Poland
18. Sanofi, Chilly-Mazarin, France
19. Sanofi, Cambridge, MA, USA
20. University of Kansas Medical Center, Department of Neurology, Kansas City, KS, USA

Objectives: Report efficacy/safety of avalglucosidase alfa (AVAL) in participants with late-onset

Pompe disease in the extended-treatment period (ETP) of COMET (NCT02782741) at 145 weeks from treatment initiation.

Methods: Following a 49-week primary-analysis period (PAP), participants could enter the ETP. 100 participants (age 16-78 years) enrolled in the PAP.

Results: All 51 who received AVAL 20mg/kg every 2 weeks (qow) in the PAP (AVAL-arm) continued this in the ETP. Of 49 who received alglucosidase alfa (ALGLU) 20mg/kg qow in the PAP, 44 entered the ETP switching to AVAL 20mg/kg qow (Switch-arm). Improvement or stabilization trends from Baseline to Week 145 were observed for primary and secondary outcomes of respiratory and motor function. Changes (LS mean[SE]) in upright forced vital capacity %predicted: AVAL-arm, +1.40(1.21); Switch-arm, +1.18(1.32) and 6-minute walk test distance: AVAL-arm, +20.65(9.60)m; Switch-arm, +0.29(10.42)m. Similar trends occurred in other Week-145 outcomes. Treatment-emergent adverse events (AEs) in the ETP occurred in 49(96.1%) AVAL-arm and 43(97.7%) Switch-arm participants. Five discontinued during the ETP for 6 treatment-emergent AEs; 4 treatment-related (ocular hyperemia, erythema [in same participant], urticaria, respiratory distress) and 2 non-treatment-related (acute myocardial infarction, pancreatic adenocarcinoma). In the ETP, 13(25.5%) AVAL-arm and 12(27.3%) Switch-arm participants had treatment-emergent serious AEs (SAEs); 3 and 2 of them, respectively, had treatment-related SAEs. Switch-arm participants showed no safety/immunogenicity-related concerns.

Conclusions: Week 145 results show sustained treatment effect and continued benefit with AVAL beyond the PAP, and stabilization of treatment effect after switching from ALGLU to AVAL, supporting long-term maintenance of clinically meaningful outcomes with AVAL. Funding: Sanofi

PATIENTS IN THE POMPE REGISTRY WHO SWITCHED FROM ALGLUCOSIDASEALFA TO AVALGLUCOSIDASE ALFA: REAL-WORLD EXPERIENCE

Benedikt Schoser[1],Mary-Alice Abbott[2],Antonio Toscano[3],Meredith Foster[4],Magali Periquet[5],Susan Sparks[4],Priya S. Kishnani[6]

1. LMU Klinikum München
2. Baystate Health, Springfield, MA, USA
3. Department of Clinical and Experimental Medicine, Reference Center for Rare Neuromuscular Disorders, University of Messina, Messina, Italy
4. Sanofi, Cambridge, MA, USA
5. Sanofi, Berlin, Germany
6. Duke University Medical Center, Durham, NC, USA

INTRODUCTION: Avalglucosidase alfa (AVAL), a recombinant human acid α-glucosidase enzyme replacement therapy, has received marketing authorization in several countries for infantile-onset (IOPD) and/or late-onset Pompe disease (LOPD); US approval: August 2021 for LOPD patients aged ≥1y.

OBJECTIVE: Characterize demographic/clinical characteristics of IOPD and LOPD patients who switched from alglucosidase alfa (ALGLU) to AVAL enrolled in the ongoing international, observational, voluntary Pompe Registry (NCT00231400).

METHODS: For this analysis, patients had ≥1 ALGLU record immediately pre-switch to AVAL. Demographic/treatment histories were collected. Respiratory, ambulatory, and biomarker data were assessed pre-/post-switch for LOPD only (IOPD excluded due to small cohort). Patients who received ALGLU for <5 and ≥5y pre-switch were compared.

RESULTS: As of December 2, 2022, 89 switch patients were identified (LOPD, 81[91%]; IOPD, 8[9%]). LOPD: United States, 72(89%); male,43(53%). IOPD: Europe, 5(63%), female 5(63%). Patients switched at mean±standard deviation age of 44.9±21.94 (range:1.0-83.0)y for LOPD and 11.0±5.15 (range:3.0-17.6)y for IOPD. Most had ≥5y experience on ALGLU pre-switch (LOPD, 55[68%]; IOPD, 6[75%]). For LOPD, last assessments pre-switch were upright forced vital capacity %predicted: 59.1±22.48 (n=69), 6-minute walk test: 359.1±149.86m (n=41), urine glucose tetrasaccharide/hexose tetrasaccharide: 9.7±17.29mmol/mol creatinine (n=56), and serum creatine kinase: 517.6±465.69U/L (n=65). Mean changes among LOPD patients with both pre- and up to 1-y post-switch assessments showed stabilization in respiratory and ambulatory function and biomarker improvement.

SUMMARY/CONCLUSION: The Pompe Registry continues to accrue data for patients switching from ALGLU to AVAL, which will support our understanding of AVAL's effectiveness on respiratory and ambulatory outcomes and biomarker levels in the real-world. Funding:Sanofi.

Glycogen storage myopathies diagnosed by muscle biopsy in Iran, A referral center 15 years of experience

Yalda Nilipour[1],Shahriar Nafissi[2],Parvaneh Karimzadeh[2]
1. Pediatric pathology research center, research institute for children's health, Shahid Beheshti University of Medical sciences, Tehran, Iran.

Introduction: The glycogen storage myopathies (GSD) are caused by enzyme deficiency in the glycogenolytic or in the glycolytic pathway in striated muscle fibers. Metabolic myopathies are a class of rare diseases, many of which are ultra-rare. Most of the GSDs are autosomal recessive and are more prevalent in Iran due to consanguineous marriages.
Method: Muscle biopsy is still an important tool to diagnose patients with metabolic myopathy presentations. Classic Hematoxylin and eosin stain reveal vacuolar myopathy in many GSD cases and PAS staining is particularly useful in GSD. Interpretation of PAS stain is very important as there are multiple artefacts mimicking accumulations of PAS positive materilas. Immunohistochemical study of sarcolemmal proteins could be helpful in diagnosis of lysosomal vacuoles in Pompe disease.
Results: We diagnosed multiple cases of GSD revealing vacuolar myopathy by muscle biopsy, however we were able to diagnose other ultra-rare cases of GSD as well by muscle biopsy. In this study we present numbers of common and rare cases of GSD diagnosed by muscle biopsy and we present very interesting images of muscle biopsy in these patients.
Conclusion: Muscle biopsy is still an important tool to diagnose patients with metabolic myopathy presentations.

Clinical-pathological study and pathogenesis of lipid storage myopathy

Zhenyu Ke,Yingmei Wang,Qian Zhang,Junfeng Wu,Shuyan Zhao,Jian Liu,Qing Li,Yuqiao Xu
Xijing Hospital, Fourth Military Medical University

Objective: To summarize the clinical, pathological and molecular features of lipid storage myopathy (LM), analyze the potential mechanism of lipid accumulation, and explore its diagnosis and differential diagnosis, in order to enhance the understanding of this disease.

Methods: Twenty cases of LM admitted to our hospital from 2010 to 2023 were collected. The study involved analyzing the clinical manifestations, auxiliary examinations, special stains, histological observations, electron microscope results, and gene detections of these cases.

Results: There were 10 males and 10 females, ranging in age from 12 to 51 years (median age 20.5 years). The duration of disease ranged from 1 to 159 months (median 6.5 months). The main clinical manifestations were intermittent or progressive weakness of limbs and hard to stand up, accompanied by muscle pain in 11 cases, dropped head in 9 cases, difficulty with chewing in 11 cases, weight loss in 7 cases, dizziness, nausea or vomiting in 2 cases, numbness of limbs in 1 case, red rash of trunk in 1 case, hard to lift the wrist in 1 case, heart palpitation with shortness of breath in 1 case, and swelling of lower extremities in 1 case. One case had a confirmed family history, 4 cases had a history of smoking, and 3 had the history of alcohol consumption. Among them, 2 with hypertension, 6 with fatty liver, 6 with dyslipidemia, and 4 with hyperhomocysteinemia. Electromyography showed myogenic lesions in 12 cases. Laboratory tests revealed elevated levels of Creatine Kinase (16/16), Lactate Dehydrogenase (18/18), and high blood lactate concentration in 8 cases. Morphological observation: In this group of cases, irregular vacuoles of various sizes were observed in the muscle fibers under light microscopy. Some muscles exhibited degeneration or even necrosis, along with inflammatory cell infiltration. Additionally, a few cases showed the presence of internal nuclei within the fiber. Oil red O staining revealed a significant amount of lipid deposition in muscle cells, primarily in type I fibers. Furthermore, electron microscopy revealed excessive lipid droplets arranged in string or clusters, located between the myofibrils and under the sarcolemma. Some cases exhibited abnormal morphology or an increased number of mitochondria, accompanied by slight hyperplasia and expansion of the sarcoplasmic reticulum. Genetic testing was conducted on three cases, and an ETFDH gene mutation was detected in all 3 cases, which can cause multiple acyl-CoA dehydrogenase deficiency (MADD), thus lead to an abnormal electron transfer of the oxidative respiratory chain in mitochondria, resulting in lipid accumulation.

Conclusion: The diagnosis of LM needs to be differentiated from other diseases that can cause lipid storage inside the muscle, such as muscular dystrophy, inflammatory myopathy, myasthenia gravis, and mitochondrial myopathy. Exploring the mechanisms of lipid accumulation may provide a basis for effective prevention and treatment during clinical practice.

SAME GNE VARIANT IN UNRELATED PATIENTS IN PAKISTANI POPULATION: CASE SERIES

Shafaq Saleem
Aga Khan University and Hospital

Introduction: GNE (bifunctional UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase) myopathy is a progressive distal myopathy with rimmed vacuoles. This acquired disorder has over 200 identified disease-causing variants with few patterns showing common ethnicity.

Objective: We present four unrelated patients with GNE myopathy harboring a variant P. Val727Met in the Pakistani population.

Cases Review: In our cohort from the Neurology and Genetics Clinics at a tertiary care hospital, out of 111 patients (n=6, 5.4%) had a genetic test result positive for GNE myopathy. Interestingly, out of them, four patients harbored a common variant, 2179G>A P. Val727Met, which is previously reported to be a common GNE variant in the Indian population. In two patients, the variant was presenting in a homozygous state, while in the other two, it co-existed with another disease-causing variant in a compound heterozygous state. Among these patients, three were born to consanguineous couples, whereas all four harbored heterozygous P. Val727Met. The age of onset of symptoms was in adolescence for three patients while one patient had a presentation at birth. Among four patients only 2 patients have been wheelchair bound, one with at-birth presentation and the other after 10 years of symptoms onset. The other 2 patients have a progressive weakness though they are still not wheelchair bound.

Conclusion: Hence it can be concluded that GNE c.2179G>A PVal727Met is not just specified to the Rajasthani population, but also shows a possibility of being a common variant even in the Pakistani population. As the cost of genetic testing continues to decline knowledge about ethno-specific diseases will continue to expand leading to improved patient care

Non-coding CGG repeat expansion in LOC642361/NUTM2B-AS1 is associated with a phenotype of oculo-pharyngodistal myopathy

Xinyu Gu[1],Jiaxi Yu[2],Kexin Jiao[1],Jianwen Deng[2],Kai Qiao[1],Nachuan Cheng[1],Dongyue Yue[3],Mingshi Gao[4],Chongbo Zhao[1],Jihong Dong[5],Gongchun Huang[6],Xiaobei Liu[6],Xilu Wang[7],Jingli Shan[8],Chuanzhu Yan[8],Li Di[9],Yuwei Da[9],Wenhua Zhu[1],Zhaoxia Wang[2],Jianying Xi[1]

1. Huashan Hospital Fudan University
2. Department of Neurology, Peking University First Hospital, Beijing, China
3. Department of Neurology, Jing' an District Center Hospital of Shanghai, Shanghai, China
4. Department of Pathology, Huashan Hospital, Fudan University, Shanghai, China
5. Department of Neurology, Zhongshan Hospital, Fudan University, Shanghai, China
6. Department of Neurology, The First People's Hospital of Pinghu, Zhejiang, China
7. Ministry of Education Key Laboratory of Contemporary Anthropology, Department of Anthropology and Human Genetics, School of Life Sciences, Fudan University, China
8. Department of Neurology and Research Institute of Neuromuscular and Neurodegenerative Diseases, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Shandong, China
9. Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China

Background Oculopharyngodistal myopathy (OPDM) is a rare adult-onset neuromuscular disease, associated with CGG repeat expansions in the 5' untranslated region (5' UTR) of LRP12, GIPC1, NOTCH2NLC and RILPL1. However, the genetic cause of a proportion of pathoclinically confirmed cases remains unknown.

Methods Twenty-six OPDM patients with unknown genetic cause(s) from 4 tertiary referral hospitals were included in this study. Clinical data and laboratory findings were collected. Muscle samples were observed by histological and immunofluorescent staining. Long-read sequencing was initially conducted in 6 OPDM patients. Repeat-primed polymerase chain reaction was used to confirm the CGG repeat expansions in LOC642361/NUTM2B-AS1 in all 26 patients.

Results We identified CGG repeat expansion in the non-coding transcripts of LOC642361/NUTM2B-AS1 in another 2 unrelated Chinese cases with typical pathoclinical features of OPDM. The repeat expansion was more than 70 times in the patients but less than 40 times in the normal controls. Both patients showed no leukoencephalopathy but one showed mild cognitive impairment detected by Montreal Cognitive Assessment (MoCA). Rimmed vacuoles and p62-positive intranuclear inclusions were identified in muscle pathology.

Conclusions We identified another 2 unrelated cases with CGG repeat expansion in the long non-coding RNA (lncRNA) of the LOC642361/NUTM2B-AS1 gene, presenting with a phenotype of OPDM. Our cases broadened the recognized phenotypic spectrum and pathogenesis in the disease associated with CGG repeat expansion in LOC642361/NUTM2B-AS1.

Pseudoexon activation by deep intronic sequence variation in GNE myopathy with thrombocytopenia

Kexin Jiao, MD[1,2,3*], Nachuan Cheng, MD[1,2,3*], Xiao Huan, MD, PhD[1,2,3*] , Xinghua Luan[4], Mingshi Gao, MD[5], Xingyu Xia,MD[1,2,3], Ningning Wang, MD[1,2,3], Jianying Xi, MD, PhD [1,2,3], Sushan Luo, MD, PhD[1,2,3], Chongbo Zhao, MD, PhD[1,2,3], Dongyue Yue, MD[6], Wenhua Zhu, MD, PhD[1,2,3]

1 Department of Neurology, Huashan Hospital, Fudan University, Shanghai 200040, China

2 Huashan Rare Disease Center, Shanghai Medical College, Huashan Hospital, Fudan University, Shanghai, China

3 National Center for Neurological Disorders (NCND), Shanghai, China

4 Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine

5 Department of Pathology, Huashan Hospital, Fudan University, Shanghai 200040, China

6 Department of Neurology, Jing'an District Center Hospital of Shanghai, Shanghai, 200040, China

7. Huashan Rare Disease Center, Shanghai Medical College, Huashan Hospital, Fudan University, Shanghai, China

8. National Center for Neurological Disorders (NCND), Shanghai, China

9. Department of Neurology, Huashan Hospital, Fudan University, Shanghai 200040, China

Introduction

GNE myopathy is a rare autosomal recessive disorder caused by mutations in the GNE gene, which is essential for the sialic acid biosynthesis pathway. Although over 200 GNE variants have been reported, some patients remain undiagnosed with only one heterozygous mutation. This study aims to analyze the entire GNE genomic region to identify novel mutations.

Methods

Patients with clinically compatible GNE myopathy and mono-allelic mutations in the GNE gene were enrolled. The other GNE mutation was searched using a combination of Sanger sequencing, targeted next-generation sequencing (NGS), exon2 qPCR, and Nanopore long-read single-molecule sequencing (LRS). Verification of pseudoexons was performed by RT-PCR and sequencing of complementary DNA (cDNA) derived from frozen skeletal muscle tissue.

Results:

Ten patients were enrolled, who exhibited typical symptoms, such as foot drop, walking difficulty, or distal weakness affecting both hands and lower legs. Three patients had idiopathic thrombocytopenia (ITP) and one had increased platelet count. The median age at onset was 33 years (25-44 years).

A novel deep intronic variant (DIV), c.862+870C>T, was detected in nine patients from eight unrelated families. It was predicted by SpliceAI to create new splice donor sites and lead to pseudoexon inclusion. Splice-site strength scoring methods supported these predictions, indicating high probabilities of abnormal splicing. RT-PCR and sequencing of cDNA derived from muscle

tissues revealed a 146 bp inserted fragment between GNE exon 5 and 6, which would result in a premature stop codon. RNA sequencing confirmed abnormal GNE splicing and expression, causing the inclusion of a pathogenic pseudoexon in GNE mRNA.

Discussion

This study identified a novel deep intronic disease-causing mutation in the GNE gene. It located at the allosteric region of the UDP-GlcNAc-2-epimerase (GNE) domain, which is also associated with ITP. Further research is necessary to better understand the molecular mechanisms underlying thrombocytopenia resulted from this mutation.

Conclusion

The discovery of novel mutations in GNE, such as the deep intronic mutation activating pseudoexon inclusion, expanded the mutational spectrum of GNE myopathy. A modified genetic test algorithm covering the entire region of GNE gene will optimize the molecular diagnosis in the future.

6’-sialyllactose supplementation in GNE myopathy over 96 weeks

Jinhong Shin[1,3],Young-Eun Park[2,3],Yuri Je[2],Dae-Seong Kim[1,3]
1. Pusan National University Yangsan Hospital
2. Pusan National University Hospital
3. Pusan National University, School of Medicine

Introduction

GNE myopathy is an inherited myopathy, by biallelic mutations of GNE gene. It may present as bilateral foot drop or proximal weakness, and eventually progresses quadriplegia over decades. GNE is the rate limiting enzyme of sialic acid biosynthesis pathway. Supplementation of sialic acid or related metabolites has shown promise in mice models.

Methods

We performed a pilot trial of 6’-sialyllactose (6SL) in GNE myopathy to test its biochemical efficacy and functional improvement. We measured 6SL as well as sialic acid bound to the RBC membrane. Twenty patients with biallelic GNE mutations were assigned to daily 3 g or 6 g of 6SL, or placebo. Six patients from placebo group were reassigned either to daily 3 g or 6 g group after completing the initial 12 weeks. We measured motor power by hand-held dynamometer, muscle MRI, 6-minute walk test, and a questionnaire for functional activities

Results

Muscle performances were superior in the daily 6 g group to the 3 g group. It was more evident in larger joints like shoulders, elbows, and hips. Interestingly knee extension power improved over the whole study period in both 3 g and 6 g groups. Fat fraction of muscle by MRI was attenuated more in the 6 g group than 3 g group. Sialic acid bound to RBC membrane was significantly higher in both of the treatment groups compared with placebo.

Conclusion

This 96-week trial shows that supplementation of 6SL improved muscle power of GNE myopathy patients by attenuating muscle degeneration. The current trial compares daily 6 g of 6SL with placebo over 48 weeks without reassignment, which will further demonstrate the efficacy of 6SL over placebo.

Clinical and pathological characteristics of OPDM4 patients at the end stage

Haixia Tang,Ying Xiong,Kaiyan Jiang,Yu Shen,Yusen Qiu,Dandan Tan,Daojun Hong,Min Zhu,Pengcheng Huang,Yilei Zheng
The First Affiliated Hospital of Nanchang University

Introduction: Oculopharyngodistal myopathy (OPDM) is a group of rare hereditary neuromuscular disorders clinically characterized by progressive ptosis, ophthalmoplegia, facial weakness, bulbar paralysis, and distal muscle weakness. Most cases with genetically identified OPDM have been reported in Japan and China until now. Especially, the OPDM4 patients were only described by two research teams from China, and the number of reported OPDM4 patients was very limited. In this study, we summarized the clinical features of OPDM4 patients in a large family, and discussed the myopathological characteristics of OPDM4 patient at the end stage.
Methods: In an autosomal dominant inherited family (Family 1), a total of 8 affected individuals and 12 unaffected individuals were recorded or interviewed. The detailed medical history was obtained from the subjects and their relatives. Information regarding age of onset, progression of disease, and other clinical manifestations was collected. And the patient was examined by muscle MRI, muscle biopsy and gene sequencing.
Results: The affected individuals showed a sequential disease progression, most developing lower limb weakness and reduced walking ability at 20-30 years old, ptosis and ophthalmoplegia, difficulty in swallowing and speaking at 30-50 years old, and wheelchair dependence at 50-70 years old. Muscle MRI in the index patient showed severe fatty infiltration of pelvic girdle and lower limb muscles, accompanied by mild edema-like changes in the residual rectus femoris, sartorius, and gracilis muscles. Muscle biopsy showed an end-stage change characterized by adipose connective tissue replacement, while multiple eosinophilic, p62-, and polyG/A- positive intranuclear inclusions were observed in the proliferated adipose connective tissues. RP-PCR revealed that an abnormal CGG repeat expansion in the 5'UTR of the RILPL1 gene.
Conclusion: The clinical, radiological, and pathological features add new phenotypic spectrum to OPDM4 patients at the end stage. Newly synthesized polyG and polyA proteins might involve in the gain-of-function pathogenesis of OPDM4.

GNE myopathy and N-acetylmannosamine

May Malicdan[1],Marjan Huizing[1],Francis Rossignol[2]
1. National Institutes of Health (NIH), National Human Genome Research Institute (NHGRI)

GNE myopathy is a rare genetic disorder characterized by progressive muscle weakness, primarily affecting the lower limbs. The disease typically manifests in adults and can result in debilitating disability over time. The disorder is caused by mutations in the GNE gene, which plays a vital role in the biosynthesis of sialic acid, a key substance for muscle function.

The GNE gene encodes the rate-limiting, bifunctional enzyme of sialic acid biosynthesis, UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE). Bi-allelic variants, mostly of the missense type, lead to GNE myopathy, which is a recessively inherited adult-onset progressive myopathy. The disease stems from decreased sialylation of muscle glycoconjugates. Due to advancements in molecular testing and the inclusion of GNE in neuromuscular disease panels, the diagnosis and identification of new GNE gene variants have significantly increased. However, the clinical presentation at the onset of the disease is non-specific, and since the majority of GNE variants are missense mutations, interpreting the pathogenicity of each variant for an accurate diagnosis remains a challenge. The disease is estimated to affect at least 2.5 individuals per 1 million people globally. This translates to about 20,000 patients worldwide and approximately 850 in the United States.

Due to its rarity and the nonspecific nature of its initial symptoms, the disease is often underdiagnosed or misdiagnosed. Advances in molecular testing have helped improve diagnostic rates, but many challenges remain, particularly in interpreting the pathogenicity of different GNE variants. Targeted therapies like ManNAc offer promise but are still under investigation. Increased awareness among healthcare professionals and continued investment in clinical research are essential for advancing our understanding and management of this debilitating condition.

We present herein updates on our efforts to increase awareness on GNE mypaty, and provide a review of the clinical trials for GNE myopathy.

test

Yan Cao
fudan university

Background

Spinal muscular atrophy (SMA) affects individuals with a broad age range and spectrum of disease severity. Risdiplam (EVRYSDI®) is a centrally and peripherally distributed, oral survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier that has been approved in over 90 countries worldwide.

SUNFISH (NCT02908685) is a multicenter, two-part, randomized, placebo-controlled, double-blind study in patients with Types 2 and 3 SMA (inclusion criteria: aged 2–25 years at enrollment). Part 1 (N=51) assessed the safety, tolerability and pharmacokinetics/pharmacodynamics of different risdiplam dose levels in patients with Types 2 and 3 SMA (ambulant and non-ambulant). Part 2 (N=180) assessed the efficacy and safety of the Part 1-selected dose of risdiplam versus placebo in Type 2 and non-ambulant Type 3 SMA. In Part 2, participants were treated with risdiplam or placebo for 12 months; participants then received risdiplam in a blinded manner until Month 24. At Month 24, patients were offered the opportunity to enter the open-label extension phase.

Objectives

To determine the efficacy and safety of risdiplam in patients with Types 2 and 3 SMA after 4 years (48 months) of treatment.

Results

The primary endpoint (Part 2) of change from baseline in the 32-item Motor Function Measure (MFM32) total score in patients treated with risdiplam (n=120) versus placebo (n=60) was met at Month 12. These increases in motor function were sustained in the second and third year after risdiplam treatment, as measured by changes in the MFM32, Hammersmith Functional Motor Scale – Expanded, and Revised Upper Limb Module. At Month 36 (data-cut: 6 September 2021), there were no treatment-related safety findings leading to withdrawal from either SUNFISH Part 1 or 2. Here we present 4-year efficacy and safety data from SUNFISH.

Conclusions

SUNFISH is ongoing and will provide further long-term efficacy and safety data of risdiplam in a broad population of children, teenagers and adults with SMA.

Longitudinal Changes in Compound Muscle Action Potential and Their Associations with Motor Function in Infantile-onset SMA Children in ENDEAR/SHINE

Charlotte Sumner[1],Bora Youn[2],Michelle A Farrar[3,4],Ben Tichler[5],Zdenek Berger[2],Cong Zhu[2],Angela D Paradis[2]

1. Johns Hopkins University School of Medicine
2. Biogen, Cambridge, MA, USA
3. School of Clinical Medicine, UNSW Medicine and Health, UNSW Sydney, Sydney, Australia
4. Department of Neurology, Sydney Children's Hospital Network , New South Wales, Australia
5. Biogen, Baar, Switzerland

Introduction: Compound muscle action potential (CMAP) is a validated, noninvasive and simple-to-perform electrophysiological technique that can be used to provide physiologic information about motor units. Understanding the longitudinal changes of CMAP and their association with motor function outcomes in children with spinal muscular atrophy (SMA) can help evaluate CMAP as a potential biomarker for therapeutic effects in SMA.

Methods: Our analysis included 105 participants with infantile-onset SMA who initiated nusinersen in ENDEAR or long-term extension study SHINE (27 Aug 2019 datacut).

Results: The mean (SD) of ulnar and peroneal CMAP amplitude at the time of first nusinersen dose (baseline) were 0.20 (0.18) and 0.35 (0.30) mV. CMAP amplitudes were significantly correlated with age at first dose and other disease severity measures at baseline, including disease duration and motor function (measured by Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP INTEND]) (p-values from Spearman correlations <0.05). Both ulnar and peroneal amplitude increased significantly after nusinersen initiation. The mean (SD) changes from baseline for ulnar and peroneal amplitudes were 0.26 (0.36) and 0.65 (0.75) mV at Day 394, and 0.49 (0.67) and 1.17 (1.22) mV at Day 818, respectively. Increases were greater for participants who were younger at first dose. CMAP amplitudes changes were moderately correlated with CHOP INTEND changes at most visits, suggesting that physiological changes in motor units correspond with observed clinical outcomes after nusinersen initiation. Correlations between changes in CMAP and CHOP INTEND at Day 394 were 0.45 ($p<0.01$) and 0.28 ($p=0.03$) for ulnar and peroneal amplitude; the corresponding correlations were 0.45 ($p<0.01$) and 0.40 ($p<0.01$) at Day 818.

Conclusion: CMAP's role as a potential biomarker for reaching developmental milestones in infantile-onset SMA, such as achieving independent sitting, will be further examined.

Swallowing Function in Children with Later-Onset Spinal Muscular Atrophy Treated with Nusinersen: CHERISH-SHINE Results

Francesco Muntoni[1],Thomas O Crawford[2],Diana Castro[3],Mariacristina Scoto[1],Cong Zhu[4],Corinne Makepeace[5],Zdenek Berger[4],Russell Chin[4],Stephanie Raynaud[4],Angela D Paradis[4]

1. UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital Foundation Trust
2. Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
3. Dept of Pediatrics and Neurology, Univ of Texas Southwestern Medical Center, Dallas, TX USA
4. Biogen, Cambridge, MA, USA
5. Biogen, Maidenhead, Berkshire, UK

Introduction: Swallowing and feeding issues commonly occur among individuals with later-onset spinal muscular atrophy (SMA). Tube feeding is often required among those with SMA Type II. Limited data are available on bulbar function among later-onset SMA patients treated with nusinersen.

Methods: CHERISH was a randomized, sham-procedure-controlled study for non-ambulatory participants most likely to develop SMA Type II/III. Participants were eligible to enroll in the ongoing SHINE open-label extension. Swallowing function was assessed in SHINE using the Parent Assessment of Swallowing Ability (PASA) questionnaire. Item-level PASA scores were examined for the overall cohort (n=119) and by age at first nusinersen dose.

Results: As of the 27 August 2019 datacut, the PASA was administered a median of 4 times over 1 year starting at a median of 2.7 years after treatment initiation. At the last PASA assessment, median age was 8.0 (range:6.0–12.9) years with a median time on nusinersen of 3.7 years. For items on general feeding, drinking liquids, and eating solid foods, participants were consistently rated over time as never to rarely experiencing difficulties, with no notable differences by age at first nusinersen dose. On the parental assessment of swallowing concerns, parents generally and consistently disagreed with having such concerns. Three participants were reported to be tube fed on >=1 PASA assessments; of these participants, one was often, one was sometimes, and one was no longer tube fed at their last assessment.

Conclusion: All later-onset SMA participants treated with nusinersen maintained the ability to swallow at their last visit.

Bibliometric Analysis of Spinal Muscular Atrophy Research Trends and Therapeutic Strategies from 1995 to 2023: A Deeper Insight

Wenhua Zhu[1],Cuijie Wei[2],Dan Sun[3],Li Zhang[4],Yanyan Xia[4],Zhiying Wu[5]

1. Department of Neurology,
2. Department of Pediatrics, Peking University First Hospital, Beijing, China
3. Department of Pediatric Neurology, Wuhan Children's Hospital, Wuhan, China
4. Biogen Biotechnology (Shanghai) Co., Ltd, Shanghai, China
5. Department of Medical Genetics, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Introduction: Spinal muscular atrophy (SMA) is the most common monogenic hereditary neurodegenerative disease, affecting α-motor neurons of the brain stem and spinal cord, leading to progressive muscle wasting and atrophy. Survival motor neuron (SMN) gene mutations are the major pathological contributors to SMA onset. In this bibliometric analysis, we explored the current global trends in SMA research and therapy and assess the status of SMA research in China.

Methods: A total of 8086 articles, indexed in the Web of Science Core Collection (WOSCC) database and published between 1995 and 2023, were screened for the eligibility criteria, finally selecting 6443 articles for bibliometric analysis using online bibliometric tools, VOSViewer, and R-bibliometrix. SMA research and therapy trends; topic themes; author, journal, citation, country/region contributions, and the most collaborative author/institute were analyzed.

Results: SMA research has been increasing in recent years, especially since 2019, with 6443 articles globally and 323 articles in China. The USA (38.90%) ranked first, followed by the UK (11.13%) and Germany (11.05%) based on the total number of SMA publications. In recent years, the most frequently used terms in China related to SMA were single nucleotide, messenger-RNA, phenotype, and survival. Top-cited papers and authors were focused on genetics, disease mechanism, and therapeutic advancements, including SMN gene therapy and restoration of SMN level by targeting its mRNA 5´-UTR with a combination of antisense oligo (ASO) and a splice-switching oligo (SSO) to promote muscle strength in pre-clinical animal models. Many clinical trials have assessed the clinical potential of nusinersen in restoring the level of full-length functional SMN protein and improving motor function in SMA patients.

Conclusion: This bibliometric analysis demonstrates a comprehensive overview of SMA research to date, highlighting the significant advances and identifying future directions to achieve further success in SMA disease management. Our findings offer critical insights for researchers, clinicians, and policymakers.

Characterization of Genetic Modifiers associated with Spinal Muscular Atrophy phenotypic variability: A systematic review

Chun Hing She,Sophelia Hoi Shan Chan,Wanling Yang
The University of Hong Kong

Spinal muscular atrophy (SMA) is a group of clinically heterogeneous disorders. While most cases were characterized by homozygous deletion of exon 7 in SMN1, substantial phenotypic variability was observed for unknown cause. Since SMN2 copy number was initially characterized as a positive genetic modifier of SMA, modifiers were also reported in other loci (including SMN and other loci involved in downstream signalling pathways) were also reported. However, not all modifiers were associated with known mutations. For modifiers beyond the SMN locus, studies only revealed dysregulated gene expression of the associated protein products, but not the exact mutations associated with the observed modifying effect. The current study includes a systematic review of genetic modifiers implicated in differential phenotypic manifestation of SMA. The modifying effect of genetic modifiers will be compared across different populations to highlight the need for replication studies in different populations.

To expand on the current knowledge of genetic modifiers, we propose to study (i) the genotype-phenotype correlation of SMA genetic modifiers in different populations, and (ii) the genotype-phenotype correlation between different combinations of genetic modifiers: the strength of the modifying effect and how the effect is mediated by combinations of genetic modifiers, by leveraging multi-center 5q SMA data from different regions/Asian countries. Ultimately, we hope to devise a model to explain phenotypic variability using the collection of genetic modifiers in patients with 5q SMA. Our results will provide a clearer understanding of the effect of SMA modifiers across different populations and how individual modifiers interact to elicit the modifying effect. This helps inform disease progression and helps healthcare professionals to make informed decisions in time.

Effectiveness of Nusinersen in Infantile-Onset Spinal Muscular Atrophy (SMA): A Systematic Literature Review of Clinical Trials and Real-World Studies

Angela D Paradis[1],Bridget A Neville[1],Marika Pane[2],Astrid Pechmann[3],Janbernd Kirschner[3],Richard S Finkel[4],Xinyue Liu[1],Tammy Jiang[1],Nicole B Johnson[1],Bora Youn[1],Eugenio Mercuri[2]

1. Biogen, Cambridge, MA
2. Paediatric Neurology, Universita Cattolica del Sacro Cuore, Rome, Italy
3. Department of Neuropediatrics and Muscle Disorders, Faculty of Medicine, University of Freiburg, Freiburg, Germany
4. Center for Experimental Neurotherapeutics, St. Jude Children's Research Hospital, Memphis, TN, USA

Introduction: The efficacy and safety of nusinersen in infantile-onset SMA was demonstrated in the phase 3 ENDEAR trial. Following its approval as the first disease-modifying therapy for SMA, real-world (RW) experience with nusinersen has accumulated. In addition, the clinical approach to infantile-onset SMA has evolved, with greater emphasis on early screening and treatment initiation to improve outcomes.

Methods: We conducted a systematic literature review (SLR) to assess efficacy/effectiveness of nusinersen in symptomatic infantile-onset SMA across a broad range of outcomes. The search strategy included papers published up to October 12, 2022 that reported on ≥5 nusinersen-treated, infantile-onset SMA patients with ≥6 mo follow-up.

Results: Of 801 publications identified, 35 publications on 29 studies (3 clinical trials, 26 RW studies) in 848 individuals met the prespecified SLR inclusion criteria. Variation was observed in age at first nusinersen dose and baseline motor function. Outcomes included Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (27/35), and respiratory (22/35), and nutritional (16/35) outcomes. Among 11 publications that reported sitting (n=425), 24.0% (n=102) individuals achieved sitting, but findings varied across clinical trials and RW studies. In clinical trials, 8.2% (6/73) of participants from ENDEAR and 46.2% (6/13) from CS3A achieved sitting during a median follow-up of roughly 9 and 36 mo. In RW studies, 26.5% (90/339) reached this motor milestone (range: 9.5%-45.5%). Among the smaller subset of individuals with ≥12 mo follow-up in RW studies, 27.0% (73/270) achieved sitting. Data suggested that individuals continued to gain motor milestones with longer duration of nusinersen treatment.

Conclusions: Our findings underscore the importance of conducting RW studies based on a broader population with longer follow-up data to achieve a comprehensive understanding of the benefits of nusinersen in infantile-onset SMA.

A National Registry for Adult Patients with Spinal Muscular Atrophy in China: Preliminary Report of Design, Progress and Patient Characteristics

Yi Dai[1],Yuying Zhao[2],Huifang Shang[3],Wenhua Zhu[4],Xiaoli Yao[5],Qiang Meng[6],Daojun Hong[7],Yaling Liu[8],Juanjuan Chen[9],Wanjin Chen[10],Ken Chen[11],Li Zhang[12],Maerhaba Mai[12],Liying Cui*[1]

1. Chinese Academy of Medical Sciences & Peking Union Medical College Hospital
2. Qilu Hospital of Shandong University
3. West China Hospital, Sichuan University
4. Huashan Hospital, Fudan University
5. The First Affiliated Hospital, Sun Yat-sen University
6. The First People's Hospital of Yunnan Province
7. The First Affiliated Hospital of Nanchang University
8. The Second Hospital of Hebei Medical University
9. Peking University Shenzhen Hospital
10. The First Affiliated Hospital of Fujian Medical University
11. IQVIA Solutions Enterprise Management Consulting (Shanghai) Co., Ltd
12. Biogen Biotechnology (Shanghai) Co., Ltd

* Corresponding author

Objectives

Spinal muscular atrophy (SMA) is a rare neuromuscular disorder characterized by progressive degeneration and irreversible loss of the anterior horn cells in the spinal cord. SMA has been associated with enormous socioeconomic burden due to its high mortality and morbidity particularly before the availability of disease modifying therapies (DMTs). Based on age of disease onset and highest motor milestone reached, SMA is classified into four different subtypes (Types I-IV). From the natural history of SMA, Type I patients show symptoms in early childhood and their life expectancy without therapy is unlikely past 2 years without respiratory support. Most Type II and III patients show symptoms in childhood and reach adulthood with variable degrees of disability. Type IV patients usually show symptoms in adulthood; however, adult patients with SMA include patients with different disease subtypes. Development of DMTs has dramatically changed the natural history of SMA. For both natural history and DMT effectiveness and safety, the data is limited among Chinese adult patients with SMA. The need for a registry that closely monitors adult patients with SMA is critical. The registry reported here observes adult patients with SMA in the long term to achieve a better understanding of the natural history, disease outcomes, effectiveness, and safety of DMT among adult SMA patients in China. The aim of this analysis is to describe the protocol and preliminary characteristics of 50 adult patients with SMA in the registry in China.

Methods

This is a longitudinal, multicenter disease registry for treated and untreated adult patients with SMA in a real-world setting in China. This registry is planned to recruit approximately 200 patients at 18 years old or above from 10-15 sites in China and was started in January 2023. Patients are observed at regularly scheduled visits.

This registry includes both retrospective and prospective data collection. The total duration of study participation after enrolment for each participant will be up to 60 months, while if patients receive DMT prior to enrolment, data will also be retrospectively collected via medical chart review starting from the date when patients initiated DMT. Collected data fields include patient demographics, disease characteristics, and SMA-related tests and assessments. The data fields are consistent with other registry studies conducted globally (e.g., Treat-NMD, iSMAc, and SMArtCARE). Anonymized aggregated data for currently enrolled patients at enrollment is reported here.

Results

As of April 25th, 2023, there were 50 eligible patients from 8 sites enrolled in the study. Of the 50 patients, 38 (76.0%) started DMT before enrollment, thus their data was collected both retrospectively and prospectively. Among the enrolled patients, 17 (34.0%) were females and the mean age at enrollment was 28.3 years old (Standard deviation = 8.1, ranging from 18 to 49 years). In terms of SMA type, 23 patients (46.0%) had Type III SMA, followed by Type II (18 patients, 36.0%), Type IV (7 patients, 14.0%), and Type I (2 patients, 4.0%). Regarding survival motor neuron (SMN)2 copy number, 10 (20.0%) had 4+ copies, 18 (36.0%) had 3 copies, 1 (2.0%) had 2 copies, 0 (0.0%) had 1 copy, and 21 (42.0%) had unknown copy number. At enrollment, 31 patients (62.0%) had a diagnosis of scoliosis. For treatment, 44 patients (88.0%) were on nusinersen and 2 patients (4.0%) were on risdiplam at enrollment. In terms of gross motor function, 2 patients (4.0%) were non-sitters, 27 patients (54.0%) were sitters, and 21 patients (42.0%) were walkers at enrollment.

Conclusion

This registry, the first national registry on adult patients with SMA in China, provides a platform to collect longitudinal clinical data on adult Chinese patients with SMA and makes it possible to develop a comprehensive disease profile of these patients, and the long-term effect of treatment in adult Chinese patients with SMA.

Disclaimer

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SUNFISH Parts 1 and 2: 4-year efficacy and safety data of risdiplam in Types 2 and 3 SMA

Wenhua Zhu[1],John W Day[2],Nicolas Deconinck[3,4],Elena S Mazzone[5],Andres Nascimento[6],Maryam Oskoui[7],Kayoko Saito[8],Carole Vuillerot[9,10],Giovanni Baranello[11,12],Odile Boespflug-Tanguy[13,14],Nathalie Goemans[15],Janbernd Kirschner[16],Anna Kostera-Pruszczyk[17],Laurent Servais[13,18,19],Jessica Braid[20],Marianne Gerber[21],Carmen Martin Martin[20],Wai Yin Yeung[20],Renata S Scalco[22],Eugenio Mercuri[5]

1. Huashan Hospital, Fudan University
2. Stanford University
3. Centre de Référence des Maladies Neuromusculaires, Queen Fabiola Children's University Hospital
4. Neuromuscular Reference Center
5. Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS
6. Neuromuscular Unit, Neuropaediatrics Department, Hospital Sant Joan de Déu, Fundacion Sant Joan de Déu
7. Departments of Pediatrics and Neurology Neurosurgery, McGill University
8. Medical Genetics Institute, Tokyo Women's Medical University
9. Department of Pediatric Physical Medicine and Rehabilitation, Hôpital Mère Enfant, CHU-Lyon
10. Neuromyogen Institute, CNRS UMR 5310 - INSERM U1217, Université de Lyon
11. The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health University College London, & Great Ormond Street Hospital Trust
12. Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta
13. IMotion Institut de Myologie AP-HP, Hôpital Armand Trousseau
14. Université Paris Cité, UMR 1141, NeuroDiderot
15. Neuromuscular Reference Centre, Department of Paediatrics and Child Neurology, University Hospitals Leuven
16. Department of Neuropediatrics and Muscle Disorders, Faculty of Medicine, Medical Center-University of Freiburg
17. Department of Neurology, Medical University of Warsaw
18. MDUK Oxford Neuromuscular Centre, Department of Paediatrics, University of Oxford
19. Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège
20. Roche Products Ltd
21. Pharma Development, Safety, F. Hoffmann-La Roche Ltd
22. Pharma Development Neurology, F. Hoffmann-La Roche Ltd

IntroductionSpinal muscular atrophy (SMA) affects individuals with a broad age range and spectrum of disease severity. Risdiplam (EVRYSDI®) is a centrally and peripherally distributed, oral survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier that has been approved in over 90 countries worldwide.

Methods

SUNFISH (NCT02908685) is a multicenter, two-part, randomized, placebo-controlled, double-blind study in patients with Types 2 and 3 SMA (inclusion criteria: aged 2–25 years at enrollment). Part 1 (N=51) assessed the safety, tolerability and pharmacokinetics/pharmacodynamics of different risdiplam dose levels in patients with Types 2 and 3 SMA (ambulant and non-ambulant). Part 2 (N=180) assessed the efficacy and safety of the Part 1-selected dose of risdiplam versus placebo in Type 2 and non-ambulant Type 3 SMA. In Part 2, participants were treated with risdiplam or placebo for 12 months; participants then received risdiplam in a blinded manner until Month 24. At Month 24, patients were offered the opportunity to enter the open-label extension phase.**Results**

The primary endpoint (Part 2) of change from baseline in the 32-item Motor Function Measure (MFM32) total score in patients treated with risdiplam (n=120) versus placebo (n=60) was met at Month 12. These increases in motor function were sustained in the second and third year after risdiplam treatment, as measured by changes in the MFM32, Hammersmith Functional Motor Scale – Expanded, and Revised Upper Limb Module. At Month 36 (data-cut: 6 September 2021), there were no treatment-related safety findings leading to withdrawal from either SUNFISH Part 1 or 2. Here we present 4-year efficacy and safety data from SUNFISH.

Conclusions

SUNFISH is ongoing and will provide further long-term efficacy and safety data of risdiplam in a broad population of children, teenagers and adults with SMA.Funding

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Use of gait analysis in detecting the functional changes of patient with spinal muscular atrophy

Nar Chi Chan[1],Miko LM Lao[2],Ivy KK Wong[2],Helen KF Chan[2],Joyce HY Lai[1],Stephen WW Chan[1],Sophelia SH Chan[3]

1. HKCH
2. Physiotherapy Department, Tuen Mun Hospital
3. Dept of Paediatrics and Adolescent Medicine, The University of Hong Kong

Introduction

Patients with Spinal Muscular Atrophy (SMA) encounter different degrees of progressive muscle weakness which affects motor functions including movement and walking. Recent studies show that the use of medications (nusinersen) can preserve or even improve the function of patients with SMA. However, for those with SMA type III, the usual functional assessment scale sometimes may not be sensitive enough to detect the changes. The aim of the present study is to find the change of gait parameters for patients with type III SMA after nusinersen treatment.

Methods

One patient with SMA type III was recruited in the gait analysis study. In addition to the usual clinical assessment using the Six-minutes-walk test (6MWT) and Hammersmith Functional Motor Scale Expanded (HFMSE), 3D gait analysis using the Vicon system and AMTI® forceplates was done. The tests are to detect the kinematics and kinetics changes of the gait pattern for SMA type III patients after each dose of nusinersen treatment at 4-month interval.

The kinematics and kinetics data were analyzed. The Total Support Moment (TSM) during stance phase was assessed to compare the changes over time after each treatment. TSM is the sum of the total moment over hip, knee and ankle, indicating the total extension support of lower limbs during walking. The sum of hip, knee and ankle moments in the sagital plane were calculated individually in each trial to provide a more comprehensive view on their contributions towards the body support.

Results

A total of 6 gait analyses from July 2020 to May 2022 were done for a patient with SMA type III (10 years old boy) who received the nusinersen treatment every 4 months. The trends of TSM were increased bilaterally over time, from 11.4 ± 2.3Nm/kg to 20.2 ± 4.8 Nm/kg over the left side; from 22 ± 2.5 Nm/kg to 40.2 ± 2.1 Nm/kg over the right side. While the 6MWT and HFMSE were changed from 456m to 500m and 63 to 64 out of 66 respectively. The increasing trends of TSM were perhaps a result of substantially growing contribution of ankle plantarflexion moment (24.7 ± 1.23 Nm/kg to 32.1 ± 3 Nm/kg over the left side and 31.6 ± 4.3 NM/kg to 43.5 ± 1.6 Nm/kg over the right side), coupled with an increasing tendency of hip extension moment in the saggital plane over the 6 visits (-8.2 ± 1.8 Nm/kg to -5.9 ± 2.8 Nm/kg over the left side and -3.7 ± 3.8 Nm/kg to -4.0 ± 2.3

Nm/kg over the right side). A slight downward trend of knee extension moment contribution were observed (-5.1 ±2.6 Nm/kg to -6.0 ± 2.0 Nm/kg for left side and -5.9 ± 2.2 Nm/kg to 0.7 ±1.6 Nm/kg for right side).

Conclusion

The results indicated the improvement in TSM in the sagittal plane which help the child to walk with a more upright or extended pattern. Particularly, the hip and ankle contribute more or compensate with the decreased knee extension moment which is comparable with our clinical observation. The gait analysis can act as an adjunct assessment in addition to the usual clinical assessment for high-functioning patients with SMA.

The value of long-read sequencing in the diagnosis of complex spinal muscular atrophy: a case series

Ningning Wang[1,2,3],Kexin Jiao[1,2,3],Jin He[4],Nachuan Cheng[1,2,3],Jian Sun[1],Lan Chen[5],Wanjin Chen[4],Lingyun Gong[1],Kai Qiao[1],Jianying Xi[1,2,3],Chongbo Zhao[1,2,3],Wenhua Zhu[1,2,3]

1. Department of Neurology, Huashan Hospital, Fudan University, Shanghai, China
2. National Center for Neurological Disorders (NCND), Shanghai, China
3. Huashan Rare Disease Center, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China
4. Department of Neurology and Institute of Neurology, First Affiliated Hospital, Fujian Medical University, Fuzhou, C Fujian Key Laboratory of Molecular
5. Department of Neurology, the Second Affiliated Hospital of Nantong University, Nantong First People's Hospital, Jiangsu, Nantong, China

Introduction: Spinal muscular atrophy (SMA) is one of the most common autosomal recessive neuromuscular disorders caused by deletion or mutation of the survival motor neuron 1 (SMN1) gene. In this study, we aim to study the value of longread sequencing (LRS) on diagnosis of three SMA patients.

Methods: Clinical characteristics of three SMA patients who were dignosed by LRS were collected. The SMN1 and SMN2 gene copy number was determined by using the multiplex ligation-dependent probe amplification (MLPA). In the patients with deleted SMN1 allele and an intragenic mutation in the other allele, specific amplification of SMN1 was performed by long-range PCR and nested PCR plus Sanger sequencing to detect point mutations. At last, we performed LRS to analysis the potential disease-causing variants of the three patients.

Results: A missense mutation in SNM1 exon 5, which was not detected by the traditional method, was revealed by LRS in patient 1 with heterozygous SMN1 deletion. An Alu/Alu-mediated rearrangement spanning the SMN1 promoter and exon 1 was identified in patient 2 by combination of multiplex ligation-dependent probe amplification (MLPA), LRS and Gap-PCR. The third case born to a consanguineous family carried four copies hybrid SMN genes with a structure of SMN2 exon 7- SMN1 exon 8, of which the genomic structures were determined by LRS. LRS identified the SMN1-SMN2 ratio as 0:2, whereas MLPA indicated that the SMN1-SMN2 ratio was 0:4, and the SMN2 copy number, the discordance between two methods suggested the limit of LRS on SMA diagnosis.

Conclusion: In conclusion, this newly modified long PCR based on third generation sequencing represents an additional approach for SMA diagnosis and offer complementary strengths to traditional methods. In addition, we cannot ignore the limitation of LGS on determine the copy number of SMN gene.

Application of nusinersen to Korean adult patients with spinal muscular atrophy shows improvement in neurofilament light chain of cerebrospinal fluid: real-world experience

Jong-Mok Lee
Kyungpook National University Hospital
School of Medicine, Kyungpook National University

The introduction of nusinersen has an impact on neuromuscular disorders as one of the genetic treatments. However, the clinical trial of nusinersen focused on infant or children patients. Meanwhile, neurofilament is widely used to evaluate the current status of many neurologic disorders. Here, we report that nusinersen can improve the level of neurofilament in adult patients with spinal muscular atrophy (SMA) from real-world experience. Two patients, SMA type 2 and 3a, were enrolled. Both patients completed 7th injection of nusinersen. The neurofilament light chain (NfL) was measured from cerebrospinal fluid (CSF) taken from every intrathecal injection of Nusinersen via a single molecular array. The level of NfL was markedly decreased after loading dosages in both patients. Our study implicated nusinersen was also effective in adult patients with SMA from the aspects of biomarkers in real-world experience.

Selecting high-risk adults/adolescents for spinal muscular atrophy screening: A single-center exploratory study in the Chinese Cohort.

Ningning Wang[1,2,3],Jian Sun[1],Yi Dong[1],Yan Chen[1],Kai Qiao[1],Wenhua Zhu[1,2,3]

1. Department of Neurology, Huashan Hospital, Fudan University, Shanghai, China

2. National Center for Neurological Disorders (NCND), Shanghai, China

3. Huashan Rare Disease Center, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China

Introduction: Spinal muscular atrophy (SMA) is a degenerative motor neuron disorder and a prominent genetic cause of infantile death with an incidence of 1/11,000 births and a prevalence of 1–2/100,000 persons. SMA is caused by a homozygous deletion or mutation of the survival motor neuron 1 (SMN1) gene. Due to the lack of specificity of early clinical manifestations of hereditary neuromuscular diseases, it is easy to misdiagnose. A few specific treatments are currently available for SMA, but early, or preferably presymptomatic, initiation of treatment seems to be critical. Our study aim to explore clinical and electrophysiological high-risk screening criteria to detect SMA at earlier stages, ultimately improving outcomes for patients.

Methods: According to the literature and the clinical and electrophysiological characteristics of patients diagnosed with genes in our center, the high-risk criteria for SMA were preliminarily established. The electrophysiological high-risk criteria for SMA are as follows: 1) age ≤40 years at the time of examination; 2) Acute/chronic neurogenic damage, possibly degeneration of the anterior horn cells of the spinal cord; 3) Both upper and lower limbs are involved; 4) The symptoms of muscle weakness are roughly symmetrical on both sides. The clinical high-risk criteria for SMA were proposed to include criteria 1) Delayed motor development milestones; 2) Progressive and symmetrical muscle weakness and atrophy; 3) Loss of tendon reflexes ; Exclusion criteria: 1) the presence of upper motor neuron signs; 2) Facial and bulbar muscle weakness. Firstly, all patients who underwent EMG examination in Huashan Hospital Affiliated to Fudan University from January 2022 to February 2023 were screened, followed by further screening of clinical history and physical examination results for cases meeting SMA electrophysiological high-risk criteria, and recall patients meeting SMA clinical high-risk criteria to further improve case data and physical examination. The SMN gene was detected by multiplex ligation-dependent probe amplification (MLPA).

Results: A total of 6053 patients were included, and 45 suspected SMA patients (0.74%) were screened by electrophysiological high-risk criteria. By analyzing the medical records, 9 patients (0.15%) meeting the clinical high-risk criteria for SMA were further screened. After genetic testing, a total of 4 patients (0.07%) were genetically diagnosed with SMA, of which 3 patients are currently receiving therapy. The other 5 patients had negative MLPA results, and the final diagnosis was

hereditary spastic paraplegia (1 case), motor neurone disease (3 cases), and progressive spinal muscular atrophy (1 case).

Conclusion: Potential SMA patients can be effectively screened through clinical and electrophysiological high-risk screening for SMA. The sensitivity and specificity of high-risk criteria still need to be further studied with larger samples.

Electrophysiological follow-up analysis of spinal muscular atrophy treated with nusinersen

Ningning Wang[1,2,3],Jian Sun[1],Chongbo Zhao[1,2,3],Kai Qiao[1],Wenhua Zhu[1,2,3]
1. Department of Neurology, Huashan Hospital, Fudan University, Shanghai, China
2. National Center for Neurological Disorders (NCND), Shanghai, China
3. Huashan Rare Disease Center, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China

Introduction: spinal muscular atrophy (SMA) is a recessive inherited neuromuscular disease caused by mutations in the survival motor neuron 1 (SMN1) gene, which is characterized by progressive and symmetrical limb weakness and atrophy. The proximal muscle weakness was greater than distal, and the lower limb was greater than the upper limb. The clinical manifestations of SMA are heterogeneous, and the response to drug treatment is also different. The aim of this study is to explore the electrophysiological characteristics of upper and lower limb muscles in SMA patients treated with nusinersen, and the application value of electrophysiological parameters in evaluating the efficacy of drug treatment.

Methods: The clinical data of 27 patients treated with nusinersen in the Department of Neurology, Huashan Hospital, Fudan University from October 2022 to July 2023 were retrospectively analyzed. The demographic characteristics, genetic testing results, motor scale scores and electrophysiological results were obtained. The patients were divided into independent walking group (group W) and non-independent walking group (group S) according to their motor function status. The changes of CMAP values of upper limbs (abductor digiti minimi, abductor pollicis brevis, trapezius, deltoid) and lower limbs (extensor digital brevis, tibialis anterior, abductor pollicis) treatment were compared with pretherapy and post-treatment, and the patients with upper limb motor function score (RULM) with a near-perfect score were screened. The changes of CMAP values of the four muscles of the upper limb after treatment were compared, and the data were collected for statistical analysis.

Results: A total of 27 patients were included in the study, of which 55.6% were male, and the mean age at treatment was 26.59±8.60 years. Patients with type 3 SMA accounted for 85.2%, and type 2 SMA for 14.8%. 15 patients walked independently, and 11 patients had upper limb RULM close to the full score (36 or 37). The CMAP of the distal muscles of the upper limb (abductor digi minimi and abductor pollicis brevis) after treatment was significantly higher than that before treatment (N=25, $P< 0.05$). There was no significant difference in lower limb muscles before and after treatment (N=23,$P>0.05$). After treatment, the increase of CMAP in distal upper limb muscles was significantly higher than that in proximal muscles (N=22, $P< 0.05$). The increasing of CMAP in the four muscles of the upper limb in W group (N=14) was significantly higher than that in subgroup S (N=8) ($P< 0.05$). For the three muscles of the lower limbs, the the observed magnitude

of improvement of CMAP in the W subgroup (N=14) was significantly higher than that in the S subgroup (N=7) (P< 0.05). Among patients with a near-perfect RULM score, the CMAP of the four upper limb muscles still continued to rise significantly after treatment (N=11, P<0.05).

Conclusions: Our study found that the improvement of distal muscles was better than that of proximal muscles, upper limb muscles better than lower limb muscles. The later the muscles are affected, tthe greater the improvement in electrophysiology. In addition, patients with better motor function had more obvious improvement of treatment, which provided an electrophysiological theoretical basis for "early detection and early treatment". It is further suggested that electrophysiological indicators are important markers for evaluating the therapeutic effect of SMA, which can make up for the "ceiling effect" of traditional upper limb motor function scores.

Improvement in motor function, health-related quality of life and self-reported outcomes in patients and their families with spinal muscular atrophy

Hoi Ning Hayley Ip[1],Michael Kwan Leung Yu[2],Pui Kei Cheng[1],Wilfred Hing Sang Wong[2],Yuk Shuen Chau[1],Sophelia Hoi Shan Chan[1,2]

1. Queen Mary Hospital

2. Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

Introduction: Spinal muscular atrophy (SMA) is a neurodegenerative disease characterized by muscle weakness, leading to ventilatory insufficiency, swallowing impairments, and premature death. This study investigates the real-world clinical outcomes, motor function, health-related quality of life (HRQOL), and parent/patient-reported outcomes (PROs) of nusinersen and risdiplam in Hong Kong.

Methods: In this prospective cohort study, patients with at least 0.5 years of nusinersen or risdiplam treatment were recruited between May 2018 and February 2023. They were evaluated by clinical outcomes, motor function, HRQOL score, and PRO survey.

Results: 27 patients had nusinersen treatment (SMA1: 9; SMA2: 11; SMA3: 6; Pre-symptomatic: 1). Six patients switched to risdiplam due to severe scoliosis and intrathecal-access problems. Eight patients had risdiplam treatment (SMA1: 3; SMA2: 4; SMA3: 1). After first year of treatment, motor function improved in the nusinersen group [CHOP-INTEND (24.3 vs 30.0, p=0.031)]; RULM: 19.8 vs 21.7, p=0.002)] and the risdiplam group (MFM32: 10.5 vs 14.8, p=0.068). Parents in the nusinersen group and risdiplam group also reported a significant HRQOL improvement in the PedsQL-Family impact survey (47.5 vs 56.9, p=0.024) and the PedsQL-NMD survey (51.5 vs 63.0, p=0.046) respectively. In both groups, all parents/patients perceived improvements in motor function. Other perceived improvements include respiratory, feeding, and speaking functions. However, most patients' ambulatory status remained unchanged, and one-third of nusinersen-treated patients stepped up ventilatory support or had scoliosis or hip subluxation progression.

Conclusion: Our findings support the efficacy of nusinersen and risdiplam in patients with SMA. PROs are important measures to evaluate disease-modifying therapies. However, clinical outcome progression also reflects the natural disease course, hence we recommend multidisciplinary collaborations for a high standard of care.

Prediction of disease progression in patients with amyotrophic lateral sclerosis by electromyography

wenwen xu,junxiong yin
Brain Hospital Affiliated to Nanjing Medical University

Introduction

As a conventional diagnostic method for amyotrophic lateral sclerosis (ALS), electromyography is widely used because of its high accuracy. However, correlation between electrophysiological parameters and clinical characteristics of ALS was seldom reported. In this study, the neurophysiological indicators of the left median nerve and the right tibial nerve, and the quantitative indicators of active denervation (AD) and chronic denervation (CD) were studied to evaluate the rate of disease progression and survival status of ALS patients.

Methods

This study included 42 ALS patients, who were divided into two groups according to the rate of progression. The following parameters were recorded: age, site of onset, survival rate, MRC scale (assessment of muscle strength), PUMNS (assessment of lower limb condition), LMNS (assessment of upper limb condition), ALSFRS-R, MITOS, KSS stage. In addition, 9 muscles were examined by EMG, and quantitative scores of active and chronic denervation were calculated by the presence or absence of spontaneous potentials and amplitude.

Results

It was found that there were significant differences in the neurophysiological indexes of the median nerve between the two groups. The neurophysiology of tibial nerve showed a positive correlation with PUMNS scale. Patients with higher quantitative scores of chronic denervation had higher KSS stage and were negatively correlated with MRC score.

Conclusion

Studies have confirmed that EMG is not only a diagnostic tool, but also its related parameters can reflect the speed of disease progression and survival stage of ALS patients to a certain extent. Neurophysiological indicators of the median nerve and quantitative scores of chronic denervation can be used as reliable predictors of disease progression and survival, and can determine dysfunction in ALS patients.

Spinal muscular atrophy complicated with epilepsy: a case report

Ying Wu,Cui Jie Wei,Hui Xiong
Peking University First hospital

Objective To summarize the clinical phenotype and genotype characteristics of spinal muscular atrophy with epilepsy caused by coexistence of two kinds of genetic variants.

Methods The clinical data of one patient with spinal muscular atrophy and epilepsy at Pediatrics clinic of Peking University First Hospital in May 2022 were retrospectively analyzed. The literature was retrieved to summarize characters of these children.

Results The patient was myasthenia from birth, weak cry and disable to Limbs off the bed. Multiplex ligation-dependent probe amplification(MLPA) found homozygous deletion of exons 7 and 8 of SMN1 gene derived from heterozygous parents. Luckily, she got Risdiplam, disease-modifying therapeutic drug for SMA, at the age of 4 months. And muscle strength was improving day by day. At the age of 5 months, she had twice seizures without incentives during 24 hours. What's more, there was regression of motor function. The electroencephalogram showed a large number of diffuse slow waves in each phase of waking and sleeping and paroxysmal spikes can be seen in interparoxysmal periods. No abnormality was found in cerebral MRI. The whole exon gene sequencing showed a de novo heterozygous variation in the SCN1A gene c.3879+1 G>A that was rated "pathogenic" by ACMG. The seizures were controlled by levetiracetam and movement ability was gradually restored.

Conclusion For this patient, two kinds of gene variations cause different clinical manifestations，SMN1 for muscle weakness and SCN1A for seizures. The co-existence is no precednet reported and no evidence suggests possible mechanism. That may be a coincidence.

Ultrasound-guided interlaminar approach for nusinersen administration in patients with spinal muscular atrophy with spinal fusion or severe scoliosis

Cuijie Wei[1],Zhenwei Liang[2],Ying Wu[1],Jianxing Qiu[3],Lingchao Meng[4],Chunde Li[5],Xinhua Bao[1],Zhaoxia Wang[4],Luzeng Chen[2],Hui Xiong[1,6]

1. Peking University First Hospital
2. Department of Ultrasonography, Peking University First Hospital, Beijing 100034, China
3. Department of Radiology, Peking University First Hospital, Beijing 100034, China
4. Department of Neurology, Peking University First Hospital, Beijing 100034, China
5. Department of Orthopedic/Spine Surgery, Peking University First Hospital, Beijing 100034, China
6. Beijing Key Laboratory of Molecular Diagnosis and Study on Pediatric Genetic Diseases, Beijing 100034, China

Background: Intrathecal injection of medications can be challenging in spinal muscular atrophy (SMA) patients with severe scoliosis or after spine surgery. In this study, we report our experience with real-time ultrasound-guided intrathecal injections of nusinersen in SMA patients after spinal fusion or patients with severe spinal deformities and provide detailed technical points to encourage the use of real-time ultrasound in theintrathecal administration of nusinersen.

Methods: Seven patients (six children and one adult) with either spinal fusion or severe scoliosis were enrolled. We performed intrathecal injections of nusinersen under US guidance. The efficacy and safety of US-guided injection were explored.

Results: Seven patients received intrathecal injections of nusinersen under real-time ultrasound guidance. Two patients were diagnosed with type 1c SMA, three with type 2a SMA, and the other two with type 3a SMA. Five patients had undergone spinal fusion, while the other two presented severe scoliosis. Success was achieved in 19/20 lumbar punctures (95%), 15 of which were performed through the near-spinous process approach. The intervertebral space with a designated channel was selected for the five postoperative patients, while the interspaces with the smallest rotation angle were chosen for the other two patients with severe scoliosis. In 89.5% (17/19) of the punctures, the number of insertions was no more than two. No major adverse events were observed.

Conclusion: Given its safety and efficacy, real-time US guidance is recommended for SMA patients with spine sur- gery or severe scoliosis, and the near-spinous process view can be used as a interlaminar puncture approach for US guidance.

Nutritional and Lipid Profile Status of Children with Spinal Muscular Atrophy in China: a retrospective case-control study

Liya Jiang,Yue Yan,Yijie Feng,Shanshan Mao
the Children's Hospital of Zhejiang University School of Medicine

Introduction: Spinal muscular atrophy (SMA) is a progressive neuromuscular disorder with multiple organ system involvements. We aimed to investigate the specific alterations in nutritional status and serum lipid profiles in Chinese children with SMA.

Methods: This hospital-based, case-control study included 91 children with SMA and 91 age- and gender-matched healthy children in a single center in China. Data of nutritional status, serum lipid profiles, and body composition (in a subgroup of patients > 3 years) were collected for descriptive analysis and case-control comparison tests.

Results: The prevalence of malnutrition and dyslipidemia was higher in children with SMA than in healthy controls (50.55% vs 23.08% and 62.64% vs 34.07%, respectively; $P < 0.01$). Patients with SMA, especially type II and III, tended to have sarcopenic obesity, characterized by a higher fat mass index and fat mass percentage and lower lean body mass index. The prevalence of lower levels of high-density lipoprotein (HDL, < 1.04 mmol/L) and apolipoprotein A1 (Apo A1, < 1.20 g/L) was significantly higher in children with SMA than in healthy controls (34.07% vs 7.69% and 50.55% vs 6.59%, respectively; $P < 0.001$). Ratios of total cholesterol (TC)/HDL, low-density lipoprotein (LDL)/HDL, and apolipoprotein B (Apo B)/Apo A1 in SMA patients were higher than those in control children ($P < 0.01$).

Conclusions: Children with SMA tended to have malnutrition, combined with sarcopenic obesity and dyslipidemia. Further studies are warranted to identify effective nutritional management strategies for these patients, to prevent future risk of cardiovascular diseases and related conditions.

A case of X-linked spinobulbar muscular atrophy with muscular fatigue and decremental response to repetitive nerve stimulation

Qiongqiong Zhai,Fang Xue
The Second Hospital of Hebei Medical University

Introduction: X-linked recessive spinobulbar muscular atrophy (X-SBMA), or Kennedys disease, is a slowly progressive neuropathy characterized by an adult-onset weakness and atrophy of proximal limbs and bulbar muscles with prominent muscle cramping and fasciculations. Repetitive nerve stimulation (RNS) is a widely-employed examination to evaluate the function of the neuromuscular junction, and is used as a routine test to diagnose and evaluate patients with myasthenia gravies (MG) and other neuromuscular junction disorders. Decremental response in RNS is rarely observed in X-SBMA. Here we reported a case of X-SBMA with decremental responses in repetitive nerve stimulation (RNS) and clinical muscular fatigue.

Method: We retrospectively analyzed the clinical features, laboratory tests, and electrophysiological results of a Kennedy patient with rare electromyographic phenomena decremental response to repetitive nerve stimulation.

Result: A 52-year-old male presented with a history of insidious onset, gradually progressive, symmetric weakness and fatigability in the arms and legs for the past 3 years. He also had facial muscle myokymia, difficulty in swallowing and dysarthria. Physical examination revealed decreased muscle strength in the limbs, more prominent in the proximal muscles of the limb, reduced tendon reflex. Laboratory test results are normal except for a modestly elevated creatine kinase (CK) level 1164.3U/L, MYO 346.0ng/ml; Spinal cord MRI imaging showed diffuse thinning of the spinal cord, narrowing of the anterior and posterior diameters. Nerve conduction study (NCS) revealed normal compound muscle action potentials (CMAPs), with normal motor distal latencies and conduction velocities. Sensory NCSs revealed reduced sensory nerve action potentials (SNAPs) from all examined upper and lower limb nerves. Needle EMG showed neurogenic changes, including reduced recruitment of large, prolonged duration, polyphasic motor unit action potentials (MUAPs) in affected muscles. A decremental response to RNS was observed in trapezius muscle and abductor pollicis brevis muscle, which implied an impairment of neuromuscular transmission in this patient. Genetic analysis (Cytosine Adenine Guanine (CAG) revealed 44 CAG repeats (normal range 9–36). Finally, the patient was diagnosed as Kennedy's disease based on clinical manifestations, electrophysiological features, imaging findings, and genetic test.

Conclusion:

This case showed that myasthenic symptoms and abnormal decremental responses to low-rate RNS can be observed in X-BSMA. Clinicians should therefore understand the limitations of the RNS test and take care not to overinterpret the results of electrophysiologic studies.

Genetic stress susceptibility peripheral neuropathy caused by loss of PMP22 gene heterozygosity: a case report

Shuang Li
Peking University First Hospital

Introduction: Hereditary neuropathy with liability to pressure palsy(HNPP)is an autosomal dominant peripheral neuropathy caused by the deletion or point mutation of the peripheral myelin protein 22 (PMP22) gene on 17p11.2. It is manifested as recurrent demyelinating neuropathy. Electrophysiological examination of the nerve often shows that the latency of the peripheral nerve is prolonged and the conduction velocity is slowed down in the generalized multiple nerves, especially in the areas prone to entrapment. We report a case of hereditary stress-prone peripheral neuropathy caused by loss of PMP22 gene heterozygosity with axonal injury as the main electrophysiological feature.

Methods: The clinical phenotype and electrophysiological test results of one case of hereditary stress-prone peripheral neuropathy caused by point mutation of PMP22 gene were analyzed.

Results: Male, 9 years old, was admitted to the Department of Pediatrics of Peking University First Hospital in November 2021 due to "left lower limb weakness accompanied by paresthesia for more than 5 months". The child suddenly developed weakness of the left lower limb in the morning more than 5 months ago, mainly in the distal end, accompanied by "hosier-like" numbness and hyperalgesia below the knee joint. The disease reached its peak on the day of onset. The EMG image showed that the CMAP amplitude of the left common peroneal nerve and tibial nerve were reduced, and the sensory and motor conduction velocity were normal. The left calf gradually atrophied. Previous and personal history: Her parents were married without Cousins, and she was delivered by cesarean section at full term. After birth, she was found to have "multiple digits and double digits on her right foot", and underwent surgical treatment at the age of 3. No such history in the family. Admission to hospital for physical examination: left lower limb lameness, left foot dorsiflexor muscle strength grade 3, plantar flexor muscle strength grade 4, left knee extension grade 4, hip flexor grade 5, left lower limb muscle volume decreased, calf as usual, left knee tendon reflex and Achilles tendon reflex disappeared, left leg lateral pain slightly weakened compared to the opposite side, right lower limb and both upper limbs muscle strength, muscle tension, tendon reflex were normal. Re-examination of the EMG images after admission showed that the amplitude of CMAP of the left common peroneal nerve and tibial nerve was reduced and the conduction velocity was normal, suggesting left lower limb peripheral neuropathy, mainly axonal injury. MLPA detection of PMP22 gene showed that PMP22 gene heterozygosity was missing. During follow-up, the weakness of the left lower limb gradually improved, but the dorsiflexion strength of the foot was still weak, and the left lower limb atrophy was still left.

Conclusion: The genetic stress susceptibility peripheral neuropathy is mostly manifested as recurrent demyelination neuropathy, and the main electrophysiological feature of axonal injury is rare. This study enriches its clinical and electrophysiological phenotypes, suggesting that the possibility of hereditary stress susceptibility to peripheral neuropathy should be taken into account for mononeuropathy or multiple mononeuropathy.

Good Syndrome-A rare association with myasthenia gravis

Ting Yoong Tee
Hospital Kuala Lumpur
Ting Yoong TEE [1],Yin Yin TAN[1],Dhayalen KRISHNAN[1],Shanthi VISWANATHAN[1]
1Department of Neurology,Hospital Kuala Lumpur,Malaysia

Introduction

Good Syndrome(GS) which is characterised by presence of thymoma and hypogammaglobulinaemia was described in 1954.Autoimmune manifestations associated with GS include pure red cell aplasia,myasthenia gravis and others.We describe a patient with refractory generalised seropositive myasthenia gravis associated with GS.

Case presentation

A 52 years old lady of Chinese ethnicity presented with easy fatiguability and double vision for 1month on August 2008.Her progressive predominantly proximal weakness impaired her mobility and gradually affected her swallowing.Physical examination noted bilateral ptosis with diplopia on lateral upper quadrants.There was proximal myopathy of bilateral limbs with neck flexion grade 4/5(MRC) and nasal speech.Electrophysiological studies showed significant decremental response over trapezius and nasals muscles.Her serum anti-acetylcholine receptor antibody was positive.She was diagnosed to have myasthenia gravis and treated with a course of IV Immunoglobulin(IVIG) ,steroids and pyridostigmine.Her computed tomography(CT)thorax showed no evidence of thymoma.She relapsed on October 2008 which required intensive care unit(ICU) admission.Subsequently she proceeded with thymectomy on 3rd April 2009 which histopathological report showed normal thymic tissue.From 2009 till 2012,she remained symptomatic despite of optimum steroids,pyridostigmine and azathioprine.She relapsed on July 2012 which was treated with plasma exchange.In view of poor response to azathioprine, her immunosuppressants was switched to methotrexate.However,she developed respiratory distress on April 2015 which necessitated ventilatory support.Bronchoscopy done noted positive culture for atypical mycobacterium-mycobacterium fortuitous chelonei complex.She was promptly treated with streptomycin,clarithromycin and ethambutol in addition to 5 cycles of plasma exchange.Due to concern of exacerbation of myasthenia symptoms by non-tuberculous mycobacterium treatment and possibility of lung fibrosis attributed by methotrexate, her immunosuppressants was changed to mycophenolate mofetinil.From 2015-2016,she was given 3monthly plasma exchange with 6monthly rituximab as maintenance therapy.In 2018,she developed severe hair loss that was diagnosed as alopecia areata.Her serum immunoglobulin levels of IgA,IgM,IgG sent were low with absence of B lymphocyte count.Repeated CT thorax showed recurrence of thymoma with 18F-FDG PET scan confirmed local recurrence.She was scheduled for repeat thymectomy.

In conclusion,clinicians should have high index of suspicion of Good Syndrome when encountering adult onset immunodeficiency with recurrent infections and autoimmune complications.Astute clinical acumen about the clinical and immunological profile of this syndrome may prevent morbidity and mortality.

Multidisciplinary treatment for myasthenic crisis: A Single-center experience

Sushan Luo[1],Caihua Xi[1],Lei Yang[1],Jianming Zheng[1,2],Yuan Wang[1],Yafang Xu[2],Qingyu Huang[1],Weining Wang[1],Chongbo Zhao[1]
1. Huashan hospital

Myasthenia crisis (MC) is a life-threatening state of patients with myasthenia gravis (MG) who develop respiratory failure with mechanical ventilation demands. Patients at MC presented a high in-hospital mortality as well as a long ICU stay. The establishment of the MC Unit in NICU with a multidisciplinary effort from neurology, critical care, infectious disease, blood transfusion department, cardiology, nursing, and rehabilitation, should shed new light on the path to provide more comprehensive and individualized service for patients with MC. Here the single-center experience in the multidisciplinary treatment of MC was briefly introduced to explore the future directions of patient-centered clinical management.

A Predictive Model for Response to Low-dose Rituximab in Myasthenia Gravis

Yufan Zhou[1],Zhe Ruan[2],Sisi Jing[3],Jun Lu[1],Rongjing Guo[2],Sushan Luo[1],Lei Zhou[1],Jie Song[1],Chong Yan[1],Chongbo Zhao[1],Ting Chang[2],Jianying Xi[1]

1. Huashan Hospital, Fudan University
2. Tangdu Hospital, The Fourth Military Medical University
3. Banan Hospital, Chongqing Medical University

Introduction: This study attempts to investigate the clinical and genetic predictors for clinical response of myasthenia gravis (MG) treated with single low-dose rituximab and develop the predictive model.

Methods: We retrospectively reviewed 108 patients who received low-dose rituximab (600mg/every six months) in Huashan Hospital and Tangdu Hospital. Of them, 76 patients from Huashan Hospital were enrolled to form a derivation cohort for predictive model. Then, the model was externally validated using 32 patients from Tangdu Hospital. Baseline characteristics, clinical severity scores, single nucleotide polymorphisms of FCGR3A, FCGR2A and BAFF were analyzed as predictors of clinical response. Univariate and multivariate logistic regression were used to screen independent factors. The discrimination was measured by the area under the receiver operating characteristic curve (AUC-ROC). The Hosmer-Lemeshow test and calibration plots were applied to assess the calibration.

Results: After 6 months of single RTX treatment, 58 patients responded and 18 patients did not respond in the derivation cohort. Disease duration (β=-0.013, OR=0.987, p=0.032), anti-muscle specific tyrosine kinase (MuSK) antibody positive, (β=2.983, OR=19.8, p=0.007) and genotypes in FCGR2A rs1801274(AG: β=-2.032, OR=0.131, p=0.024; GG: β=-3.291, OR=0.037, p=0.010) were independently associated with clinical response to rituximab in MG patients. A multivariate logistic regression model consisting of these factors has good predictive power as the AUC was 0.875(95%CI, 0.798-0.952) in the derivation cohort and 0.741(95%CI, 0.501-0.982) in the validation cohort, and Hosmer-Lemeshow good of fit test showed a good calibration (derivation: chi-square=3.181, p =0.923; validation:chi-square=8.098, p = 0.424).

Conclusion: MuSK antibody-positive MG patients with shorter duration from disease onset to rituximab treatment and AA genotype in FCGR2A rs1801274 had better clinical response 6 months after rituximab treatment.

Clinical Features, Treatment and Prognostic Factors of Childhood-onset Myasthenia Gravis in A Large Chinese Cohort

Zhuajin Bi,Jing Lin,Mengcui Gui,Bitao Bu
Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China

Objectives: To describe the clinical features of childhood-onset myasthenia gravis (CMG) patients and explore predictors affecting the treatment outcomes.
Methods: A retrospective, observational cohort analysis of 859 CMG patients with disease onset before the age of 14 years were performed at Tongji Hospital.
Results: Patients in the pubertal onset group (n=148) had a worse disease course than those in the prepubertal group (n=711), including a higher incidence of generalized MG (GMG) at presentation, generalization of ocular MG (OMG), and more severe Myasthenia Gravis Foundation of America (MGFA) classification. All patients were initially treated with pyridostigmine, 657 with prednisone, and 196 with immunosuppressants. However, 226 patients were resistant to prednisone treatment. Multivariate analysis revealed that thymic hyperplasia, higher MGFA class, disease duration before prednisone administration, and thymectomy before prednisone administration were independent predictors of prednisone resistance. At the last visit, 121 out of the 840 OMG patients had developed GMG after a median of 10.0 years from symptom onset, and 186 patients (21.7%) achieved complete stable remission (CSR). In multivariable analysis, age at onset, thymic hyperplasia, prednisone, and IS treatment were associated with generalization; while age at onset, disease duration, anti-acetylcholine receptor antibodies (AChR-ab), MGFA class II, short-term prednisone treatment, and IS treatment were associated with CSR.
Conclusions: The majority of CMG patients have mild clinical symptoms and favorable outcomes, especially those with earlier onset age, shorter disease duration, and negative AChR-ab. In addition, early prednisone and IS are shown to be effective and safe for most CMG patients.

Clinical and immune-related factors associated with exacerbation in adults with well-controlled generalized myasthenia gravis

Zhuajin Bi,Jing Lin,Mengcui Gui,Bitao Bu
Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China

Objectives: To describe the clinical predictors and immune-related factors for exacerbation in adults with well-controlled generalized myasthenia gravis (GMG).
Methods: We conducted a retrospective analysis of 585 adults with well-controlled GMG from our institution to explore the risk factors for exacerbation. Furthermore, propensity score matching (PSM) was used to compare the proportions of lymphocyte subsets, and the levels of immunoglobulin, complement, and anti-acetylcholine receptor antibody (AChR-ab) in the peripheral blood of 111 patients with exacerbations and 72 patients without exacerbations.
Results: A total of 404 patients (69.1%) experienced at least one exacerbation, and the median (interquartile range) time to the first exacerbation was 1.5 years (0.8-3.1 years). Multivariable Cox regression analysis showed that age at onset, disease duration before enrollment, Myasthenia Gravis Foundation of America classification (MGFA) class III vs. class II, MGFA class IV-V vs. class II, AChR-ab levels, anti-muscle specific kinase antibody levels, thymus hyperplasia, prednisone plus immunosuppressants vs. prednisone treatment, and thymectomy were independent predictors for exacerbations [hazard ratio (HR) = 1.011, 1.031, 1.580, 1.429, 2.007, 2.033, 1.461, 0.798, and 0.651, respectively]. Propensity-matched analysis compared 51 patient pairs. After PSM, the peripheral blood proportions of CD3-CD19+ B cells, ratios of CD3+CD4+/CD3+CD8+ T cells, and AChR-ab levels were significantly increased, and the peripheral blood proportions of CD3+CD8+ T and CD4+CD25+CD127low+ regulatory T cells (Tregs) were significantly lower in patients with exacerbation than in those without exacerbation (all $p < 0.05$).
Conclusion: Myasthenia gravis (MG) exacerbations were more frequent in those patients with older onset age, longer disease duration, more severe MGFA classification, positive AChR-ab, and lack of combined immunotherapy or thymectomy treatment. On the other hand, CD3-CD19+ B cells, CD3+CD8+ T cells, Tregs, and AChR-ab in peripheral blood may be involved in the course of GMG exacerbation

Safety And Efficacy Of Tofacitinib In Patients With Refractory Myasthenia Gravis: A Pilot Study

Rui Zhao,Chong Yan,Sushan Luo,Chongbo Zhao
Huashan Hospital

Myasthenia gravis is a B-cell-mediated, T-cell-dependent autoimmune disease that involves the postsynaptic membranes of neuromuscular junctions. It is mainly mediated by autoantibodies such as anti-acetylcholine receptors and complement. Epidemiological studies have shown that the annual incidence of myasthenia gravis is about 10-29 cases per million people, and the prevalence is 100-350 cases per million people. Although the majority of patients with myasthenia gravis can achieve satisfactory results after treatment, there are still 10% of patients with refractory systemic myasthenia gravis, who have a higher risk of disability and poor quality of life. They are the difficult problems in the management of myasthenia gravis patients. At present, there are still rare treatment methods for refractory myasthenia gravis, mainly including rituximab targeting CD20 antigen on mature B cell surface, Eculizumab targeting complement component C5 and Belimumab targeting B cell activator, but there are still problems such as expensive treatment and poor accessibility. Therefore, it is still necessary to explore the pathogenesis of refractory myasthenia gravis so as to develop new targets and inhibitors. Tofacitinib is a first-generation inhibitor of JAK kinase and acts non-selectively on JAK1, JAK2, and JAK3 kinases. Currently, it has been approved to treat rheumatoid arthritis, ulcerative colitis, psoriatic arthritis and other autoimmune diseases. Our research group conducted a pilot study to enroll 20 patients with refractory MG, and followed they up for 4 months to evaluate the safety and effectiveness of tofacitinib in the treatment of refractory myasthenia gravity patients.

A total of 20 patients with refractory generalized myasthenia gravis were enrolled in this pilot study to verify the efficacy of tofacitinib in the treatment of refractory gMG patients. The enrollment criteria included ① 18-65y, fluctuating myasthenia, MGFA IA to IVA; (2) RNS > 10%, high frequency did not increase significantly; ③ Refractory (patients with poor efficacy in combination with azathioprine (100mg/d) for 6 months or tacrolimus (3mg/d and above) for a full course of glucocorticoids (therapeutic dose 0.75-1mg/kg for 3-6 months) or unable to tolerate traditional immunotherapy; ④ Signed informed consent and compliance is good. We evaluate the ADL, QMG, MGC and other clinical MG score monthly, the protein and mRNA levels of serum cytokines were detected, and the lymphocyte subsets of the patients' peripheral blood cells were determined by flow cytometry.

This pilot study showed that taking tofacitinib for 4 months can effectively reduce the clinical scores of QMG, ADL, MGC and MG-QOL in patients with refractory MG, assist patients with hormone reduction, and alleviate their symptoms.

Combination of droplet digital PCR and next generation sequencing for etiological diagnosis of pneumonia in patients with myasthenia gravis

Manqiqige Su[1],Yeting Luo[2],Chongbo Zhao[1],Jianming Zheng[1],Sushan Luo[1]
1. Huashan Hospital Affiliated to Fudan University
2. Ganzhou People's Hospital

Purpose: Due to the long-term immunotherapy, dysphagia or dyspnea, patients with myasthenia gravis are susceptible to pneumonia and tend to develop into crisis easily. Accurate and effective anti-infection therapy based on etiology results is necessary to improve the prognosis of patients, but the traditional sputum culture often takes too long and has narrow spectrum of pathogen detection. To increase the sensitivity and specificity, the development of new technologies such as droplet-based digital PCR (ddPCR) or next generation sequencing (NGS) has greatly optimized the detection of pathogens. On the basis of the previous research in our center, we selected the appropriate ddPCR detection spectrum, compared the differences in the detection of pathogens among the traditional culture, ddPCR and NGS, and discussed the potential of early diagnosis of pathogens with the combined application of ddPCR and NGS.

Materials and methods: We enrolled a 22 inpatients diagnosed with myasthenia gravis and pneumonia in the Department of Neurology, Huashan Hospital Affiliated to Fudan University from December 2022 to July 2023. 23 Sputum samples were detected synchronously by traditional culture, ddPCR and NGS. Additionally, there were 3 blood simultaneous samples obtained for ddPCR. Considering traditional sputum culture as the standard results, the sensitivity and specificity of ddPCR and NGS in detecting pathogens were compared. We also analyzed the detection differences between ddPCR and NGS in the specific 16 pathogens and 7 drug resistance genes covered by the detection spectrum of ddPCR.

Results: A total of 44 pathogens were detected by sputum culture in 19 patients with positive results, mainly including Pseudomonas aeruginosa (n=10), Klebsiella pneumoniae (n=8), Acinetobacter baumannii (n=8) and stenotrophomonas maltophil (n=6). Compared with the results of traditional sputum culture, the positive rates of ddPCR and NGS were 57.69% (15/26) and 69.23% (18/26) respectively, and the false negative rates were all 11.54% (3/26). The positive rates of the three detection methods on Klebsiella pneumoniae were significantly different ($p=0.011$), and both ddPCR and NGS were likely fail to detect Klebsiella pneumoniae. For the 16 pathogens covered by ddPCR spectrum, the proportion of double positive detection rate by both ddPCR and NGS was 32.38±29.25%. Compared with NGS, ddPCR had a significantly higher overall positive detection rate for these specific pathogens ($p<0.001$), and was more sensitive to Escherichia coli, Acinetobacter baumannii, Candida, Streptococcus, and coagulase-negative staphylococci ($p<0.05$). In the detection of 7 drug resistance genes, ddPCR had a higher detection rate of mecA

(p=0.001), while NGS had a higher detection rate of OXA (p=0.001).

Conclusion: ddPCR is a fast method for the detection of pathogens in pneumonia patients with myasthenia gravis. Although its detection positive rate is slightly lower than that of NGS, ddPCR has a higher positive detection rate in the target pathogen spectrum, which is conducive for early diagnosis and follow-up. However, ddPCR has the limitation of pathogen spectrum, and NGS has a wider range of detection pathogen spectrum such as fungi and mycoplasma compared with ddPCR. Therefore, the detection spectrum of ddPCR should be optimized flexibly. The combination of ddPCR and NGS can offer added diagnostic value for early and accurate diagnosis to improve the prognosis of patients.

Eculizumab Treatment for Refractory Generalized Myasthenia Gravis Crisis: A Case Series

Jie Song[1],Yeting Luo[2],Zhongyan Zhao[3],Sushan Luo[1],Chongbo Zhao[1]
1. Huashan Hospital Fudan University
2. Ganzhou City People's Hospital
3. Hainan Provincial People's Hospital

Introduction

Refractory generalized myasthenia gravis (MG) with positive acetylcholine receptor (AChR) antibody is a challenging condition in clinical management. Eculizumab, a monoclonal antibody targeting complement protein C5, has shown efficacy in clinical trials for treating this condition. In June 2023, the China National Medical Products Administration (NMPA) approved the use of eculizumab for refractory generalized MG in adult patients with AChR antibody positivity. We present two cases of severe myasthenic crisis treated with eculizumab and evaluate its therapeutic efficacy.

Methods

We collected data from two cases of refractory generalized myasthenic crisis patients positive for Acetylcholine Receptor (AChR) antibody. These patients had undergone previous treatments including steroids, intravenous immunoglobulin, plasma exchange, and rituximab, but experienced unsatisfactory outcomes. Eculizumab was added as a treatment option. Clinical classifications, Quantitative Myasthenia Gravis (QMG) scores, Activities of Daily Living (ADL) scores, Myasthenia Gravis Composite (MGC) scores, and ultrasound measurements of diaphragm activity were collected before and after treatment to observe the clinical effects of eculizumab.

Results

Case 1: A 71-year-old man, newly diagnosed with AChR antibody-positive non-thymomatous generalized myasthenia gravis (gMG), presented with dysphagia, dysarthria, ptosis, and respiratory distress worsening over one week. Due to respiratory failure, the patient required intubation and mechanical ventilation. A diagnosis of myasthenic crisis was made, and the patient received intravenous immunoglobulin (IVIG) for 5 days and methylprednisolone 40mg daily. However, there was no significant improvement in symptoms. IVIG was repeated for 5 days starting on Day 28, alongside comprehensive anti-infection and supportive treatment. Methylprednisolone 40-80mg daily was added after infection improvement, but no significant improvement was observed. The patient underwent three sessions of lymphoplasmapheresis, but remained dependent on ventilator support. Eculizumab was initiated on Day 55 as an additional treatment. After receiving two doses of eculizumab (900mg each), the patient's symptoms significantly improved. Successful weaning from mechanical ventilation was achieved, MGFA score decreased from 21 to 2, ADL score decreased from 21 to 0, MGC score decreased from 38 to 0. Ultrasound evaluation showed

an increase in right diaphragm activity from 9mm to 31.67mm.

Case 2: A 37-year-old male patient was diagnosed with WHO type B2 thymoma. The patient had experienced thymoma recurrence in 2018 and 2022, and had undergone chemotherapy twice. In March 2023, the patient presented with right-sided eyelid ptosis, diplopia, limb weakness, dysphagia, and respiratory distress, leading to a diagnosis of generalized myasthenia gravis. Intravenous immunoglobulin (IVIG) and prednisone were administered at doses of 20mg daily, gradually increased to 30mg daily. Tacrolimus was added at a dose of 3mg daily, resulting in some symptom improvement. On April 28th, 2023, the patient's symptoms recurred with eyelid ptosis, limb weakness, difficulty swallowing, and respiratory distress, requiring non-invasive ventilatory support. IVIG was repeated, and methylprednisolone 500mg intravenously was administered for 5 days, followed by a tapering dose of 60mg daily. Tacrolimus was continued at a dose of 3mg daily. The patient experienced mild improvement in symptoms.On May 20th, the patient's condition worsened with increased respiratory distress, inability to lie flat, and difficulty swallowing. Chest CT scan revealed recurrent small right pleural mass. A gastrostomy tube was placed for enteral feeding, and non-invasive ventilatory support was continued. The patient underwent plasmapheresis 5 times, accompanied by methylprednisolone 40mg daily, discontinuation of tacrolimus, and rituximab administration (100mg+500mg) intravenously. However, the patient's symptoms did not significantly improve. From June 8th to June 12th, IVIG was administered for an additional 5 days, resulting in slight improvement. The patient subsequently underwent surgery on June 13th under general anesthesia, involving Video-Assisted Thoracoscopic Surgery (VATS) for thymic tumor resection and right upper lobectomy. While the surgery was successful, the patient's symptoms worsened postoperatively, requiring tracheostomy and three more sessions of plasmapheresis. Despite these interventions, the patient still experienced generalized weakness. Eculizumab was initiated on June 25th. After two doses, some improvement in symptoms was noted, with ADL score decreasing from 21 to 18, MGC score decreasing from 45 to 39, and MGFA score, unfortunately, increasing from 16 to 25. Ultrasound assessment demonstrated an increase in the activity of the right diaphragm from 1.8mm to 12mm.

Conclusion

In these two cases of refractory myasthenic crisis with positive acetylcholine receptor (AChR) antibodies, eculizumab demonstrated some improvements in the patients' conditions. Further investigation is warranted, involving longer observation periods and a larger number of cases, to fully explore the therapeutic effects of eculizumab in patients with myasthenia gravis. Additionally, as the number of immune intervention targets increases, there may be an elevated risk of infection in patients, necessitating long-term follow-up and close monitoring.

Efficacy of multi-course low-dose rituximab treatment in myasthenia gravis: a single-center prospective study

Yufan Zhou[1],Sisi Jing[2],Jun Lu[1],Sushan Luo[1],Lei Zhou[1],Jie Song[1],Chong Yan[1],Xiao Huan[1],Chongbo Zhao[1],Jianying Xi[1]

1. Huashan Hospital, Fudan University

2. Banan Hospital, Chongqing Medical University

Introduction: The study aims to investigate the efficacy of multi-course low-dose rituximab (RTX) treatment in myasthenia gravis (MG).

Methods: The prospective observational study included a total of 93 MG patients who visited Huashan Hospital from June 2015 to June 2023 and received 600 mg RTX every 6 months. The severity of clinical symptoms was assessed at baseline and every 6 months after RTX treatment, using quantitative myasthenia gravis (QMG) and MG-Related activities of daily living (MG-ADL). Clinical response was defined as a decrease in QMG score by ≥ 3 points within 6 months after each medication. The proportion of patients with clinical response, the time to achieve the minimal symptom expression (MSE, measured by an ADL score of 0 or 1) and the number of treatment courses, the last follow-up time and the time of recurrence after drug withdrawal were recorded.

Results: The follow-up period was 6-40 months. Of the 55 patients with positive anti-acetylcholine receptor (AChR) antibody, 16/55 (29.1%) achieved MSE after single RTX treatment, 7/29 (24.1%) achieved MSE after two courses of RTX, 5/14 (35.7%) achieved MSE after three courses of treatment, and 1/5 (20%) achieved MSE after four courses of treatment. Among the 38 patients with positive anti-muscle-specific tyrosine kinase (MuSK) antibody, 26/38 (68.4 %) achieved MSE after single RTX treatment, 4/10 (40%) achieved MSE after two courses of RTX, 1/7 (14.3 %) achieved MSE after three courses of treatment, and 1/3 (33.3% achieved MSE after four courses of treatment. The median time to MSE was 15 months and 6 months for AChR-MG and MuSK-MG, respectively ($p<0.001$). The overall rates of achieving MSE were 52.7% (29/55) and 84.2% (32/38), respectively. Of the 93 patients, 5 were lost to follow-up, and 20 (21.5%, 18 AChR-MG, 2 MuSK-MG) had a QMG score decrease of < 3 points or no decrease after single RTX treatment. Among the 20 patients who did not respond to single RTX, 4/20 patients withdrew from the study, 6/16 patients were followed up for less than 12 months, 2/16 patients were lost to follow-up, 5/16 patients had a QMG score of ≥ 3 points lower than the baseline or single treatment after two courses of treatment, 2/16 patients who did not respond in two courses of RTX finally had a QMG score decrease of ≥ 3 points after three courses of treatment, and 1/16 patients did not respond to three courses of treatment. Among the 16 AChR-MG patients who did not relapse after discontinuation, the longest duration of remission was 74 months. After discontinuation of RTX, most of the patients were treated with immunosuppressive agents, including prednisone

(average daily dose of 2.5 ~ 20 mg), azathioprine and tacrolimus. And four patients relapsed, of which two relapsed after asymptomatic. The longest duration of remission was 47 months in 21 cases of MuSK-MG after discontinuation of RTX. After discontinuation of RTX, most patients had no immunotherapy, and a total of seven patients relapsed, including four patients relapsed after asymptomatic.

Conclusion: Most refractory MG patients can achieve MSE after multi-course low-dose RTX treatment. Patients with poor response after single RTX treatment can still benefit further in the subsequent course of treatment. Most MuSK-MG patients can maintain asymptomatic for a long time without immunotherapy after discontinuation of RTX, while AChR-MG still needs traditional immunosuppressive therapy.

A musk antibody-positive generalized myasthenia gravis refractory to rituximab but effective to ofatumumab therapy: case report and literature review

Chong Yan,Yufan Zhou,Yan Wang,Dingxian He,Chongbo Zhao,Jianying Xi
Huashan Hospital

Objective: This study aims to report the distinct therapeutic responses of musk antibody-positive refractory myasthenia gravis by receiving rituximab and ofatumumab, and investigate the underlying mechanism.

Method: We reported the demographic information, labortary examiniation, therapy procedure, clinical scores, antibody titers, peripheral blood B cell profile, and FCGR3A genetic polymorphisms in detail. The reported cases and potential mechanism of ineffectiveness to rituximab were reviewed.

Results: A 63-year-old male presented with diplopia, ptosis, difficulty in swallowing and speaking. Low frequency repetitive nerve stimulation was positive, and thymus scan was unremarkable. He was diagnosed as MuSK antibody-positive myasthenia gravis (MG). After receiving adequate therapeutic course of steroids and pyristigmine, he worsened and required rescue therapy. Then, he was given three cycles of low dose-rituximab administration (100mg D1+500mg D2) within one year (September 2021, March 2022, July 2022). However, the ADL score changed from 10 to 11, and QMG score increased from baseline 16 to 20. During the rituximab treatment, he underwent three courses of plasma exchange and intravenous immunoglubumin to prevent acute exacerbation. In November 2022, we found a remaining group of CD19+CD20+B lymphocytes in his peripheral blood (0.32% in lymphocytes) and his FCGR3A V158F polymorphism. He subsquently was administrated with ofatumumab 20mg qw for 4 weeks. In the following 6 months, he showed remarkable improvement, as both ADL and QMG score reduced to 3, and the percentage of peripheral blood CD19+CD20+B lymphocytes reduced to 0.076%.

Conclusion: This essay reported a musk antibody-positive generalized myasthenia gravis refractory to rituximab but effective to ofatumumab therapy. A subgroup of CD19+CD20+ B lymphocytes escaped from the clearance of rituximab and could be deleted by ofatunumab, which might be one explanation for rituximab-refractory MG. This study supplemented the pathogenic mechanism of MuSK antibodies-positive MG.

Clinical Outcome And Peripheral Immune In Myasthenic Crisis With COVID-19: A Case Series

Xiao Huan,Manqiqige Su,Huahua Zhong,Rui Zhao,Jianying Xi,Sushan Luo,Chongbo Zhao
HUASHAN HOSPITAL

OBJECTIVE: COVID-19 infection increases the risk of new-onset MG, myasthenic crisis, and mortality due to cytokine storm in MG patients. Meanwhile, moderate-to-severe myasthenia gravis, long-term steroid use, and old age are risk factors for severe COVID-19, which may contribute to each other. And myasthenic crisis (MC), a life-threatening state that occurs when myasthenia gravis rapidly deteriorates, is a major clinical challenge. The present study was designed to investigate the clinical outcome and peripheral immune characteristics of myasthenic crisis combined with SARS- CoV-2 infection.

Methods: Patients with myasthenic crisis at Huashan Hospital of Fudan University were prospectively collected during the SARS-CoV-2 pandemic in Shanghai, China, during December 2022-January 2023 and May-June 2023, and were divided into the group of MC with COVID-19 infection (CMC) and the group of MC without COVID-19 infection (non-CMC). The basic clinical characteristics (demographic information, initial MGFA typing, disease duration, comorbidities, triggers, MG antibody type and titer, and treatment during the crisis period), hospitalization outcomes (days of mechanical ventilation, days in ICU, days of hospitalization, and mortality rate), and peripheral immune characteristics (hematology, T，B lymphocyte subpopulations, and cytokines) were observed in these patients.

RESULTS: A total of 11 cases of myasthenic crisis with COVID-19 infection and 9 cases without COVID-19 infection were included. The cases of CMC were predominantly female (7/11,63.6%), aged 49.09±21.68(20-75) years old, with the most TAMG (5/11,45.5%), 3 each of LOMG and EOMG. The duration of the group was 74.41±80.89(1.8-261.6) months. All of them had AChR antibodies with titres of 56.04±67.72(1.77-162.8) nmol/l (ELISA). All were treated with steroid, PLEX in 7 cases and IVIG in 8 cases during the critical phase. The vast majority (8/11,72.7%) were combined with bacterial infections of defined pathogens. In terms of hospitalization outcome, the CMC group had 16.2±18.47(3-66) days of mechanical ventilation, 20.8±17.61(4-67) days in ICU, 28.2±17.52(8-70) days in hospital, and the mortality was 0, which was not statistically different from that of Non-CMC. Regarding peripheral immunity, CMC had a significantly higher proportion of abnormal IL-6 (90% vs 33%,p=0.0357), a significantly higher proportion of CD8+T (41.11±12.11[16.5-55.05]% vs 23.3±5.64[18.5-31.09]%, p=0.0336), and a significantly higher proportion of activated CD4+T (CD38+CD4+T) (41.11±12.11 [16.5-55.05] % vs 23.3±5.64 [18.5-31.09] %, p=0.0336), and Treg percentage was significantly higher (11.89±3.053 [7.95-17.6] % vs 6.695±4.275 [4.02- 15.2]%,p=0.0293), while the absolute value of the neutrophils, lymphocytes,

monocytes, the neutrophil-lymphoid ratio, as well as the proportion of total CD4+ T and other subpopulations, B cells, and NK cells were not statistically different from that of the Non-CMC group.

CONCLUSION: During the SARS-CoV-2 epidemic, in which omicron is the predominant variant, the clinical outcome of myasthenic crisis with COVID-19 infection is not inferior to that of without COVID-19 infection. However, CMC had significantly elevated peripheral IL-6, CD8+T, CD4+T, and Treg, showing stronger immune-inflammatory responses and self-stabilization. However, this study has some limitations due to the small sample size this study.

Not only adaptive immune cells, but innate immune cell populations are markedly dysregulated in myasthenia gravis

Rui Fan,Wenjun Que,Zhuoting Liu,Wei Zheng,Xia Guo,Linqi Liu,Fei Xiao
The First Affiliated Hospital of Chongqing Medical University

Introduction: The pathogenesis and progression of myasthenia gravis (MG), an autoimmune disease, involve abnormal function and composition of several immune cell populations. However, details of this dysregulation remain unclear.

Methods: We performed a cross-section analysis using cytometry time-of-flight on blood samples from 12 generalized MG without glucocorticoid or other immunosuppressant treatment, and 10 sex- and age-matched healthy controls. Combining data from an external validation cohort (MG n = 38, control n = 21), bulk-RNA sequencing and single-cell RNA sequencing, alterations in immune cell populations and differential expression of immune check point were revealed.

Results: Several switched memory B cell subsets (CD3- CD19+ CD27+ IgD- CD38+/−) were increased in MG patients. Classical T cell subsets showed no significant change; however, the expression of VISTA, LAG3, CTLA4, and CXCR5 was higher in T cells from MG patients. Interestingly, we found that the innate immune cell population showed more significant alteration than the adaptive immune cell population. the number of CD56+ CD16+ NK cells and CD56+ CD16+ CD8+ NK cells were decreased in MG patients and positively correlated with QMG. VISTA+ monocytes were increased in MG patients. The expression of CD38 was higher in neutrophils from MG patients. The external validation cohort validated the dysregulation of NK cell subtypes, and differences were also observed in subgroups of patients. Bulk-RNA sequencing also revealed increased mRNA expression of VSIR in monocytes of MG patients compared to those from healthy controls, and the antigen presentation and processing pathway was identified as enriched in the functional characterization of VISTA+ monocytes via single-cell RNA sequencing.

Conclusion: Our study revealed alterations in several immune cell subsets and identified potential cellular biomarkers for MG diagnosis and disease severity assessment. In addition, the abnormal expression of multiple immune checkpoints in MG provides further rationale for the investigation of immune-checkpoint-related therapy.

Changes and Potential Regulatory Mechanism of NK cells in Patients with Myasthenia Gravis

Qing Zhang,Bitao Bu
Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Introduction: Emerging evidence has identified natural killer (NK) cells have an immunoregulatory function in myasthenia gravis (MG). In this study, we identified the changes in NK-cell phenotypes and functions with MG severity, and explored the involved possible mechanism.

Methods: 58 MG patients not accepted glucocorticoids or other immunosuppressants were collected. NK-cell killing activity was measured after NK cells co-incubated with K562 cell line. CD4+ T cells and NK cells were isolated by a flow cytometry cell sorter MoFlo XDP. NK cells were further sequenced by BGISEQ sequencing platform with high throughput.

Results: The severity of MG was negatively correlated with the percentages of NK cells, CD56dimCD16+ NK cells and IFN-γ+ NK cells, but positively correlated with plasma IL-21. The proportions of living NK cells reduced while the late apoptotic/necrotic cells NK cells increased in co-cultures with autoreactive CD4+T cells. After using IL-21 receptor to competitively inhibit the activity of IL-21, the proportions of living NK cells increased while the late apoptotic/necrotic cells decreased. 27 up-regulated genes and 4 down-regulated genes were detected by mRNA-seq in MGFA Ⅰ Ⅰ -V group compared with MGFA Ⅰ group. GO and KEGG pathway analysis showed that differential genes were mainly enriched in the IgA immunoglobulin complex, neutrophil aggregation, TLR4 binding, and IL-17 signaling pathway.

Conclusion: NK cells, CD56dimCD16+ NK cells, IFN-γ+ NK cells, and plasma IL-21 can be used as indicators to evaluate the severity of MG disease. IL-21 produced by autoreactive CD4+ T cells can mediate NK-cell depletion in vitro. Inhibition of IL-21 signal pathway and recovery of NK-cell ability to inhibit autoimmunity may be a new direction in the treatment of MG. Key genes and related pathways that may regulate the depletion of NK cells in MG patients provide new clues for the treatment of MG based on NK cells.

Validation of EGRIS score in Iraqi patients during COVID-19 pandemic

Mustafa Shahni
Diwaniyah teaching hospital

Background: Guillain-Barre syndrome (GBS) is an acute flaccid paralysis due to autoimmunity, characterized by progressive weakness and areflexia, reaching plateau within 4 weeks with variable severity, disease course, clinical variants and outcome. As an auto-reactive disease, its incidence increases after pandemics of infections. Patients with GBS had a high risk of developing acute respiratory insufficiency and may need ventilatory support. Because respiratory failure in GBS is unpredictably progress without traditional warning signs of respiratory compromise, early recognition is of paramount importance.

Methods: we prospectively followed 73 GBS patients at 2 major hospitals in Baghdad/Iraq (medical city complex and Saad Al Witry hospital for neurosciences) between (20th July 2020 to 20th of January 2022).

Results: total patients were 73, (50 (68.5%) males vs 23 (31.5%) females). Of them, 49 (67.1%) were COVID-19 positive. Mean age was 45.7 (+/- 18.0) years. Forty patients had facial or bulbar involvement but only 22 patients (30.1%) required mechanical ventilation. MV patients scored higher on EGRIS score with statistical significance (4.68 ± 1.61 vs 2.98 ± 1.39; $p < 0.001$). Area under ROC curve was 0.80. COVID-19 state had no effect on EGRIS score.

Conclusion: EGRIS is clinically useful prediction tool and can guide management plans during infectious emergency situations where health systems may be exhausted.

The Value of Muscle Thickness of Lower Limbs in Detection of Diabetic Peripheral Neuropathy

Abdulnasir Ameer
University of Baghdad\ College of Medicine

Background: Neuropathy stands out as the highest-prevalence diabetes-related complication, impacting no less than 50% of individuals with diabetes throughout their lifespan. As The most common reason for disability due to walking difficulties, foot ulcerations, and limb loss, DPN is worthy of study, and early diagnosis of DPN signs is required.

Objectives: This study aims to aid in the identification of diabetic peripheral neuropathy (DPN) by determining the muscle thickness of the lower extremities in patients with DPN.

Patients and Methods: The study included 24 subjects with diabetic peripheral neuropathy (DPN) and 25 individuals as a control group, subdivided into 8 diabetic patients without DPN and 17 healthy individuals. Both control and DPN subjects underwent bilateral peroneal and tibial motor nerve conduction studies (NCS) and high-resolution muscle ultrasounds to measure muscle thickness. Abductor hallucis muscle (AH), extensor digitorum brevis muscle (EDB), extensor hallucis longus muscle (EHL), tibialis anterior muscle (TA), and rectus femoris muscle (RF) were evaluated on both sides using ultrasound.

Results: Comparing the tested muscles to the control group, the study revealed a statistically significant decrease in the thickness of many of the muscles being tested when compared to the control group.

Conclusions: These findings point to the possibility that quantitative muscle ultrasound could be beneficial in identifying muscle changes associated with DPN. It is necessary to conduct additional studies to verify the results in larger samples of diabetic patients.

Acute-onset Chronic Inflammatory Demylinating Polyradiculoneuropathy With Autonomic Nerve Damage And Facial Palsy: a case report and literature review

hai chen,Yuwei Da,Min Wang,Yan Lu,Suobin Wang,Li Di
Xuanwu Hospital Capital Medical University

Background: Diagnosis and treatment of acute-onset chronic inflammatory demyelinating polyradiculoneuropathy (A-CIDP) may be a challenge in early stage.

Case presentation: We report a Chinese case of a 25-year-old man with weakness and numbness in his bilateral limbs for 10 months. He presented with numbness and weakness in his lower limbs. After three days, the patient presented with fatigue, walking difficulty, bilateral limbs numbness, upper extremities weakness and drink cough, accompanied with nausea which could be relieved by vomiting and bilateral facial palsy. He was diagnosed with Guillain-Barré syndrome (GBS). He was treated with methylprednisone and tapered. His symptoms were improvement. The weakness of bilateral lower limbs aggravated after sevral days. He was given intravenous immunoglobulin and the symptoms of weakness and numbness were improved. Three months later, the numbness in bilateral limbs worsened and he developed walking difficulty with step-on-cotton feeling. Cerebrospinal fluid revealed light yellow coloration, elevated opening pressure (220mmH2O), elevated protein (308mg/dl). We diagosed him as acute-onset chronic inflammatory demyelinating polyradiculoneuropathy (A-CIDP) and treated him with glucocorticoids long time. His symptoms was totally improved.

Conclusions: We conclude that A-CIDP can exist autonomic and cranial symptoms and suggest that A-CIDP should be early distinguish from GBS with maintenance treatment.

Clinical, genetic characteristics and follow-up in 14 patients with transthyretin familial amyloid polyneuropathy

Haoran Liu,Yanan Sun,Min Xu,Hai Chen,Li Di,Jianying Duo,Yuwei Da
Xuanwu Hospital, Capital Medical University

Introduction The clinical and genetic profiles of transthyretin familial amyloid polyneuropathy (TTR-FAP) remain elusive in mainland China. We aim to the summarize the genotypes and phenotypes of TTR-FAP in a Chinese cohort.
Methods Fourteen unrelated TTR-FAP patients diagnosed at Xuanwu Hospital, Capital Medical University from September 2014 to February 2022 were retrospectively reviewed. The clinical manifestation, electrophysiology, cardiac function, biopsy and gene mutation were analyzed.
Results In the 14 patients (13 males, 1 female) diagnosed as TTR-FAP, the mean age at onset was 53.9 years (range: 33.0-71.0 years), with a mean course from symptom-onset to diagnosis of 4.1 years. The late-onset type occurred in 9 cases. Seven patients had a family history of TTR-FAP. Distal paresthesia of lower limbs was the commonest initial symptom (8 cases), with sensorimotor neuropathy and autonomic dysfunction seen initially in 4 and 2 cases, respectively. Cardiac involvement occurred in 6/8 of the patients. Nerve conduction studies indicated extremely axonal impairment with demyelinating features. Sural nerve biopsies showed moderate to severe axonal loss of myelinated fibers and the positive rate of Congo red staining was 8/14. Of 8 different TTR mutations detected, V50M was the most common (appearing in 5 cases). No obvious neuropathy progression was seen in the 5 patients who received tafamidis and 2 patients died of dyscrasia.
Conclusion TTR-FAP is more common in males, with sensorimotor axonal polyneuropathy, autonomic dysfunction and cardiac subclinical damage as the predominant symptoms. V50M is the commonest mutation. Tafamidis can delay the progression of disability.

Characteristics and Clinical Course Forms of Refractory CIDP: Insights from a Comprehensive Study

Yongsheng Zheng,Jie Lin,chong Sun,Chongbo Zhao
Fudan University Huashan Hospital Department of Neurology

Objective: The objective of this study was to describe the clinical presentation, disease course form, laboratory and electrophysiological characteristics, and potential risk factors associated with refractory chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods: The study utilized data from the Huashan Peripheral Neuropathy Database, which included patients with suspected CIDP. The clinical features, disease duration, treatment response, laboratory investigations, and electrophysiological findings were analyzed. Patients were categorized into refractory CIDP and non-refractory CIDP groups based on treatment response.

Results: 58 patients with CIDP were analyzed (32 refractory CIDP, 26 non-refractory CIDP). Refractory CIDP patients showed more severe functional impairment, longer disease duration, and a higher proportion of CIDP variants compared to non-refractory CIDP patients. Motor nerve conduction studies revealed more severe axonal impairment and demyelination in refractory CIDP. The clinical course forms of refractory CIDP included relapsing-remitting, stable, and progressive forms. Multivariate logistic regression analysis identified follow-up duration, INCAT score, ulnar nerve compound muscle action potential, ulnar nerve distal motor latency, median nerve distal motor latency, and sural nerve conduction velocity as prognostic factors for evolving to refractory CIDP.

Conclusion: This study provides a comprehensive description of refractory CIDP, highlighting its clinical features, electrophysiological characteristics, and prognostic factors. The findings contribute to a better understanding of this challenging subset of CIDP and can inform management and treatment strategies.

Efficacy of hematopoietic stem cell transplantation treatment in refractory chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review and meta-analysis

Yongsheng Zheng,Jie Lin,jianian Hu,chong Sun,Chongbo Zhao,Jie Lin
Fudan University Huashan Hospital Department of Neurology

Introduction: Treatment options for chronic inflammatory demyelinating polyneuropathy (CIDP) are intravenous immunoglobulin (IVIg), plasmapheresis (PE), corticosteroids and immunosuppressive drugs. However, a substantial proportion of patients with CIDP remain refractory to treatment and develop severe functional disability. We performed a systematic review and a meta-analysis of the efficacy of hematopoietic stem cell transplantation (HSCT) treatment in refractory CIDP patients.

Methods: Through queries in PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Web of science and clinicaltrials.gov databases on 4 December 2022. Articles that met our eligibility criteria were included after screening. Patients' characteristics, treatment regime and outcome measure were extracted.

Results: Eighty-nine patients in 11 studies were included. The pooled estimate of responsiveness among the four included studies was 87.04% (95% CI 66.7–99.5%) and the pooled estimate of freedom of all immune modulating or suppressive drugs was 80.75% (95% CI 71.2–90.2%).

Conclusion: This meta-analysis and systematic review suggested that HSCT can be effective in the treatment of refractory CIDP. While there are risks involved, HSCT may be a beneficial and viable therapy for refractory CIDP when carefully evaluated.

Efficacy and safety of patisiran for ATTR-PN: a systematic review and meta-analysis

Xinyue Huang,Chong Sun,Haofeng Chen,Chongbo Zhao,Jie Lin
Huashan Hospital, Fudan University, Shanghai, China

Background: Transthyretin amyloid polyneuropathy (ATTR-PN) is a rare, progressive and fatal autosomal dominant disorder. Therapies such as liver transplantation and TTR stabilizations have some limitations and unsatisfactory curative outcomes. Patisiran is a small interfering RNA (siRNA) that provides a potential breakthrough in therapy for ATTR-PN at the genetic level. However, the current findings on the efficacy and safety of patisiran for ATTR-PN are still limited.

Objectives: This study aimed to further clarify the efficacy and safety of patisiran for ATTR-PN by meta-analysis.

Methods: After English literature searches in PubMed, Ovid MEDLINE, Embase, JBI EBP, Cochrane and ClinicalTrials.gov databases on June 7, 2023, 10 studies with 463 patients were included and data including the first author, publication year, age, gender, treatment regimen and disease conditions were extracted.

Results: The results illustrated a statistically significant improvement in mNIS+7 scores, with a standardized mean difference (SMD) of -0.18 (95% CI -0.32 – -0.03) and a p-value 0.018, and in Norfolk QOL‐DN, with a standardized mean difference (SMD) of -0.23 (95% CI -0.38 – -0.09) and a p-value 0.001. Eight studies with 447 patients recorded 404 adverse events (AEs) (90.4%), 152 serious AEs (SAEs) (34.0%) and 33 deaths (7.4%). Most of the adverse events (AEs) were mild to moderate which may interfere but not prevent daily activities. None of the deaths were considered related to patisiran. The most common death cause were cardiovascular events.

Conclusion: In conclusion, patisiran was effective and safe for ATTR-PN patients in our meta-analysis. More large-scale clinical trials and long-term studies are needed to further clarify the efficacy and safety of patisiran for ATTR-PN.

An anti-caspr1 antibody positive autoimmune Ranvier's node disease combined with myasthenia gravis

Quantao Zeng,Kai Chen,Jie Yang,Song Tan
Sichuan Provincial People's Hospital

Ranvier's node is an important structure of myelinated nerve fibers, which enables the "hopping" information transmission on axons in the central and peripheral nervous system. Currently, Ranvier's node is divided into three regions: nodal region, paranodal region, and near-paranodal region. Anti-caspr1 antibody acts on the paranodal region and disrupts the axial glial interaction.
In this case, a 53-year-old patient presented with progressive limb numbness and unstable walking. Subsequent development of cranial nerve damage combined with poor response to traditional anti-immunotherapy such as immunoglobulin and high-dose glucocorticoid led us to the final diagnosis of autoimmune Ranvier's node disease. So 8 times of protein A immunoadsorption and 4 times of ofatumumab were administered, and the patient was intermittently treated with 3 times of dupilumab for eczema during the treatment period. After these treatments, the patient's INCAT score decreased from 6 to 4, but then he developed significant facial muscle weakness, ptosis, dysphagia, cervical flexor weakness and obvious fatigue intolerance. The patient's neostigmine test was positive. We performed serum antibodies associated with MG and it showed AchR antibody 1:320. The appearance of MG was considered to be caused by immune drift due to the patient's multiple monoclonal antibody use. Then protein A immunoadsorption treatment was performed again 5 times on alternate days, and later we retested the serum anti-AchR and anti-Caspr1 antibodies negative. The patient was finailly discharged with an INCAT score 2 and had no clinical manifestations of MG.
This case highlights the importance of differentiating autoimmune Ranvier's node disease from CIDP, especially in cases with poor therapy response to glucocorticoid and immunoglobulin. We should also pay attention to the risk of immune drift inducing new immune diseases in the course of anti-immunotherapy.

Quantitative Muscle Ultrasound as a Disease Biomarker in Hereditary Transthyretin Amyloidosis with Polyneuropathy

Cheng Yin Tan,Siew Yin Tan,Mohd Azly Yahya,Nortina Shahrizaila,Khean Jin Goh
University of Malaya

Introduction: There is an increasing need for a reproducible and sensitive outcome measures for Hereditary Transthyretin Amyloidosis (ATTRv) with polyneuropathy (PN) due to the emergence of disease modifying therapies. In the current study, we aimed to investigate the role of quantitative muscle ultrasound (QMUS) as a disease biomarker in ATTRv-PN.

Methods: 20 genetically confirmed ATTRv amyloidosis patients (9 symptomatic, 11 pre-symptomatic) were enrolled prospectively between January to March 2023. Muscle ultrasound was performed on six muscles at standardized locations. QMUS parameters included muscle thickness (MT) and muscle echo intensity (EI). 25 age- and sex-matched healthy controls were recruited for comparison. Significant QMUS parameters were correlated with clinical outcome measures.

Results: Muscle volume of first dorsal interosseus (FDI) muscle [measured as cross-sectional area (CSA)] was significantly lower in symptomatic patients compared to healthy controls and pre-symptomatic carriers (98.3±58.0 vs 184.4±42.5 vs 198.3±56.8, p<0.001). EI of biceps and FDI for symptomatic ATTRv-PN patients were significantly higher compared to the other two groups (biceps: 76.4±10.8 vs 63.2±11.5 vs 59.2±9.0, p=0.002; FDI: 48.2±7.5 vs 38.8±7.5 vs 33.0±5.3, p<0.001). CSA of FDI and EI of biceps and FDI correlated with previous validated outcome measures [Polyneuropathy Disability score, Neuropathy Impairment Score, Karnofsky Performance Scale, Rasch-built Overall Disability Scale, European Quality of Life (QoL)-5 Dimensions and Norfolk QoL Questionnaire - Diabetic Neuropathy].

Conclusion: QMUS revealed significant difference between ATTRv amyloidosis patients and healthy controls, and showed strong correlation with clinical outcome measures. QMUS serves as a sensitive and reliable imaging biomarker of disease severity in ATTRv-PN.

A real-world study of tacrolimus in maintenance treatment of CIDP

Li Di,Hai Chen,Yuwei Da
Xuanwu Hospital Capital Medical University

Objective: To evaluate the efficacy and safety of tacrolimus in immune maintenance therapy of patients with CIDP

Methods: We retrospectively analyzed patients enrolled in the CIDP database of Xuanwu Hospital of Capital Medical University from January 2020 to December 2022, including INCAT score, recurrence (INCAT score worsening by more than 1 point) and the use of immunotherapy drugs at baseline, 3 and 6 months follow-up and side effects.

Result: From January 2020 to December 2022, a total of 74 cases were included in the CIDP database of Xuanwu Hospital, Capital Medical University. Forty cases were excluded from the present study for the following reasons: autoimmune nodopathies (n=27), accompanied by MGUS (n=4), incomplete follow-up data (n=4), and INCAT score≤1 point (n=5). A total of 34 CIDP patients completed two follow-up visits at 3 and 6 months, 25 males and 9 females. The mean age was 48 (16-75) and the mean duration of disease was 36 months (2-229 months). Twenty-three patients received steroid therapy and 11 patients received IVIg for induce remission. Maintenance treatment phase steroid monotherapy in 18 cases, tacrolimus + steroid group in 16 cases. There were no significant differences in age, gender, duration of disease and adjusted Inflammatory Neuropathy Cause and Treatment score (INCAT) at baseline among all groups. There was no significant difference in the proportion of patients treated with steroid or IVIg in the induced remission period. At 3 months, the proportion of INCAT score improvement ≥1 point was 55.6% (10/18) in the steroid group and 75.0% (12/16) in the tacrolimus + steroid group (P=0.029). At 6 months, the proportion of INCAT score improvement ≥1 point was 66.7% (12/18) in the steroid group and 81.3% (13/16) in the tacrolimus + steroid group (P=0.035). After 6 months of follow-up, 6/18 patients (33.3%) in the steroid therapy group and 2/16 patients (12.5%) in the tacrolimus + steroid group had relapse. There was a statistical difference in the relapse rate between the two groups (P=0.021). The mean daily steroid dose during 6 months was 30.1±23.3mg/d in the steroid therapy group and 10.5±9.3mg/d in the tacrolimus + steroid group. A total of 32 adverse events were reported in the two groups, including 15 in the steroid group, 17 in the tacrolimus + steroid group. Two cases had elevated serum creatinine in the tacrolimus + steroid group, and 1 case had osteonecrosis of the femoral head in the steroid group. Both groups experienced hyperglycemia, the incidence rate in the tacrolimus + steroid group was higher than that in the steroid group, and no serious adverse reactions occurred under drug control.

Conclusions: Tacrolimus + steroid therapy improved symptoms in CIDP patients better than steroid therapy alone, and reduced the risk of relapse and steroid use dose within 6 months.

Chronic inflammatory demyelinating polyradiculoneuropathy concomitant with nephropathy

Nan Hu[1],Jingwen Niu[2],Mingsheng Liu[2]
1. Peking Union Medical College Hospital

Objective: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is one of the most common autoimmune peripheral neuropathies in adults. Membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS), and other nephropathy have been reported in CIDP patients and are possibly correlated to CIDP pathogenesis. This study reviewed the previously described cases of patients with CIDP and nephropathy in order to provide comprehensive evidence on the diagnosis and treatment regarding CIDP patients in the context of renal diseases.
Method: We reviewed our database to identify patients with CIDP and nephropathy. Online database including PubMed, EMBASE, and OVID were searched for relevant cases.
Results: We identified a total of 18 cases with CIDP and nephropathy, including 2 cases from our database and 16 ones from online searching. A predominance of male was observed [14 (77.8%)] with the mean age of 53.3 (standard deviation, SD: 16.6) years old. Almost all patients complained paresthesia in distal limbs (94.4%), except one only presented weakness of four extremities. Corticosteroids were prescribed for 14 (77.8%) patients, and 10 showed responsiveness. Three patients experienced relapses during the gradual tapering of steroids.
Conclusion: The same immune-mediated pathogenesis may be involved in CIDP and concomitant nephropathy. Male and sensory-predominant CIDP are red flags for complications of renal diseases in CIDP patients. Corticosteroids remain the first-line treatment for CIDP when complicated with renal diseases. Slower tapering or long-term maintenance of steroids may be beneficial for the prognosis of patients with CIDP and nephropathy.

The diagnosis and treatment of a case of paederus dermatitis and the characteristics of its nerve damage

Zhiru Qiu1,Shaoping Wang2,Junjie Wang2,Xiaoyan Zhang2,Wenshu Zhang2
1. Zhengzhou First People's Hospital

Objective To summarize the characteristics of nerve damage in the neurological complication of paederus dermatitis.

Methords One patient diagnosed with paederus dermatitis in our hospital was followed up.The results of EMG were analyzed and the characteristics of nerve damage were summarized, combined with the prognosis of the patient .

Results 1. The distribution of nerve damage was related to the location of the dermatitis. Both sensory and motor nerves near the lesion can be involved. 2.The acute stage of nerve damage in paederus dermatitis is characterized by demyelination with axonal loss, but demyelinating damage was the main.

Conclusion Complication of nerve damaged in paederus dermatitis, with early detection、early diagnosis and early treatment, the patient can have a good prognosis.

Long-term follow-up of relapse and remission of chronic inflammatory demyelinating polyradiculoneuropathy after immune treatment in a Chinese cohort

Jingwen Niu,Liying Cui,Mingsheng Liu
Peking Union Medical College Hospital

Introduction: We aim to describe the long-term outcome of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) after immune treatment in a Chinese cohort.

Methods: Between March 2015 and March 2023, 89 patients fulfilling the criteria for CIDP were followed up for a median of 22 months after treatment. Nine had positive antibodies against nodal-paranodal cell-adhesion molecules. Patients were treated according to clinical requirements with prednisone, intravenous immunoglobulin (IVIg), and/or immunosuppressant.

Results: A total of 78/89 patients had decreased inflammatory neuropathy cause and treatment (INCAT) scores at the last follow-up. For CIDP patients treated with steroids, 35 were stable without relapse after cessation or with a small maintenance dose; two relapsed at a high dose (20 mg/d); 15 relapsed at a low dosage (<20 mg/d); and 11 didn't respond. The INCAT before treatment was significantly lower in those without relapse (median INCAT 2 vs 3, P=0.030). The percentage of relapse was higher in Lewis Sumner syndrome (LSS) and lower in distal or pure motor CIDP than in typical CIDP, without statistical significance. IVIg was effective in 37/52 CIDP patients. Twenty-eightCIDP patients and 4 autoimmune nodopathy patients were treated with immunosuppressants. The average INCAT was 3.3±1.9 before and1.9±1.3 after immunosuppressant treatment (P=0.001) in CIDP.

Discussion: The long-term prognosis of CIDP patients was generally favorable. The risk of relapse was higher in those with high INCAT and LSS and lower in those with a short disease duration when treated and distal and pure motor CIDP. We recommend slowly tapering prednisone over 2 years.

The distribution pattern of nerve enlargement in different clinical subtypes of CIDP

Jingwen Niu,Liying Cui,Mingsheng Liu
Peking Union Medical College Hospital

Backgrounds: We aim to investigate nerve enlargement patterns and their correlation with clinical subtypes and treatment response using multiple-site ultrasonographic measurements in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Methods: Between March 2015 and December 2021, 135 patients with CIDP were recruited. Nerve ultrasound and electrophysiological studies were performed on the median and ulnar nerves. The responses to immunoglobulin (IVIG) or prednisone were evaluated with the inflammatory neuropathy cause and treatment (INCAT) disability score.

Results: There were 99 typical CIDP, 10 Lewis-Sumner syndrome (LSS), 15 distal acquired demyelinating symmetric neuropathy (DADS), 9 pure motor CIDP, and 2 pure sensory CIDP. Sixty (61%) typical CIDP and 7 (78%) pure motor CIDP had moderately increased or normal CSA, and 10 (67%) DADS and 7 (70%) LSS had significantly increased CSA. The peripheral nerve showed a diffuseenlargement pattern in 46 (51%) typical CIDP, 5 (50%) LSS, 3 (25%) DADS, and 3 (33%) pure motor CIDP and a proximal regional enlargement pattern in 11 (12%) typical CIDP, 1 (10%) LSS, 6 (50%) DADS, and 4 (44%) pure motor CIDP patients. Patients with diffusely moderate enlargement patterns and those with proximal regional enlargement showed a higher response rate to glucocorticoidsthan to IVIG.

Conclusions: Various distribution patterns of nerve enlargement existed in CIDP. Although almost all patterns could be detected in each CIDP subtype, diffusely moderate enlargement was more common in typical CIDP and LSS, while proximal regional enlargement was more common in DADS and pure motor CIDP. Different enlargement patterns might indicate different treatment responses.

Nerve ultrasound performances in differentiating POEMS syndrome from CIDP

Jingwen Niu,Qingyun Ding,Liying Cui,Mingsheng Liu
Peking Union Medical College Hospital

Background and Objective:
Chronic inflammatory demyelinating polyneuropathy (CIDP) and polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome are both acquired demyelinating polyneuropathies. The aim of our study was to explore the different features of ultrasonographic changes between CIDP and POEMS syndrome.
Methods:
Nerve ultrasonographic studies were performed in 120 patients with CIDP and 34 patients with POEMS syndrome. Cross sectional areas (CSAs) were measured on the bilateral median, ulnar nerves and brachial plexus. Nerve conduction studies (NCS) were performed on median and ulnar nerves to detect motor conduction blocks (CB).
Results:
CSAs at all sites were larger in patients with CIDP and POEMS syndrome than in healthy controls. Maximal CSA [median, (min to max)] was 14 (6-194) for median nerve, 9(4-92) for ulnar nerve, 14(7-199) for brachial plexus in CIDP, and 11(8-16) for median nerve, 8.5(6-13) for ulnar nerve, 14(10-20) for brachial plexus in POEMS syndrome. The ratio of maximum/minimum CSA of the median nerve was significantly larger in CIDP (2.8±2.8) than in POEMS syndrome (1.7±0.3). The percentage of patients with markedly enlarged CSA was significantly higher in CIDP than in POEMS syndrome (27.5% vs 8.8%, P=0.023). CBs or probable CBs were detected in 60 out of 120 CIDP patients but in none of the POEMS syndromes. For distinguishing CIDP and POEMS syndrome, a two-step protocol using CB and maximum/minimum CSA of the median nerve yields a sensitivity of 93% and a specificity of 79%.
Conclusions:
Compared with CIDP, nerve CSA enlargement was more homogeneous along the same nerve in individual POEMS patients, as well as among different POEMS patients. The addition of nerve ultrasound to NCS significantly improves thedifferential diagnosis between the two diseases.

Intermediate Charcot-Marie-Tooth disease due to NEFH variants with destruction of paranodal architecture

Zhenyu Li[1],Xujun Chu[1],Jianwen Deng[1],He Lv[1],Lingchao Meng[2],Wei Zhang[1],Zhaoxia Wang[1],Yun Yuan[1]

1. Peking University First Hospital

Neurofilament heavy chain (NEFH) gene mutations cause autosomal dominant axonal Charcot-Marie-Tooth disease (CMT2CC), intermediate CMT, spinal muscular atrophy and some patients combined with prominent proximal muscles involvement, increased serum creatine kinase levels and pyramidal signs. However, the Pathological pathway remain to be delineated. We report 1 8-year-old boy with CMT 2CC with early involvement of proximal muscles of the lower limbs. The nerve conduction study showed intermediate CMT with no amplitude in sensory nerves. The heterozygous frameshift variant of NEFH was identified: c.3057dupG (p.Lys1020Glyfs.43). Sural biopsy showed normal myelinated fiber density, however with demyelinated fibers, axonal degeneration and obvious destruction of paranodal architecture. Thus, our results provide a pathological explanation for intermediate CMT in affected patient.

Novel mutations in FLVCR1 Cause tremors, sensory neuropathy with retinitis pigmentosa

Zhenyu Li,Yize Li,Xujun Chu,Meng Yu,Jianwen Deng,He Lv,Wei Zhang,Zhaoxia Wang,Lingchao Meng,Yun Yuan
Peking University First Hospital

The mutations of the feline leukemia virus subgroup C receptor-related protein 1 (FLVCR1) caused ataxia with retinitis pigmentosa. Recent studies indicated a large variation in the phenotype of FLVCR1-associated diseases. In this report, we have described an adult male who manifested firstly with tremors in his third decade, followed by retinitis pigmentosa, sensory ataxia, and sensory neuropathy in his fourth decade. While retinitis pigmentosa and sensory ataxia are well-recognized features of FLVCR1-associated disease, tremor is rarely described. Whole exome sequencing revealed novel compound heterozygous pathogenic FLVCR1 variants: c.498 G > A; p.(Trp166*) and c.369 T > G; p.(Phe123Leu). In addition, we have highlighted the ultrastructural abnormalities of the sural biopsy in this patient.

Fasciculation evolution in multifocal motor neuropathy: A longitudinal muscle ultrasound study

Lei Zhang,Jingwen Niu,Qingyun Ding,Liying Cui,Mingsheng Liu
Peking Union Medical College Hospital

Introduction: Fasciculations could occur in multifocal motor neuropathy. However, the evolution of fasciculations and its potential role in disease evolution during the longitudinal follow-up period remained unclear.

Methods: 14 consecutive treatment-naïve MMN and 14 age- and sex- matched healthy controls were recruited. All MMN patients underwent routine needle electromyography (EMG) and nerve conduction studies (NCS), and muscle ultrasound studies (MUS) were conducted in 19 muscle groups in each patient before treatment. 7 patients underwent repeated MUS over a period of 6 – 12 months. Medical research council sum score (MRCSS) and the overall neuropathy limitations scale (ONLS) were used to evaluate functional changes under treatment.

Results: Focal and discontinuous fasciculations were commonly observed in limb muscles, while abundant fasciculations were present in only 43% treatment-naïve MMN. MUS parameters did not correlate with onset age, disease duration, MRCSS or ONLS at baseline. All patients experienced clinical improvements after immune therapies. In those 7 MMN patients who underwent repeated MUS, the fasciculation intensity elevated in those muscle groups with improved strength, and the fasciculation intensity sum scores (FISS), as well as the total number of muscle groups with abundant fasciculations, were significantly increased during follow-up ($p < 0.05$).

Conclusion: Fasciculations accumulate in MMN patients after effective treatments, especially in muscle groups with increased strength. Hence, assessment of fasciculations with MUS might be useful in therapeutic monitoring.

Electrophysiological features of patients with segmental zoster paresis

Yake Guo,Shen Zhang
Zhengzhou Central Hospital Affiliated to Zhengzhou University

Objective：To investigate the electrophysiological features of patients with segmental zoster paresis.

Methods：A retrospec‐ tive analysis was performed for the neural electrophysiological data of 11 patients who attended Electromyography Examination Room from October 2017 to October 2022.

Results：All 11 patients had abnormal electrophysiological results，and the abnormal rate of nerve conduction was 20.9%（41/196）. The abnormal rates of motor nerve conduction and sensory nerve conduction were 26.0%（26/100） and 15.6%（15/96），respectively，mainly reduction in the amplitude of the nerve involved. Compared with the contralateral side，the ipsilateral side had an abnormal rate of nerve conduction amplitude of 18.4%（36/196），with an abnormal rate of 23.0%（23/100） for motor nerve conduction amplitude and 13.5%（13/96） for sensory nerve conduction amplitude. INCAT score was positively correlated with the maximum reduction ratio of CMAP amplitude（$P<0.05$）. Needle electromyography showed neurogenic damage in the affected muscles.

Conclusion：The electrophysiological results of patients with segmental zoster paresis can be classified into nerve plexus type， nerve root type，and single nerve type， and patients mainly have axonal damage. Nerve conduction combined with needle electro‐ myography has an important value in the early diagnosis，muscle localization， and severity assessment of segmental zoster paresis.

Case report: neuronal intranuclear inclusion disease manifesting as polyneuropathy

Wotu Tian,Li Cao,Xinghua Luan
Department of Neurology, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University School of Medicine

Introduction: We report a case of neuronal intranuclear inclusion disease (NIID) with peripheral neuropathy as the only manifestation. We further explore the pathological characteristics of the peripheral nerves and small nerve fibers in this case.
Methods: Clinical data was collected from a patient with NIID. Genetic testing, peripheral neuropathy, and small nerve fiber studies were conducted.
Results: The 58-year-old male patient had numbness and weakness in the limbs since the age of 44, without apparent family history. The numbness started from hands, feet and head. The lower limb weakness gradually worsened after the age of 47. The numbness developed from the feet to the thighs. However, he had no diplopia, walking unsteadiness, or tremor. The high dose of glucocorticoid therapy was ineffective. Since the age of 57, he had swallowing difficulty, constipation, and urination. Since the age of 58, he could walk alone with dysarthria and coughing during drinking. Physical examination showed slow speed of speaking, severe cough, distal muscle atrophy, normal strength in upper limbs (5-grade), decreased strength in proximal and distal lower limbs (4-grade), weakened tendon reflex (+), decreased acupuncture sensation below the knees, without Babinski signs. The patient did not have abnormal signals on cranial MRI. Electromyographical investigation showed chronic motor and mild sensory axonal damage. The left sural nerve biopsy revealed severe axonal degeneration with mild demyelination. The antibodies against peripheral nerve and Langfeld's knot were all negative. The genetic tests showed abnormal GGC repeat expansions (108/18) in the 5' region of the NOTCH2NLC. Intranuclear inclusions were identified by anti-P62 staining and electron microscope in fibroblasts and endothelial cells of skin. His IENFD was 1.89/mm (PGP9.5) and 0/mm (GAP43) respectively, which were significantly lower than healthy male control according to EU standards (PGP9.5 staining: 6.3/mm, GAP-43 staining: 14.17 ± 5.49 /mm; P<0.0001).
Conclusions: We reported a rear NIID case with polyneuropathy as the only manifestation, without abnormal signals on DWI. He had remarkable peripheral nerve damage, also involving small nerve fibers. IENFD may efficiently work as a biological marker for evaluation or screening in NIID. In-depth research on a larger sample size will reveal the correlations between small fiber lesions and genotypes.

Novel NDRG1 mutation causing Charcot-Marie-Tooth disease type 4D in two siblings with central nervous system involvement

Fei Xia Zhan,Li Cao
Department of Neurology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine

Introduction: Biallelic NDRG1 variants are a well-established cause of autosomal recessive Charcot-Marie-Tooth disease 4D (CMT4D), which is clinically characterized by early-onset severe demyelinating neuropathy with neural deafness. Here, we described two Chinese siblings form a consanguineous family with severe demyelinating neuropathy and varying degrees of white matter lesions. We further made a literature review of NDRG1-related neuropathy to summarize the clinical and genetic characteristics and enhance the early recognition.
Methods: Detailed clinical evaluation and exome sequencing were performed. The NDRG1 mutation was confirmed by Sanger sequencing and segregation analysis. The structure of the mutant protein was furtherly predicted by computational modeling.
Results: Clinically, both the two siblings presented with early-onset severe demyelinating peripheral neuropathy accompanied with abnormal white matter signal on brain imaging. Targeted next-generation sequencing identified a novel homogenous NDRG1 mutation (c.638delA), which was co-segregated in the pedigree. Protein modeling showed the frameshift variant leading to the prematurely truncated protein and ultimately affecting the normal function may be the potential cause for the neuropathies.
Conclusion: We reported here a novel frameshift homogenous NDRG1 variant in two siblings with central nervous system (CNS) involvement, which expanded the clinical and genotypic spectrum. Our cases demonstrate that CMT4D should be considered in the differential diagnosis of recessive demyelinating neuropathy with or without hearing loss, and the symptoms and/or imaging in CNS should be evaluated in patients with NDRG1 mutations.

Novel FGD4 variants and literature review of Charcot-Marie-Tooth disease type 4H

Feixia Zhan,Li Cao,Xinghua Luan
Department of Neurology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine

Introduction: Charcot-Marie-Tooth disease (CMT) is a common hereditary motor and sensory neuropathy with highly clinically and genetically heterogeneous properties. The CMT4H subtype is an autosomal recessive demyelinating form of CMT due to the FGD4 mutations. Herein, two cases of CMT4H caused by FDG4 mutations were analyzed to explore the clinical phenotype and genotype of CMT4H.

Methods: Detailed clinical evaluations, nerve biopsy, and whole-exome sequencing were performed. The sequence and co-segregation of the variants in the family was confirmed by Sanger sequencing.

Results: The probands in two unrelated families were sporadic with onset in late childhood, manifesting as progressive postural gait abnormalities, difficulty walking, and foot deformities. Nerve electrophysiological examination showed multiple demyelinating damages to sensory and motor nerves. Nerve biopsy in one case disclosed a demyelinating neuropathy with thickened and excessively folded myelin sheath. Genetic testing revealed that both patients had compound heterozygous mutations in the FGD4 gene, all of which were novel, and co-segregated with the family members.

Conclusions: CMT4H is a very early onset demyelinating disease with variable phenotypes. We report two cases with FDG4 mutations, expanding the genotypic spectrum in the Chinese population. Based on the previous reports, CMT4H patients have the characteristics of early-onset age, rapid disease process, relatively severe symptoms. Most patients are sporadic, while a higher prevalence in consanguineous children. CMT4H may be a disease of various impaired signaling pathways.

Episodic neurological dysfunction in X-linked Charcot-Marie-Tooth disease: expansion of the phenotypic and genetic spectrum

Feixia Zhan,Wotu Tian,Yuwen Cao,Jingying Wu,Yun Yuan,Xinghua Luan,Li Cao
Department of Neurology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine

Introduction: X-linked Charcot-Marie-Tooth disease type 1 (CMTX1) is characterized by peripheral neuropathy with/without episodic neurological dysfunction. To extend the phenotypic and genetic description of CMTX1, we presented the clinical, neuropathological and genetic investigations of a series of patients with GJB1mutations.

Methods: Detailed clinical evaluations, nerve pathology, and genetic analysis were performed on CMTX1 patients.

Results: A total of 27 CMTX1 patients from 14 unrelated families with GJB1mutations were collected. Mean age at onset (AO) was 20.9±12.2 years (range, 2-45 years). Walking difficulties, weakness in legs, and pes cavus were common initial symptoms. Male patients tended to have an earlier AO (men vs women=15.4 ± 9.6 vs 32.0 ± 8.8 years, p=0.002), a longer course (16.8±16.1 vs 5.5 ± 3.8 years, p=0.034), and more severe electrophysiological results than females. Besides peripheral neuropathy, six of the patients had special episodic central nervous system (CNS) evidence from symptoms, signs, and/or reversible white matter lesions. Neuropathology showed the loss of large myelinated fibers, an increasing number of regenerated axon clusters with abnormally thin myelin sheaths and excessively folded myelin. Genetic analysis identified 14 GJB1 variants, among which 6 were novel.

Conclusions: Our findings expanded the phenotypic and genetic spectrum of CMTX1. Although CMTX1 showed high phenotypic variability and variable CNS involvement, a detailed neurological examination and nerve conduction study will provide critical clues to a correct diagnosis. Further exploration of the underlying mechanisms of connexin 32 involvement in neuropathy or CNS dysfunction is warranted to develop the promising therapy.

Intraepidermal Nerve Fiber Density Study in Chinese Breast Cancer Patients with Taxane-induced peripheral neuropathy

Xiao-wei Zhu,Ping Zhong,Li Cao,Wo-tu Tian,Xing-hua Luan
Department of Neurology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine

Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most frequent side effects in cancer patients receiving chemotherapy. Taxanes (TX), such as paclitaxel, docetaxel, and nanoparticle albumin-bound (nab)-paclitaxel, are applied for the treatment of breast cancer (BC). Skin biopsy to investigate intraepidermal nerve fiber density (IENFD) has been reported for diagnosis of CIPN small-fiber neuropathy. Besides, data regarding IENFD from the Chinese population is limited and there is no study on BC patients with Taxane-induced peripheral neuropathy (TIPN) from China.

Methods: In this study, we examined a panel of skin nerve markers in carefully characterized subjects with TIPN and healthy control (HC) participants. This study aimed to assess the efficacy and validity of evaluating IENFD by skin biopsy to objectively quantify the degree of TIPN in Chinese patients with BC.

Results: A total of 12 patients (age 49.1 ± 13.92) and 12 HC (age 47.5 ± 14.00) were screened for eligibility and underwent evaluation. All of those with BC received TIPN, including paclitaxel (2, 16.7%), docetaxel (1, 8.3%) and nab-paclitaxel (9, 75.0%). TIPN patients reported moderate-to-severe TIPN symptoms (>8 points) by EORTC-CIPN20, which were predominantly sensory. 92 skin biopsy sections of 24 subjects were used for IENFD analysis and the IENFD results was significantly lower in study participants with TIPN (14.96 ± 6.522 fibers/mm), than in HC participants (19.06 ± 6.251 fibers/mm) ($p = 0.0026$).

Conclusion: Quantitation of IENFD is a common, objective tool for evaluation of peripheral neuropathy in patients with TIPN. Larger-scale future prospective studies are necessary.

Two Charcot-Marie-Tooth type-1A cases with small fiber neuropathy

Xiao-wei Zhu,Ping Zhong,Li Cao,Wo-tu Tian,Xing-hua Luan
Department of Neurology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine

Objectives: To investigate the clinicopathological features of Charcot-Marie-Tooth type-1A (CMT1A) with small fiber neuropathy (SFN).
Methods: We reviewed the clinical presentation, genetic test results, electrophysiological and pathological features of two CMT1A patients with SFN.
Results: The two probands were male, aged 43 and 52 years old respectively, with adolescent onset of disease, and both clinically characterized by chronic progressive lower limb weakness, muscle atrophy and foot deformity. There was no limb pain, numbness or abnormal temperature sensation, slurred speech, dysphagia, urinary and defecatory abnormalities. One of them had autosomal dominant inheritance and the other had no family history. Neurophysiological assessments showed multiple motor and sensory peripheral nerve damage in the upper and lower extremities and sympathetic skin response (SSR) was abnormal in the lower extremities.
The sural nerve biopsy revealed severe chronic demyelinating peripheral neuropathologic changes with numerous "onion ball" structures. No pathogenic gene mutations were detected by whole exon sequencing (WES) of two probands. Multiplex ligation-dependent probe amplification (MLPA) suggested peripheralmyelinprotein-22 (PMP22) duplication. The skin tissue biopsy showed severely reduced intraepidermal nerve fiber density (IENFD), which was 3.55/mm and 4.26/mm, indicating severe involvement of small nerve fibers.
Conclusion: We reported two patients of CMT1A with SFN. Although it is generally believed that CMT1A only involves large diameter nerve fibers, we observed significant abnormalities in both SSR and IENFD, and none of the two patients had clinical signs of SFN or autonomic neuropathy. This report provides the pathological basis of CMT1A with SFN. However, its pathogenic mechanism and clinical significance remain to be further investigated.

A Multicenter Study of Hereditary Transthyretin Amyloidosis in China

Xujun Chu[1],Qingping Wang[2],Juan Kang[3],Hao Yu[4],Jingwen Xu[5],Haishan Jiang[6],Yuwei Da[7],Jia Li[8],Xinghua Luan[9],Chong Sun[10],Zhangyu Zou[11],Min Zhu[12],Bin Chen[13],Xiaoxuan Liu[14],Kang Du[15],Dongsheng Fan[14],Zaiiqiang Zhang[13],Daojun Hong[12],Jie Lin[10],Li Cao[9],Min Qian[8],Zhaoxia Wang[1],Yun Yuan[1],Wei Li[5],Zhiying Wu[4],Ruxu Zhang[2],Lingchao Meng[1]

1. Peking University First Hospital
2. The Third Xiangya Hospital of Central South University
3. Xi' an Central Hospital
4. The Second Affiliated Hospital Zhejiang University School of Medicine
5. Qilu Hospital,China
6. NANFANG HOSPITAL
7. Xuanwu Hospital Capital Medical University
8. Peking Union Medical College Hospital, Chinese Medical College
9. Shanghai Sixth People's Hospital
10. Huashan Hospital Affiliated to Fudan University
11. Union Hospital Affiliated to Fujian Medical University
12. The First Affiliated Hospital of Nanchang University
13. Beijing Tiantan Hospital affiliated to Capital Medical University
14. Peking University Third Hospital
15. Qujing First People's Hospital

Objective : Hereditary Transthyretin Amyloidosis (ATTRv amyloidosis) is an autosomal dominant genetic disease caused by misfolding and tissue deposition of unstable tetramer of TTR protein after dissociation into monomer caused by point mutation of TTR gene. The purpose of this study is to clarify the genotype and phenotype characteristics of Chinese patients by analyzing the data of ATTRv amyloidosis in multi-centers.

Materials and Methods : This study included 202 consecutive patients with ATTRv amyloidosis who were admitted to 14 medical centers of mainland China from January 2010 to June 2023. The genotype and phenotype characteristics of all patients were summarized, and the relationship between the degree of disease progression and genotypes of patients with ATTRv amyloidosis was analyzed.

Results: A total of 202 patients with TTR pathogenic mutations (53 females and 149 males) had a positive family history of 138 cases (68.3 %).The average age of onset was 50.6 ± 12.4 years. The average course of disease was 4.1 ± 3.5 years, and the average time from onset to diagnosis was 4.0 ± 3.6 years. There were 117 late-onset cases (57.9 %) and 85 early-onset cases (42.1%). The most common initial symptom was distal paresthesia in 110 cases (54.5%). Fifty-six patients

(27.7 %) were initially diagnosed as autonomic neuropathy. Sixteen patients (7.9 %) had blurred vision. A total of 44 heterozygous missense mutations and 1 deletion mutation (V122del) were included. The most common genotype was V30M, accounting for 19.8 %, followed by A97S. The average age of patients with V30M was 61.0 ± 8.0 years old, and the average age of patients with A97S was 58.2 ± 7.0 years old. 14 patients with E54 K were early-onset (87.5 %), and 10 patients with G83R were early-onset (90.9 %). The average age of onset of G83R patients was 40.6 ± 5.2 years old, which was earlier than that of V30M and A97S patients. In our cohort, 92 patients (45.5 %) were from South China and the remaining patients were from North China. Of the 40 patients with V30M, 36 were from the North China, and the remaining patients with A97S were from South China except for one. The time from onset to crutch was 3.9 ± 2.7 years in 44 patients, the time from onset to wheelchair was 5.0 ± 3.2 years in 30 patients and the time from onset to death of 27 patients was 7.1 ± 3.4 years. There was no significant difference in the time from onset to death between V30M and non-V30M patients. A total of 39 patients died with an average age of 56.1 ± 13.5 years. There was no significant difference in survival time between V30M patients and non-V30M patients. The median survival time of V30M patients was estimated to be 15 years, and that of non-V30M patients was 11 years. There was no significant difference in survival time between males and females.

Conclusion : ATTRv amyloidosis patients in China have a high proportion of males, more late-onset than early-onset, high heterogeneity of initial symptoms, mainly sensory disorders, and V30M is the most common genotype. The average time from onset to death of V30M and non-V30M patients is similar to that reported abroad. It is hoped that this study will improve the understanding of ATTRv amyloidosis, early detection, early diagnosis and early treatment of the disease.

A case of leprosy neuropathy and spastic paraplegia diagnosed with Next-generation sequencing of sural nerve

Jia Li,Min Qian,Minsheng Liu,Lin Chen
Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College
Pathological Case discussion

Case presentation: A 54-year-old man, with a history of skin lesions diagnosed and treated as leprosy, reported progressive weakness and stiffness of bilateral lower extremities for 5 years. He developed painless skin ulcers of lower limbs since 15 years ago. The skin ulcer healed and bacilloscopy was negative since the diagnosis and treatment of leprosy 7 years ago. He presented with difficulties in walking 5 years ago and physicial examination revealed spastic paraplegia. Numbness and thermohypesthesia of all limbs appeared 3 years ago, along with progressive distal muslce weakness. Physical examination on adimission showed mixed upper and lower motor neuron signs, which indicates the coexistence of peripheral neuropathy and spastic paraplegia. Nerve condction study and electromyography is consistent with axonal mononeuropathy multiplex. Ultrasonography showed enlarged median and ulnar nerve with increased vascularity of ulnar nerve. Sural nerve pathology revealed diffuse perineurial infiltration of lymphocytes and vasculitis. Acid-fast staining was negative, while metagenomic next-generation sequencing(mNGS) of fresh nerve samples identified DNA of Mycobacterium leprae. However, no pathogen was detected by mNGS of cerebrospinal fluid and no neuroimaging abnormalities was demonstrated in brian and spinal magnetic resonace imaging. At the same time, suspected malignant pulmonary nodules were found in chest CT during hospitalization, and the pathological results after pulmonary wedge lobectomy were consistent with invasive pulmonary adenocarcinoma. Final diagnosis of leprosy neuropathy was made. Spastic paraplegia might be owing to leprosy whereas lacking direct evidence. The patient reports improvement in numbness and stiffness after treated with multidrug therapy of leprosy and baclofen.
Discussion: This case reports a case of leprosy neuropathy diagnosed with next-generation sequencing of sural nerve. The clinical manefestations, peripheral nerve ultrasound and electrophysiological features, sural nerve pathological findings were summarized. Leprosy is a chronic infectious and disabling disease caused by Mycobacterium leprae, which predominantly affects skin and the peripheral nerves. The diagnosis of leprosy neuropathy depends on nerve biopsy and acid-fast staining. Some cases of leprosy could be undected due to low sensitivity of acid fast bacilli staining. Central nervous system involvement is rare in leprosy, while a few cases of myelitis, ganglionitis and abnormal signals in the middle cerebellar peduncle have been reported. Whether this patient's spastic paraplegia was caused by leprosy needs long-time follow-up to observe the therapeutic effect. This case implies that leprosy could be characterized by chronic progressive peripheral neuropathy and spastic paraplegia. The next generation sequencing of nerve tissues can be used as a new diagnostic techniques for leprosy.

Clinico-radiological comparison between different sub-types of inflammatory myositis in a large cohort from India

Nalini Atchayaram
National Institute of Mental Health and Neurosciences

Atchayaram Nalini, Sridhar S, Saraswati Nashi, Seena Vengalil, Karthik Kulanthaivelu

Introduction: Muscle MRI is a promising tool to assess muscle edema in idiopathic inflammatory myopathies(IIM). Aim was to compare clinical and radiological features among sub-types of IIM.

Methods: A cross-sectional study on 80 patients fulfilling EULAR criteria. Demographic, clinical and lab parameters collected. Muscle power(MMT-8) used for clinical severity and modified Stramare scoring to grade edema(lower limb MRI- axial STIR, T1 & T2 sequences). Chi-square test for categorical variables and Kruskal-Wallis Test for comparing muscle edema.

Results: Among 80 patients, 20=Anti-SRP, Anti-Mi2b (21), Anti-Ro(26), seronegative(13). Anti SRP: F:M=2.3:1. Median age at diagnosis for SRP= 38 years(Q1=26, Q3=53), Mi2b= 46.5 years(Q1=36.5, Q3=53.5)' anti-SSA= 45 years(Q1=28, Q3=53.5). Median illness duration =12 months(Q1=4, Q3=27). Muscle pain and cramps common in Mi2b. All had proximal weakness at presentation but among Mi2b, 66% had distal weakness. Wasting common in SRP(85%) and skin changes in Mi2b. No significant correlation between muscle edema and MMT-8 in most. No correlation between MMT-8 and CK values by Spearman 's rho test. Based on muscle edema, most severely affected muscles in SRP: adductor magnus(p=0.021), iliopsoas, then glutei, mild diffuse involvement in legs with sparing of peronei, in Mi2b: vastii(p=0.03) the hamstrings, deep posterior compartment(tibialis posterior, flexor digitorum longus) and peroneii(p=0.023). Fascitis noted in majority in Mi2b(61%). In anti-SSA, vastii more affected and anterior and posterior muscles equally in leg. Overall severity of edema was less in anti-SSA compared to other subgroups($p<0.05$).

Conclusions: Preferential affection of muscles in different subtypes of IIM with varying severity was noted. SRP patients had more wasting. Fascitis more common in Mi2b with severe edema. Peroneus compartment preferentially affected in Mi2b. Anti-SSA had milder edema.

Quantitative muscle ultrasound as a biomarker of disease activity in idiopathic inflammatory myopathies

Cheng Yin Tan,Jie Ying Tan,Mohd Azly Yahya,Nortina Shahrizaila,Khean Jin Goh
University of Malaya

Introduction: Idiopathic inflammatory myopathies (IIM) are autoimmune neuromuscular disorders that present with proximal muscle weakness. Conventionally, muscle strength, functional status and muscle enzymes are used to evaluate disease activity. In the current study, we aimed to assess the role of quantitative muscle ultrasound in determining disease activity in IIM patients.
Methods: Various IIM, except inclusion body myositis were included. Age- and gender-matched healthy controls (HC) were recruited. All participants underwent muscle ultrasound and clinical assessments. Six different upper and lower muscles unilaterally were scanned following standardised protocol. Muscle thickness (MT) and echo intensity (EI) were determined. Results were compared with HC and correlations were made with clinical outcome measures.
Results: Twenty IIM patients and 24 healthy controls were recruited. IIM included were dermatomyositis (6), necrotizing myositis (6), polymyositis (3), anti-synthetase syndrome (3) and non-specific myositis (2). There were no significant differences in age, gender, weight, height and body mass index between the two groups. MT of rectus femoris (RF) was significantly reduced compared to HC (15.4±6.5 vs 21.6±6.3 mm; p=0.003). Muscle EI of biceps brachii (BIC) (73.3±20.3 vs 63.3±11.8; p=0.046) and vastus medialis (62.8±14.2 vs 54.7±9.9; p=0.037) in IIM patients were significantly higher compared to HC. There were significant correlations between MT of RF with modified Rankin Scale (r=-0.456; p=0.043), Physician Global Activity Assessment (r=-0.526; p=0.017) and Health Assessment Questionnaire (r=-0.485; p=0.030); and EI of BIC with Manual Muscle Testing-8 (r=-0.456; p=0.043).
Conclusion: Muscle atrophy and increased EI in proximal muscles were evident in IIM patients. Quantitative muscle ultrasound parameters correlated with clinical outcome measures. Muscle ultrasound is useful as a sensitive biomarker of disease activity in IIM.

The diagnostic value of serum YKL-40 for myocardial involvement in immune-mediated necrotizing myopathy

suqiong ji,li xu,yue li,bitao bu
Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology,

Objective: This study aimed to determine the diagnostic value of YKL-40 for myocardial involvement in immune-mediated necrotizing myopathy (IMNM).
Methods: We retrospectively analyzed the data of patients with IMNM admitted to the Neurology Department at Tongji Hospital between April 2013and August 2022. Clinical data including patients' demographics; clinical characteristics (disease duration, muscle strength, atrophy, rash, dysphagia, dyspnea, and myalgia); and laboratory test results were collected from the electronic medical record system. Serum YKL-40 levels were measured using an enzyme-linked immunosorbent assay. A receiver operating characteristic (ROC) curve was drawn, and the area under the ROC curve was calculated to evaluate the diagnostic value of YKL-40 for cardiac involvement in IMNM.
Results: 29 patients with IMNM and15 sex and age-matched volunteers without history of heart diseases were recruited for the study. Compared with the healthy controls, serum YKL-40 levels were notably up-regulated [96.3 (55.5 120.6) pg/ml verus 19.6 (13.8 20.9) pg/ml; p=0.000] in patients with IMNM. We compared between 14 patients with IMNM with cardiac abnormalities and 15 patients with IMNM without cardiac abnormalities. The most important finding was that serum YKL-40 levels were higher in the patients with IMNM with cardiac involvement based on cardiac magnetic resonance (CMR) examination [119.2 (88.4 185.69) pm/ml versus 72.5 (35.7 98) pm/ml; p=0.002]. YKL-40 had a specificity and sensitivity of 86.7% and 71.4% respectively, at a cut-off value of 105.46 pg/ml for predicting myocardial injury in patients with IMNM.
Conclusion: YKL-40 could be a promising non-invasive biomarker for diagnosing myocardial involvement in IMNM. However, larger prospective study is warranted.

Protein kinase R is key to regulate MxA and MHC-I expression in dermatomyositis

Guoyong Zhang[1,2],Dandan Zhao[3],Lining Zhang[3,4],Xiaoyu Liu[1],Ying Hou[3],Kai Shao[5],Bing Zhao[6],Wei Li[3],Tingjun Dai[3],Chuanzhu Yan[3,5,7]

1. Cheeloo College of Medicine, Shandong University
2. University of Health and Rehabilitation Sciences, Qingdao, China.
3. Research Institute of Neuromuscular and Neurodegenerative Diseases and Department of Neurology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China.
4. Department of Rheumatology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong 250012, China.
5. Department of Central Laboratory and Mitochondrial Medicine Laboratory, Qilu Hospital (Qingdao), Cheeloo College of Medicine, Shandong University, Qingdao, China.
6. Department of Neurology, Qilu Hospital (Qingdao), Cheeloo College of Medicine, Shandong University, Qingdao, China.
7. Brain Science Research Institute, Shandong University, Jinan, China.

Background and Objectives: Dermatomyositis (DM) is highly associated with the type I interferon (IFN-I) pathway. However, the specific IFN-I related pathomechanism remains unclear. Protein kinase R (PKR) is an IFN-induced protein and its dysregulation has been implicated in inflammation and other autoimmune diseases. However, there are no studies on the role of PKR in DM. We aimed to explore the expression of PKR in DM.

Methods: The expression of PKR was determined initially by western blot and immunohistochemistry in muscles of DM (n=13) and other idiopathic inflammatory myopathies (IIMs, n=17). Then we assessed the sensitivity and specificity of sarcoplasmic expression of PKR in DM muscles by immunohistochemistry in larger consecutive cohort of DM (n =65), other IIMs (n=56) and muscular dystrophy (n=26), and compared them with conventional pathologic hallmarks of DM, including perifascicular atrophy or necrosis and regeneration (PFA/PFNR) and sarcoplasmic expression of myxovirus resistance A (MxA). Furthermore, we also investigated the role of PKR in human primary myoblasts under IFN-β condition in vitro.

Results: Western blot showed that PKR was significantly expressed in muscles of DM patients compared with that in other IIMs patients and normal controls. Preferentially sarcoplasmic PKR expression was identified in DM muscle biopsies with or without PFA by immunohistochemistry. The sensitivity and specificity of sarcoplasmic PKR expression in DM (92.3% and 97.6% respectively) were comparable to MxA (92.3% and 98.8%), with PFA/PFNR showing the lowest sensitivity and specificity (67.7% and 93.9%). Immunohistochemistry using serial sections showed that PKR and phosphorylated PKR (p-PKR) co-localized with MxA in major histocompatibility complex I (MHC-I) positive myofibers. In vitro study demonstrated IFN-β induced upregulation of PKR, p-PKR as well

as MxA and MHC-I in human primary myoblasts, while selective PKR inhibitor or PKR siRNA could reduce the expression of MxA and MHC-I in myoblasts.

Conclusions: Our data suggest that PKR is specifically expressed in DM muscle and can serve as a diagnostic marker for DM like MxA. In addition, PKR is involved in regulation of IFN-β-induced MxA and MHC-I expression in vitro, and may be a potential therapeutic target for DM.

Exploration of pMLKL as a pathological marker of immune-mediated necrotizing myopathy

NACHUAN CHENG,MINGSHI GAO,DONGYUE YUE,CHONGBO ZHAO,WENHUA ZHU
Huashan Hospital

Objective: Immune-mediated necrotizing myopathy (IMNM) is an independent subtype of idiopathic inflammatory myopathies (IIMs), characterized by rapidly progressive severe proximal muscle weakness, elevated creatine kinase, scattered necrotic and regenerating muscle fibers with sparse inflammatory infiltration. However, due to a lack of knowledge of the pathophysiological mechanism, IMNM still lacks highly sensitive and specific pathological markers. Recent studies suggest that necroptosis may contribute to myonecrosis in IMNM, but there is still insufficient evidence in vivo. Therefore, this study is aimed to explore the expression and spatial distribution of phospho-mixed lineage kinase domain-like protein (pMLKL), the executive molecule of necroptosis, in IMNM and to evaluate its value as a pathological diagnostic marker.

Method:

We included 46 patients from Huashan Hospital from October 2020 to October 2022 who met the European Neuromuscular Center (ENMC) IMNM diagnostic criteria, subdivided into three serotypes of anti-signal recognition particle (SRP) antibody positive, anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibody positive and seronegative. At the same time, patients with dermatomyositis (DM), antisynthetase antibody syndrome (ASS), sporadic inclusion body myositis (sIBM) were included in the IIM group, and patients with Duchenne/Becker muscular dystrophy (DMD/BMD), facioscapulohumeral muscular dystrophy (FSHD), limb-girdle muscular dystrophy (LGMD) R1 and LGMDR2 were included as non-IIM myopathy. Muscle specimens were serially sectioned for HE staining and immunohistochemical staining for pMLKL, major histocompatibility complex I (MHC-I), and complement membrane attack complex (MAC). The spatial distribution of pMLKL in muscle specimens was assessed for qualitative and semi-quantitative scoring and the co-localization of pMLKL and other pathological phenomena or biomarkers.

Result:

pMLKL was upregulated in muscle samples of IIMs and nIIM except for sIBM, with different spatial distribution patterns. In IMNM and nIIM, the typical expression pattern of pMLKL staining is the radial sarcolemmal upregulation with necrotic muscle fibers as the core, while in DM, pMLKL upregulation is around the microinfarction in the center of the muscle fascicle. The positive rate of pMLKL expression in the muscle of IMNM patients was 93.48%, among which 89.47% in the anti-SRP positive group, 94.12% in the anti-HMGCR positive group, and 100% in the seronegative group, which was higher than other IIMs (50%) and nIIMs (47.9%) patients (p<0.0001). Staining of serial sections of the patient's muscle specimens revealed no prominent colocalization of

pMLKL, MHC-I, and MAC upregulation.

Conclusion:

The widespread and significant upregulation of pMLKL in IMNM suggests a correlation between necroptosis and the pathogenesis of IMNM as well as the mechanism of myonecrosis. However, due to its upregulation in muscle specimens of various inflammatory and non-inflammatory myopathies, pMLKL is not suitable as a pathological diagnostic marker for IMNM. Furthermore, differences in the spatial distribution of pMLKL in skeletal muscle suggest a unique pathophysiology of dermatomyositis that differs from other inflammatory myopathies.

Clinical manifestation,muscle imaging and pathological characteristics of anti-SRP positive immune-mediated necrotizing myopathy

Shiyao Li,QianQian Qu,Wenhao Cui,Jiongbo Zhao,Jiaxuan Wang,Cong Hu,Haidong Lyu
Jiaozuo People's Hospital, Xinxiang Medical University, Jiaozuo, Henan 454002, China

Objective: To summarize the clinical, muscle imaging, and pathological characteristics of anti-SRP positive immune-mediated necrotizing myopathy (SRP-IMNM).

Methods:The clinical features, imaging findings and muscle pathology of 9 patients with SRP-IMNM were retrospectively analyzed.

Results: Among the 9 patients, there were 7 females and 2 males . The age of onset of the disease ranges from 18 to 59 years old. 8 patients had an acute or subacute course. All patients presented with proximal muscle weakness of the limbs, 7 patients experienced cervical flexor muscle weakness, and 5 patients were combined with dysphagia. Laboratory examination: serum creatine kinase was elevated to varying degrees in all 9 patients in this group (2289-6725 U/L). Myositis antibody test was accompanied by anti-Ro-52 antibody positivity in 4 patients (4/9),in addition to anti-SRP antibody positivity. 8 patients underwent MRI of the thigh muscles, revealed diffuse patchy skeletal muscle oedema in all cases, and the lesions mainly involved the gluteus maximus, adductor magnus and posterior thigh muscles. In 2 patients, MRI of the shank muscles was performed, showing soleus are frequently affected, the tibialis anterior and gastrocnemius muscles were affected in 1 case. Early mild fatty infiltration were observed in 7 patients, which is relatively rare in the clinic. Muscle pathology in all 9 patients showed varying degrees of scattered muscle fiber degeneration, necrosis and regeneration, accompanied by no or slight inflammation.A small number of single nucleated cells in the endomysium and degenerative necrotic muscle fibers was observed in 8 patients, and there was no significant inflammatory cell infiltration in the interstitium and perivascular. Pipestem capillaries can be seen in some patients. Immunohistochemical staining showed a small number of CD8-positive lymphocytes in the endomysium of 4 patients, and a small number of CD68-positive lymphocytes in non-necrotic myofibers of 8 patients. Positive expression of major histocompatibility complex class I（MHC-I）antibody was observed in the sarcolemma of non-necrotic muscle fibers in the majority of patients . Positive expression of membrane attack complex （C5b-9）was found in the sarcolemma of non-necrotic fibers and intramuscular capillary walls. P62 staining showed homogeneous,deep stained ,fine granules deposition in some muscle fibers of 7 patients.

Conclusion: SRP-IMNM was mostly of subacute onset, mainly manifested as proximal muscle weakness of the limbs, and some patients could be accompanied by cervical flexor weakness and dysphagia, serum CK was significantly elevated in all cases. Muscle pathology shows scattered

degenerative necrotic muscle fibers, a small number of scattered CD8 positive lymphocytes were found in the endomysium of some patients. CD68 positive lymphocytes and P62 staining positive were presented in necrotic muscle fibers of most patients. Muscle MRI shows focal oedema in skeletal muscles, which has certain value in defining the extent of muscle involvement and prognosis.

Immunotherapy responding chronic motor axonal polyneuropathy: Case series and literature review

Nan Hu,Jingwen Niu,Liying Cui,Mingsheng Liu
Peking Union Medical College Hospital

Objective: To summarize the characteristics of chronic motor axonal neuropathy cases with responsiveness to immunotherapy and provide new and comprehensive knowledge for clinical management of these patients.

Methods: We reviewed our database to identify patients with chronic motor axonal neuropathy that responded to immunotherapy. Online databases including PubMed, EMBASE, and OVID were also searched for relevant cases.

Results: A total of 15 cases of chronic motor axonal neuropathy with responsiveness to immunotherapy were identified, including 7 cases from our database and 8 cases from online searching. A predominance of male was observed [11 (73.33%)] with median onset age of 47 (range: 17-82) years old. Three (20.00%) included patients had subacute onset, while the other 12 (80.00%) patients had insidious onset. Two (13.33%) patients reported antecedent infection. Three (20.00%) were asymmetrical onset and 5 patients (33.33%) reported involvement of proximal limbs. Elevated CSF protein level was showed in 9 (60.00%) patients. Five (33.33%) patients reported positive serum anti-GM1 IgG and GD1b-IgG. Seven patients tried IVIG treatment, and six (85.71%) patients showed clinical improvement, among which one patient experienced relapses. One patient died of respiratory failure and no other patient reported severe disability during follow-up.

Conclusion: For patients that suffered from chronic motor axonal polyneuropathy, subacute onset with predisposing factors, relapsing-remitting course, asymmetrical or proximal limb weakness, cranial involvement, elevated CSF protein level, positive autoimmune antibodies, etc might be indicators of responsiveness to immunotherapy. IVIG should be the first-line treatment for these patients.

Lumbar stenosis syndrome due to hypertrophy of nerve roots in chronic inflammatory demyelinating polyneuropathy: Case report and literature review

Nan Hu,Jing Li,Jingwen Niu,Liying Cui,Mingsheng Liu
Peking Union Medical College Hospital

Objective: CIDP patients might manifested lower back and leg pain or intermittent claudication mimicking a lumbar stenosis syndrome (LSS).
Methods: We reported two cases of CIDP patients with manifestations of LSS from our database. Online database including PubMed, EMBASE, and OVID were searched for relevant cases.
Results: We identified 11 cases with typical CIDP presenting with LSS, including 2 cases from our database and 9 ones from online searching. A predominance of male was observed [8 (72.7%)] with mean age of 44.2 (standard deviation, SD: 17.1) years old. The mean time from onset of CIDP to the appearance of manifestations of LSS was 12.9 (SD: 8.3) years. All patients had paroxysmal back pain, radiating to lower limbs, which usually relieved after a rest or in a few hours. Myelopathy presented in four (36.4%) patients, manifesting pathological signs, sensory level or incontinence. Lumbar MRI and nerve ultrasound showed widely thickening of nerve roots among included patients. Eight (72.7%) patients showed responsiveness to immunosuppressive therapy. Among them, two patients experienced relapses, three patients only presented mild improvement. Decompressive lumbar operation was conducted in seven (63.6%) patients, and six of them obtained certain clinical benefits.
Conclusion: There might be obvious mismatches between clinical symptoms and electrophysiological studies/neuroimaging in CIDP patents. For refractory CIDP patients with a long course of disease, regular imaging test was necessary to monitor the dynamic changes of nerve roots. Decompressive operation might be a considerable option for CIDP patients with thickening of nerve roots that has caused LSS.

Clinical Characteristics and Outcomes of Idiopathic Inflammatory Myopathies Before and after the COVID-19 Pandemic: A Retrospective Study

Manta Yonpiam[1],Panuvich Dangchant[1],Jakkrit Amornvit[2,3]

1. Chulalongkorn University, Bangkok, Thailand

2. Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

3. King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand

Introduction: The COVID-19 pandemic has had far-reaching effects on healthcare systems globally. It is crucial to understand how the pandemic has influenced patients with idiopathic inflammatory myopathies (IIMs).

Objective

This study aimed to compare the clinical characteristics and outcomes of IIMs-diagnosed patients at King Chulalongkorn Memorial Hospital in Bangkok, Thailand, before and after emerging of the COVID-19 pandemic.

Methods:A retrospective review was conducted on patients diagnosed with IIMs before(pre-COVID) and after (post-COVID) emerging of the COVID-19 pandemic. The subtypes of IIMs are classified according to EULAR/ACR classification criteria. Manual Muscle Testing-8 (MMT-8) scores, and maximum creatine kinase (CK) levels were compared. The final MMT-8 scores were used to evaluate patient outcomes.

Results:A total of 37 patients diagnosed with IIMs were included in the study, with 18 patients in the pre-COVID and 19 patients in the post-COVID groups. The distribution of IIM subtypes differed between the two groups. In the pre-COVID group, the majority of patients were diagnosed with PM/IMNM (n=10), and DM (n=8). The post-COVID group predominantly consisted of patients with DM (n=13), followed by PM/IMNM (n=5), and NSM (n=1). The clinical characteristics revealed no significant differences: the median MMT-8 was 138 [Interquartile Range (IQR): 131-142] pre-COVID and 134 [IQR: 110-138] post-COVID ($p = 0.0667$), and the maximum CK levels were 2504 [IQR: 691-4410] pre-COVID and 4312 [IQR: 191-7545] post-COVID ($p = 0.761$). However, significant differences were found in patient outcomes: the final median MMT-8 score was 150 [IQR: 146-150] pre-COVID vs 143 [IQR: 125-150] post-COVID ($p = 0.0271$). In both groups, the PM/IMNM subtype demonstrated the most favorable outcomes.

Conclusion: The COVID-19 pandemic, while not significantly altering the clinical characteristics of IIMs, has impacted patient outcomes. These findings underscore the need for astute IIM management strategies during global health crises.

Immune Checkpoint Inhibitor-Induced Myocarditis with Myositis and/or Myasthenia Gravis Overlap Syndrome (IM3OS)-Case Series and Literature Review

Qing Sun,Qing Liu,Jiabin Zheng,Liqun Jia,Huijuan Cui,Yu Wang,Dantao Peng,Shaojie Sun,Jinxia Lv,Weihe Zhang,Renbin Wang
China-Japan Friendship Hospital

Introduction Immune checkpoint inhibitors (ICIs) enhance T-cell-mediated immune responses against cancer cells and cause activation of T-cell responses systemically, producing a range of immune-related adverse events (irAEs). Several cases of myocarditis with myositis and/or myasthenia gravis overlap syndrome (IM3OS) have been reported recently. The overlap syndrome makes the management complex, and the mortality rates are high. Our report supplied clinical experiences in the management of IM3OS.

Methods We reported a case series of 3 patients presenting with IM3OS. We presented the clinical characteristics, diagnostic procedures, treatments, and prognosis.

Results All three patients were male. The mean age was 71 years (63-83). The time intervals between ICIs initiation and disease onset were 23, 42, and 36 days, and the time intervals between disease onset and hospital admission were 4, 7, and 14 days, respectively. They all had fatigable fluctuating bilateral ptosis with or without ocular motor dysfunction, dropped head, and axial limb-girdle weakness with or without myalgia. The peak serum creatine kinase (CK) was raised at 5735, 3665, and 2517 u/l, with peak Troponin I levels(cTnI) at 4.4906, 0.2153, and 0.0562ng/ml, respectively. One patient showed myotonic discharge in the sternocleidomastoid muscle and increased jitter in single-fiber electromyography. All our patients were given medium-dose corticosteroids. One was given plasmapheresis, and one patient was given IVIG and a high-dose bolus(1g/d) of methylprednisolone due to respiratory failure. Pyridostigmine bromide was intolerant in two patients due to bradycardia and significantly prolonged PR interval. All the patients were successfully treated and had a good prognosis.

Conclusion Early recognition and treatment with corticosteroids and supportive care are critical for improving the outcomes of IM3OS patients. cTnI may be a more useful cardiac marker than cTnT in patients with myopathies in diagnosing or excluding myocardial damage. To improve the prognosis of severe patients, IVIG, plasmapheresis, and/or high-dose bolus of methylprednisolone should be administered as soon as possible. Due to the coexistence of myocarditis and MG, some IM3OS patients may be intolerant to pyridostigmine.

Comparison of Clinical Subtypes in Juvenile Idiopathic Inflammatory Myopathy, A Single Centre Retrospective-cohort Study

Yikang Wang,Yawen Zhao,Mengting Yang,Jingchu Yuan,Hongjun Hao,Hui Xiong,Feng Gao,Wei Zhang,Zhaoxia Wang,Yun Yuan
Peking University First Hospital

Objectives:
Because most studies have indicated variability among juvenile idiopathic inflammatory myopathies (JIIM) subtypes due to geographic and race/ethnicity differences, this study aimed to build a classification for Chinese JIIM patients and compare the subtypes.

Methods:
We recruited a consecutive series of 101 JIIM patients. Myositis autoantibodies, muscle magnetic resonance imaging (MRI) and muscle biopsies were performed.

Results:
Juvenile dermatomyositis (JDM, 46.5%) and juvenile immune-mediated necrotizing myopathy (JIMNM, 43.6%) were the most common JIIM subtypes, followed by juvenile anti-synthetase syndrome (JASS, 9.9%). The most frequently detected autoantibodies were anti-NXP2 in JDM, anti-HMGCR in JIMNM, and anti-Jo-1 in JASS. Clinically, proximal-predominant weakness and higher creatine kinase were the most common in JIMNM, and distal muscle weakness and skin rashes were the most common in JDM. MRI revealed extensive muscle oedema in all subtypes, with higher levels in the anterior compartment of JDM than JIMNM and higher levels in the gluteus maximus of JDM than JASS. Fatty infiltration of muscle was more extensive and severe in JASS than in JDM. Myopathologically, scattered necrotic muscle fibres were present in all subtypes but were more common in JIMNM. Ischaemic myofibrillary loss and sarcoplasmic myxovirus resistant protein A expression were present only in JDM, whereas perifascicular necrosis was observed only in JASS.

Conclusion:
Due to the high frequency of JIMNM in our series, a new classification for Chinese JIIM is highly recommended. Myositis autoantibodies, clinical features, thigh MRI and muscle biopsy can aid in the diagnosis via the distinct patterns of each subtype.

A single-center large-sample clinical and therapeutic study of Anti- signal recognition particle myopathy

Jingchu Yuan[1],Mengting Yang[1],Yikang Wang[1],Yawen Zhao[1],Meng Yu[1],Yiming Zheng[1],Hongjun Hao[1],Wei Zhang[1,2],Zhaoxia Wang[1,2],Yun Yuan[1,2,3]

1. Department of Neurology，Peking University First Hospital

2. Department of Neurology, Peking University First Hospital，Bejing Key Laboratory of Neurovascular Disease

3. Key Laboratory of Neuroscience of Ministry of Education, Peking University

Introduction: Anti signal recognition particle (SRP) myopathy is a rare subtype of immune-mediated necrotizing myopathy. This study retrospectively analyzed the clinical characteristics and treatment of a large group of patients with SRP myopathy, and explored the characteristics of patients with refractory SRP myopathy.

Methods: The clinical data of 94 patients with anti-SRP myopathy were collected and divided into refractory and non-refractory groups.

Results: Childhood-adolescent onset patients accounted for 12.8%, with an average onset age of 9.3±3.2 years; adult-onset patients accounted for 87.2%, with an average onset age of 45.9±13.1 years. 44.7% of the patients had chronic and insidious onset. The main clinical manifestations were bilateral symmetrical proximal limb weakness (93.6%), accompanied by distal limb weakness (36.2%), neck flexion weakness (78.7%), dysphagia (48.9%), muscle pain (28.7%), muscle atrophy (28.7%) and varying degrees of weight loss (44.7%). The mean CK level was 6885.8±6300.7 (574-28819) IU/L. In addition to anti-SRP antibody, other myositis antibodies were detected in the serum of some patients, and most of them (42.5%) were combined with anti-Ro-52 antibody. 67.6% of the patients had ventilatory dysfunction, mainly restrictive ventilatory dysfunction, and some patients had diffusion dysfunction. Interstitial lung disease was found in 38.4% of the patients. Muscle MRI showed muscle edema in 87.3% of the patients, and muscle fat infiltration in 77.5% of the patients. The adductor magnus muscle was the most severely affected, and the posterior group of the thigh was more severely affected than the anterior and medial groups. Skeletal muscle biopsy showed necrotizing myopathy-like pathological changes in most patients (90.8%), and some patients had muscular dystrophy-like pathological changes. The refractory patients accounted for 79.5%, and the proportion of pediatric patients and the incidence of muscle fat infiltration in thigh muscle MRI were significantly different from the non-refractory patients.

Conclusion: Compared with Caucasian patients, SRP myopathy patients in China are younger, with more children and adolescents at onset, and hypoventilation is common. The Chinese SRP myopathy patients have the characteristics of chronic onset in terms of onset pattern, skeletal muscle MRI and biopsy. The proportion of patients with refractory SRP myopathy is relatively high, which may be related to skeletal muscle fatty infiltration.

Clinical and pathological characteristics of Scleromyositis patients with positive anti-Ku or anti-PM-Scl antibodies

Yawen Zhao,Xinyu Zhang,Yikang Wang,Mengting Yang,Wei Zhang,Zhaoxia Wang,Yun Yuan
Peking University First Hospital

Objective: To summarize the clinical and pathological characteristics of scleroderma-associated antibody positive scleromyositis patients.

Method: Collect clinical and skeletal muscle pathological data of patients with positive anti-Ku or anti-PM-Scl antibodies, summarize their characteristics of muscle involvement and skeletal muscle pathological changes, and conduct subgroup analysis.

Result: A total of 70 patients were collected, of which 23 were positive for anti-Ku antibodies, 46 were positive for anti-PM-Scl antibodies, and 1 was both positive for anti-Ku antibodies and anti-PM-Scl antibodies. In these cases, male: female was 27:43, with an average onset age of 36.14 ± 18.68 years. 54 cases presented with mild to moderate muscle weakness, 48 cases (88.88%) with proximal muscle weakness, 36 cases (83.72%) with neck weakness, and 20 cases (51.28%) with skin involvement. Their serum creatine kinase was 2775.00 (995.50, 4995.75) IU/L. 12 patients (17.14%) of them were positive for Ro-52 antibody. The main pathological manifestations of skeletal muscle are inflammatory myopathy (29 cases, 41.43%) and necrotic myopathy (17 cases, 24.29%). The proportion of women in anti-Ku antibody positive patients was higher than that in anti-PM-Scl antibody positive patients (78.26% vs 52.17%, P=0.036), and the deposition of C5b-9 in anti-Ku antibody positive group is significantly higher than that in anti-PM-Scl antibody positive group (86.96% vs 60.87%, P=0.026).

Conclusion: Scleromyositis patients who are positive for anti-Ku or anti-PM-Scl antibodies are more likely to develop the disease in young and middle-age. The main manifestation is mild to moderate muscle weakness in the proximal limbs. Half of them having skin sclerosis. The pathological changes of skeletal muscle are more common in inflammatory and necrotic myositis.

Pipestem capillaries in necrotizing myopathy: a pathological and clinical characterization in Chinese patients

Xingyu Xia
Fudan University, Huashan Hospital

Necrotizing myopathy with pipestem-capillaries, a unique subtype of inflammatory myopathies characterized by muscle fiber necrosis, thickened capillaries, and rare inflammatory infiltration, has been infrequently reported in the literature. In this study, six cases exhibiting pipestem-like morphology, along with clinical and histological features, were presented. Major histocompatibility complex class I upregulation was general, but the deposition of C5b9 membrane attack complex was not predominant. Electron microscopy revealed that all cases of microangiopathy exhibited thickened basal lamina, which could be classified into two types: thickened duplication and diffuse thickening basal lamina. Although the cause of these capillary changes is still unclear, these findings contribute to a better understanding of this distinct myopathy subtype.

Immune checkpoint inhibitor-related neuromuscular complications: A single-center case series

Huiting Lin,Jinhao Ye,Wenshuang Zeng
The University of Hong Kong-Shenzhen Hospital

Introduction: Immune checkpoint inhibitors (ICI) can cause neuromuscular complications, including myasthenia gravis, myositis, myocarditis, and overlap syndrome. However, the predictors of poor prognosis remain unclear.

Methods: We studied the characteristics of 11 patients with immune checkpoint inhibitor-related neuromuscular complications at The University of Hongkong-Shenzhen Hospital. All available clinical data, laboratory examinations, therapeutic and disease-specific factors were examined. Adverse prognosis included death and symptom recurrence. Clinical predictive factors for increased adverse prognosis were analyzed using t-tests for parametric data and Wilcoxon signed-rank tests for non-parametric data.

Results: Two patients received combination ICI therapy, while the remaining nine patients received PD-1 treatment. During the analysis, eight out of the 11 patients survived, three died, and four relapsed. Our study confirmed that troponin is an early predictor of poor outcomes. Patients with a shorter time from initial use of immune checkpoint inhibitors to the onset of clinical symptoms generally had worse prognoses. Additionally, our studies have shown that reduced serum creatinine in patients who die early. In this study, no direct correlation was observed between increased NT Pro-BNP, decreased left ventricular ejection fraction, arrhythmia and poor prognosis. Combination ICI therapy has been linked to higher recurrence rate and mortality.

Conclusion: Our study examined various clinical parameters of immune checkpoint inhibitor-related neuromuscular complications, confirming that troponin is a possible predictor of poor prognosis and adding decreased creatinine as possible early biomarkers of death and recurrence in patients. The shorter the duration of the disease, the higher the probability of death or recurrence. Echocardiography has limited diagnostic value for early prognosis.

Dermatomyositis during COVID-19 pandemic: A Comparative Study of Clinical Features and Possible Shared Immunologic Pathogenesis

Panuvich Dangchant[1],Manta Yonpiam[1],Atthanee Jeeyapant[2,3],Jakkrit Amornvit[4,5],Nath Pasutharnchat[4,5]

1. Faculty of medicine, Chulalongkorn university
2. Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
3. Biostatistics Excellence Center, Research Affairs, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
4. Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
5. King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand

Introduction

COVID-19 patients may develop symptoms similar to dermatomyositis (DM), particularly the anti-MDA-5 antibody subtype with rapidly progressive interstitial lung disease. Similarities between DM and COVID-19 infection may indicate a shared immunologic mechanism, but additional research is required to confirm this hypothesis.

Methods

A retrospective study compared DM patients who developed disease prior to (pre-COVID) and subsequent to (post-COVID) the emergence of the COVID-19 pandemic. The study assessed onset and diagnosis time, muscle strength using the MRC muscle power scale, creatinine kinase (CK) levels, myositis antibody profiles (including myositis specific antibodies [MSAs], anti-synthetase antibodies, and myositis associated antibodies [MAAs]), and the presence of underlying cancer.

Results

A total of 24 patients diagnosed with DM were included, with 11 and 13 in the pre-COVID and post-COVID groups, respectively. There was a statistically significant difference in age between the two groups, with a median age of 40 [IQR; 38-50] in the pre-COVID and 54 [IQR; 47-58] in the post-COVID ($p = 0.042$). The median time to diagnosis, MRC at diagnosis, six and twelve months, and median CK at diagnosis and maximum, revealed no significant difference. In the post-COVID period, the prevalence of MSAs and MAAs, including but not limited to anti-MDA-5 antibodies, has a tendency to increase. The percentage of MSAs was 36.36% (pre-COVID) and 70% (post-COVID) ($p = 0.198$). MAAs were 27.27% (pre-COVID) and 70% (post-COVID) ($p = 0.086$), also higher in the post-COVID. Notably, the underlying cancer presence was 15.38% in pre-COVID and 40% in post-COVID ($p = 0.341$), higher in the post-COVID-19 group, yet this difference was not statistically significant.

Conclusion

The comparative analysis between pre-COVID and post-COVID DM patients demonstrated an increased tendency for MSAs and MAAs. Further research is essential to explore the multifaceted impact of COVID-19 on DM.

Rare phenotype and pathology of anti-neurofascin 155 autoimmune nodopathies

Zhenyu Li,Xujun Chu,Meng Yu,Jianwen Deng,Lingchao Meng,Wei Zhang,Zhaoxia Wang,Yun Yuan,He Lv
Peking University First Hospital

Autoimmune nodopathy is featured by antibodies against paranodal proteins, like anti-neurofascin 155 (NF155), anti-neurofascin 186 (NF186), anti-contactin 1 (CNTN1), and anti-contactin-associated protein 1 (CASPR1). This study summarized the rare phenotype and pathology of patients.

Male is dominant in patients (90%). The age on set ranges from ten to thirty-six years old, and the course of disease ranges from one month to twenty years old. The manifestation included weakness and numbness in distal limbs, paresthesia in lower limbs, and tremors in hands. Moreover, blurred vision, band feeling in the waist, and mild bucking when drinking water were observed. The physical examination shows the strength of muscles decreased, the sensation decreased in extremities, tendon reflex decreased to extremities in different degrees, and ataxia. The routine examination and sural nerve biopsy were completed.

The protein in CSF increased to 1.9 g/L, and NF155 IgG4 was all positive. The result of nerve conduction suggested demyelinating change (40%), axonal with demyelinating change (50%), and temporal dispersion (40%). The ultrasound showed diffuse thickening of peripheral nerves in limbs, and the nerve root MRI showed thickening cervical and lumbosacral nerve roots. The sural nerve biopsy indicated the demyelinating change in three patients, and the mass of onion bulbs was observed in two patients with over ten years of disease course. In addition, the giant axon change was found in one patient. Other patients with axonal or mix change. For therapy, one patient reported improving tremors after two years without any immunotherapy, three patients reported symptoms improved after glucocorticoid therapy, two patients reported symptoms improved after rituximab treatment, and symptoms improved in two patients and worse in two patients after applying glucocorticoid and IVIG.

The results indicated heterogeneity in the prognosis in pathologic changes.

DOK7 Congenital Myasthenic Syndrome mutations and manifestations

Ziaadini Bentalhoda
Kerman University of Medical Sciences

Background: Congenital myasthenic syndromes (CMS) are one of the most challenging diagnoses in neuromuscular domain. CMSs follow an autosomal pattern inheritance. Mutation in downstream of tyrosine kinase, Docking Protein 7 (DOK7) is a common cause of CMS. Ptosis, facial and neck weakness are common symptoms. The diagnosis is confirmed by genetic testing. Patients generally respond to salbutamol. The main objective of this study was to describe manifestations of DOK7 CMS.

Methods: Six patients were entered from neuromuscular clinic of Shariati hospital and Kerman medical university hospital. The diagnosis was made upon limb girdle myasthenic pattern. They were undergone 3 Hz RNS, repetitive CMAP, and whole exom sequencing. Drugs included mestinon, salbutamol, ephedrine, and 3,4-diaminopyridine. The patients were assessed by myasthenia gravis activities of daily living profile (MG-ADL) before and after the drug.

Results: The mean age and age of onset were 37.3 and 12.5 respectively. (3 female and 3 male). Their symptoms had fluctuating pattern. All patients were seronegative for myasthenic antibodies. Mean CK level was 166.5 units/L. 3-Hz RNS was decremental in 5 patients. No repetitive CMAP was seen. The mean MG-ADL before the drug trial was 6.1 and after treatment, it was 2.6. Oral salbutamol was the most effective with significant improvement in MG-ADL score of 5 patients. 1124_1127dupTGCC mutation was the most common mutation (50%). All mutations were homozygous and two of them were novel mutations.

Conclusion: It is recommend to neurologists to consider DOK7 CMS in patients with these symptoms and to prescribe salbutamol as first choice.

Diverse myopathological features in the congenital myasthenia syndrome with GFPT1 mutation

kaiyan jiang,Min Zhu,Daojun Hong
The First Affiliated Hospital of Nanchang University

Introduction: Mutations in the GFPT1 gene are associated with a particular subtype of congenital myasthenia syndrome (CMS) called limb-girdle myasthenia with tubular aggregates. However, not all patients show tubular aggregates in muscle biopsy, suggesting the diversity ofmyopathology should be further investigated.

Methods: In this study, we reported two unrelated patients clinically characterized by easy fatigability, limb-girdle muscle weakness, positive decrements of repetitive stimulation, and response to pyridostigmine. The routine examinations of myopathology were conducted. The causative gene was explored by whole-exome screening. In addition, we summarized all GFPT1-related CMS patients with muscle biopsy in the literature.

Results: Pathogenic biallelic GFPT1 mutations were identified in the two patients. In patient one, muscle biopsy indicated vacuolar myopathic changes and atypical pathological changes of myofibrillar myopathy characterized by desmin deposits, Zdisc disorganization, and electronic dense granulofilamentous aggregation. In patient two, muscle biopsy showed typical myopathy with tubular aggregates. Among the 51 reported GFPT1-related CMS patients with muscle biopsy, most of them showed tubular aggregates myopathy, while rimmed vacuolar myopathy, autophagic vacuolar myopathy, mitochondria-like myopathy, neurogenic myopathy, and unspecific myopathic changes were also observed in some patients. These extra-synaptic pathological changes might be associated with GFPT1-deficiency hypoglycosylation and altered function of muscle-specific glycoproteins, as well as partly responsible for the permanent muscle weakness and resistance to acetylcholinesterase inhibitor therapy.

Conclusions: Most patients with GFPT1-related CMS had tubular aggregates in the muscle biopsy, but some patients could show great diversities of the pathological change. The myopathological findings might be a biomarker to predict the prognosis of the disease

Congenital myasthenic syndromes overlapping with limb-girdle muscular dystrophy caused by GMPPB mutations: one case report and literature review

Guorong Zhang,Yun Chen,Yan Song,Chen Liu,Yuzhong Wang
Affilicated hospital of Jining medical university

Introducion: Mutations in GMPPB have been reported in congenital myasthenic syndromes (CMS) and limb-girdle muscular dystrophy (LGMD). However CMS overlapping with LGMD caused by the mutations in GMPPB is uncommon, it can lead to confusion and misdiagnosis among clinicians and neurologists.

Methods:In this report, one patient fulfilling the diagnostic criteria for CMS and LGMD were included from our hospital. Data collection included clinical presentation and signs,family history,neurophysiological, pathological and laboratory features.

Results: A 42-year-old female presented with progressive limb weakness for 40 years and fluctuating ptosis for two years.Her sister had similar clinical manifestations. Her creatine phosphokinase was 1200 IU/l and muscular biopsy was performed showing a dystrophic pattern. A pathological decrement of 25% was detected after repetitive nerve stimulation studies at 3Hz . We identified the GMPPB mutations: c.640+1G>A and c.1151G>A in the patient and her sisiter. The patient received pyridostigmine treatment. A follow up at six months after onset, our patient showed somewhat recovery.

Conclusions:GMPPB mutations cause CMS overlapping with muscular dystrophy. Treatment with pyridostigmine has been reported to be effective in those patients.

Limb-girdle muscular dystrophy with congenital myasthenia syndrome caused by GMPPB gene mutation:a-casereport

Huimin Zou[1],Ran Li[2],Yun Chen[1],Yanlei Hao[3],Yuzhong Wang[1]
1. Affiliated hospital of jining medical university
2. Cheeloo college of medicine,Shandong University
3. Taikang brain hospital,Ningbo

Objective: To report a case of limb-girdle muscular dystrophy with congenital myasthenia syndrome caused by guanosine diphosphate mannose pyrophosphorylase-B gene mutation.
Methods: By means of analyzing the clinical data,Detection of serum enzyme and antibody concentration,electromyography and MRI,musclebiopsy,genesequencing,from a patient diagnosed as limb-girdle muscular dystrophy (LGMD)with congenital myasthenia syndrome (CMS)in our hospital,and review the relevant literature.
Results: The patient was admitted to hospital because of"fluctuating limb weakness for more than 10years,and aggravated for 1year".The main manifestations were limited lifting of upper limbs,weakness in walking,in ability to walk for a long distance,and difficulty in squatting,which can be slightly relieved after rest.The symptoms were mild during the day and aggravated at night. In recent one year,the above symptoms were aggravated with out other discomfort.There were no positive signs in physical examination.The muscle strength of the left upper lim b proximal part was Grade3,distal part was Grade4,the right upper limb proximal part was Grade4,distal part was Grade5,and the left lower limb proximal part was Grade4-,distal part was Grade5-,the right lower limb proximal part was Grade4,distal part was Grade5.The muscle tension was normal and the tendon reflex was decreased.The sensory ataxia was normal and the double PAP sign was negative.His parents and brother had nosimilar medical history.Creatine kinase 1732U/L,creatine kinase is oenzyme MB 15.18ng/ml,lactated ehydrogenase 268U/L.Electromyography(EMG) suggested myogenic damage and abnormal repetitive nerve
stimulation.Fat infiltration in the long head of bilateral semitendinosus,Semimembranous and biceps femoris was considered in MRI of lower limbs.The neostigmine test was positive.In the musclebiopsy,HE showed that the size of muscle fibers varied,with degeneration,necrosis and regenerated of muscle fibers visible.Inflammatory cell infiltration could be seen in part of muscle intima and perimuscular membrane,without increased perimymusculumnucleus and peribundle atrophy.The pathological diagnosis was consistent with the pathological changes of muscular dystrophy.Two mutations were found in GMPPB gene:c.1151G>A(guanine>adenine) caused amino acid change:p.R384H(arginine>histidine),which was A missense mutation.c.181_183delinsaaggaaa caused amino acid change:p.E61Kfs*21,which was a frame-coding mutation.
Conclusions: GMPPB gene mutation can lead to O-glycosylation defects of α-DG and

N-glycosylation defects of β-DG in human cells and animal models.Its related phenotypes are extensive and can lead to overlap of different clinical phenotypic results,such as the overlap between LGMD and CMS like this case.GMPPB gene is autosomal recessive inheritance.Two mutations sites were found in this gene from this patient.It was verified that one of the mutation sites came from the father and the other mutation site came from the mother,which was in line with the genetic law and could cause disease in theory.Combined with further clinica lanalysis,the patient was diagnosed as LGMD combined with CMS.

The Clinical Features and TTN Mutation Spectrum in a Chinese Cohort of Patients with hereditary myopathy with early respiratory failure

Xiaoqing Lv[1],Zhe Zhao[2],Yuebei Luo[3],Chuanzhu Yan[4],Pengfei Lin[4]

1. Qilu Hospital of Shandong University, Cheeloo College of Medicine, Shandong University
2. The Third Hospital of Hebei Medical University
3. Xiangya Hospital, Central South University
4. Qilu Hospital of Shandong University

Hereditary myopathy with early respiratory failure (HMERF) is a subtype of myofbrillar myopathy. Mutations located on exon 344 of the titin-A band, the 119th fbronectin-3 domain (FN3 119), are responsible for HMERF. In this article, we retrospectively analyzed the clinical features, fndings of muscle imaging, muscle pathology, immunohistochemistry, and ultrastructural characteristics of 13 patients diagnosed with HMERF. Muscle MRI showed the involvement of semitendinosus in four patients. The common pathological features were variability in fber diameter, increased internal nuclei, endomysial fbrosis, and cytoplasmic bodies. Among the 13 patients, the median age at onset was 34 years (range 14–54). the hotspot mutation is c.95195C>T. This article also expands the clinical, pathological, mutational, and radiological spectrum of patients with LGMDR7 in China and in the world.

Episodic ataxia type 1 complicated with epilepsy caused by KCNA1 gene variation: a case report

Ying Wu,Hui Xiong
Peking University First Hospital

Objective To summarize the clinical phenotype and genotype characteristics of episodic ataxia type 1 with epilepsy caused by KCNA1 gene variation.

Methods The clinical data of one patient with episodic ataxia type 1 and epilepsy at Pediatrics clinic of Peking University First Hospital in November 2021 were retrospectively analyzed caused by KCNA1 gene mutation. The literature was retrieved to summarize characters of these children.

Results The patient was developmentally retarded from childhood. She had recurrent seizures from the age of half a month, and fever was prone to induce status epilepticus. She had episodic ataxia at the age of 2 years and 7 months. The electroencephalogram showed a large number of diffuse slow waves, generalized spike waves and spike slow waves in each phase of waking and sleeping. Craniocerebral magnetic resonance imaging showed no abnormality.The whole exon gene sequencing showed a de novo heterozygous variation in the KCNA1 gene C.1213C > T (p.p405S). Combined with literature, it was found that mutations in the S6 domain of KV1.1α subunit encoded by KCNA1 gene were prone to epilepsy.

Conclusions The clinical phenotypes of KCNA1 gene variants are different, which can be manifested as episodic ataxia and/or drug-resistant epilepsy. There is a certain genotype-phenotype relationship. Therefore, KCNA1 gene variants should be considered when patients with epilepsy and developmental delay develop episodic ataxia. Fever may induce status epilepticus, and care should be taken to avoid infection.

Anti-α-Actinin Immunostaining is Sensitive but Non-specific as a Diagnostic Marker for Sporadic Late-Onset Nemaline Myopathy

Mingshi Gao[1],Dongyue Yue[2],Nachuan Cheng[1],Kexin Jiao[1],Ningning Wang[1],Xingyu Xia[1],Chongbo Zhao[1],Wenhua Zhu[1]

1. Huashan Hospital Fudan University

2. Jing'an District Center Hospital of Shanghai

Introduction:

Alpha-actinin, an important structural protein in muscles, anchors actin filaments and stabilizes myofibrils. Some studies suggest that anti-α-actinin antibody may serve as a diagnostic marker for sporadic late-onset nemaline myopathy (SLONM), but its specificity and sensitivity remain debated.

Objectives:

To investigate the utility of anti-α-actinin antibody as a diagnostic marker for SLONM and to study its expression in other muscle diseases.

Materials and Methods:

Muscle specimens were obtained from 54 cases, including SLONM, neurogenic atrophy, rhabdomyolysis, type II fiber atrophy, dermatomyositis, immune-mediated necrotizing myopathy, inclusion body myopathy, and normal controls. The samples were stained with anti-α-actinin antibody using standard protocols, and two independent observers blinded to the sample groups evaluated the staining results.

Results:

The positive expression rate of α-actinin was highest in SLONM (11/12) but was also present in other muscle diseases. The upregulation of anti-α-actinin expression is not specific to SLONM and may occur whenever metabolic abnormalities or functional damage to muscle cells are present.

Conclusion:

In clinical practice, the expression level of anti-α-actinin alone is insufficient for diagnosing SLONM or other muscle diseases. A comprehensive diagnosis and assessment based on additional clinical and pathological characteristics is necessary.

Progressive limb weakness over 5 years

Shaohua Liao
the First Affiliated Hospital of Naval Medical University

Introduction:

We reported a 35 year old female patient with progressive limb weakness over 5 years. During the course, there was no numbness, pain, fever, and no difficulty in swallowing, or breathing. She is pregnant normally and has given birth to two boys, both of whom are developing normally. Her father passed away while sleeping at the age of 58, and her mother and brother were in good health.

Methods:

We carried out clinical physical examination, blood biochemistry, Electromyography, head and liver magnetic resonance (MRI), muscle pathology, Genetic testing, and clinical follow-up, and reached conclusions.

Results:

Clinical examination: Mainly characterized by weakness in the proximal limbs, with no abnormalities in the deep and shallow sensations of the trunk and limbs.

Blood test: CK and LDH slightly increased, while serum copper and ceruloplasmin decreased.

Electromyography indicates myogenic damage. There were no significant abnormalities in the MRI of the head and liver.

Muscle pathology: Individual axial hollow fibers are seen. Electron microscopy showed a slight increase in lipid droplets.

Genetic testing: Compound heterozygous mutation of ATP7B gene is indicated. The family verification mutations are located in different DNA strands. Protein structure prediction indicates changes in amino acid side chains.

Follow up: After 2 months of treatment with Penicillamine, the symptoms of limb weakness improved.

Conclusion:

We report a case of Wilson's disease with myasthenia as its clinical manifestation. Its clinical characteristics include: progressive limb weakness, reduced serum copper and ceruloplasmin, Electromyography indicating myogenic damage, muscle pathology showing individual axonal fibers, electron microscopy showing a slight increase in lipid droplets, and Genetic testing showing compound heterozygous mutations of ATP7B gene. After treatment with Penicillamine, the symptoms of limb weakness improved.

Targeted massive parallel sequencing and comprehensive phenome-genome assessment in neuromuscular patients without genetic etiology by conventional diagnostic methods

Anna Cho[1,3],Jong Hee Chae[2,3]
1. Seoul National University Bundang Hospital
2. Seoul National University Hospital
3. Seoul National University College of Medicine

Introduction: Neuromuscular disorders are clinically, pathologically, and genetically heterogeneous groups of disorders. The advent of next generation sequencing (NGS) technologies started a new era of molecular genetic diagnosis in the recent clinical and research fields.
Methods: NGS-based targeted sequencing panels were applied to the diagnostic workflow in the genetic characterization of 327 patients who were suspected of having hereditary neuromuscular disorders but without a definite molecular diagnosis using traditional genetic analysis. Four sets of targeted sequencing panels prepared at different times and were sequentially applied. We further performed comprehensive phenome-genome analysis after the NGS application.
Results: Pathogenic mutations were confirmed in 161 cases (49.2%) out of 327 patients. Diagnostic yields differed according to the clinical phenotype classifications. The causative mutations were found in 50 different genes and the six most frequently found genes were *COL6A1* (n = 21), *RYR1* (n = 18), *DMD* (n = 10), *COL6A2* (n = 9), *ACTA1* (n = 7), and *LMNA* (n = 7) in order. Additional diagnoses were obtained in 28 cases (16.8%) with clinical follow-up of more than 1 year and additional diagnostic tests.
Conclusion: This study illustrates the clinical utility of targeted NGS as a powerful diagnostic tool in hereditary neuromuscular disorders. Integrated phenome-genome analysis is very important for improving the diagnostic efficiency of this technique. It is necessary to establish a comprehensive diagnostic platform for the molecular diagnosis of neuromuscular disorders that integrates single gene testing and NGS based on the phenotype analysis.

Clinical and pathological characteristics and pathogenic gene analysis of two families of Andersen-Tawil syndrome caused by heterozygous mutations of KCNJ2 gene

Jiaxuan Wang,Qianqian Qu,Wenhao Cui,Cong Hu,Shiyao Li,Jiongbo Zhao,Haidong Lyu
Jiaozuo People's Hospital of Xinxiang Medical University

Objective: To summarize the clinical, myopathological and pathogenic gene mutation characteristics in two families of Andersen-Tawil syndrome (ATS), and to improve the level of clinicians' understanding.

Methods: The clinical and myopathological data of patients in two ATS families were retrospectively summarized, and genetic tests were performed on the proband and some family members.

Results: Family 1 involved 4 patients in 4 consecutive generations and Family 2 involved only 1 patient in 4 generations. The five patients in two families all started in adolescence, and the main clinical manifestations were episodic limb weakness, and the clinical diagnosis was periodic paralysis. The periodic paralysis symptoms of the proband in family 1 was always evoked by cold and exercise, and the frequency of attacks is several times a year to more than a dozen. In severe cases, it is difficult to turn over or get up, and it usually lasts 4 to 7 days and then resolves. And once laboratory tests have low blood potassium. After regular oral potassium supplementation, the frequency and severity of attacks were reduced. The weakness of the two adult females in Family 1 was always evoked by the nervousness, exertion, and Premenstrual period. The proband of Family 2 always was tired and felt fatigue in both lower limbs one day before the onset, and the next morning she had limb weakness and difficulty in movement, and the frequency of attacks was about once every two months. All 5 patients in two families have features of small mandible, high-arched palate, low-set ears, widely spaced eyes, and fifth-digit clinodactyly. Among them, 4 adult patients have short statures, and 1 child patient is in the growth and development stage that cannot be determined. None of the 4 patients in Family 1 had obvious symptoms of cardiac involvement, and all ECGs were normal. The proband of Family 2 had intermittent palpitations, and the ECG was a frequent bigeminy of premature ventricular beats. The ENMG long-exercise test of 2 probands was positive. The MRI of both lower extremities of 2 probands showed no obvious abnormalities. Muscle biopsies were performed in 2 probands, and both revealed tubular aggregates. We conducted genetic testing on 2 probands and some of their family members and found that there were KCNJ2 gene mutations. Genetic testing revealed that there was a heterozygous c.407C>T (p.Ser136Phe) mutation of the KCNJ2 gene in the first proband and his mother. And a heterozygous of c.652C>T (p.R218W) mutation was reported in the second proband.

Conclusion: Andersen-Tawil syndrome (ATS) is an autosomal dominant disorder characterized

by a triad of periodic paralysis, ventricular arrhythmias, and craniofacial skeletal deformities, which is clinically rare. And in any periodic paralysis individual presenting with ventricular arrhythmias or craniofacial skeletal deformities, ATS should be considered to avoid misdiagnosis. In some patients, tubular aggregates may be found in the muscle pathology. The discovery of KCNJ2 gene mutation by Genetic testing is an important basis for the diagnosis of ATS.

The Immune Features In Amyloid Myopathy And The Potential Mechanisms

Xinmei Wen,Li Di,Wenjia Zhu,Yan Lu,Min Wang,Yuwei Da
Xuanwu Hospital

Introduction: Systemic amyloidosis is often coined as "the great imitator" due to its diverse clinical presentation, which varies depending on the specific organs or systems that are affected. Amyloid myopathy as the initial presentation of systemic amyloidosis is a rare condition, and a diagnostic delay or even a misdiagnosis is quite common. Since its diagnosis requires confirmation of amyloid deposition in involved tissues, raising the awareness of the pathological hallmark of amyloid myopathy is of pivotal importance for prompt diagnosis.The pathophysiological mechanisms by which amyloid deposition in primary systemic amyloidosis causes myopathy is largely unknown.

Methods: Amyloid myopathy cases diagnosed in our center between 2014 and 2022 were retrospectively reviewed and only cases with myopathy as the initial manifestation were included. Clinical and neuro-electrophysiological characteristics were analyzed. Muscle biopsies were carefully evaluated. An immunohistochemical analysis of a panel of immune biomarkers was performed to characterize the immune profile. Furthermore, a comprehensive literature review was conducted, focusing on the detailed pathological characterization of immune involvement.

Results: Congo red-stained amyloid was found in muscle biopsy sample involving perivascular, perimysial and endomysial regions. By using the advantage of dual immunostaining, it's shown that amyloid deposits infiltrated peri-muscular vessels, disrupted muscle cell membranes, intruded myofibers, and might ultimately lead to complement activation mediated cytotoxic pathway.

Conclusion: Amyloid myopathy is a rare presenting manifestation of primary systemic amyloidosis and is often overlooked. Amyloid angiopathy was a frequent pathological finding and might cause ischemic injuries. The damage to the muscle system could also be caused by amyloid infiltrating the peri-muscular vessels, crashing muscle fibers directly and/or eroding (disrupting) basement membranes of the myofibers. The latter is probably mediated by complement activation and the assembly of membrane attack complex (MAC) on to the basement membrane.

A novel mutation in the myotilin gene (MYOT) causes myofibrillar myopathy： A Family Report and Literature Review

Cong Hu,Qianqian Qu,Wenhao Cui,Yaguang Zhou,Shiyao Li,Jiaxuan Wang,Jiongbo Zhao,Haidong Lyu

Jiaozuo People's Hospital of Xinxiang Medical University, Jiaozuo, China

Objective: To investigate the clinical features, muscle MRI and pathological changes, and genetic variants of Myofibrillar myopathies (MFMs) caused by MYOT gene variants.

Methods: For a large family with 30 family members, the clinical data and some genetic test **results** of 8 patients were collected in detail. Lower limb muscle MRI and pathological biopsy were performed on the proband and discussed in conjunction with relevant literature.

Results: The proband was a male, 34 years old, who gradually developed weakness in the thumb of the right hand at the age of 14, which affected writing and holding things, and about 5 years later developed weakness in the left finger, unable to do fine movements, and able to perform general physical labor.At the age of 27, the symptoms of weakness in both fingers worsened, and it was difficult to fasten buttons and hold chopsticks. And gradually appear distal weakness of both lower limbs, the right lower limb is more pronounced, can go up and down stairs, but running is significantly slower.In the past two years, the weakness of the hands has worsened, and obvious muscle atrophy has occurred, and electromyography shows myogenic pattern, and serum muscle enzymes are mildly elevated.Muscle MRI indicates that there were no obvious abnormal signal shadows in bilateral anterior and posterior thigh muscle groups; A patchy slightly longer T1 and slightly longer T2 signal shadow can be seen in the bibial anterior muscle tissue of both calves, which is more obvious on the right side, indicating partial atrophy, liposification and mild edema of the anterior calf muscles.Muscle pathology shows that muscle fibers are obviously different in size, with more round atrophic fibers and compensatory hypertrophic muscle fibers. Histopesic ATPase staining showed that type I and II myofibers were mosaicked, and Modifed Gomori trichrome (MGT) staining showed typical or atypical rimmed vacuoles (RVs) in some myofibers, and atrophic myofibers were more common. The results of next-generation sequencing of genes found that the MYOT gene c.680_683del strongly related to myofibrillar myopathy frameshift mutation.Tracing the family history revealed that 8 family members had symptoms and signs similar to muscle weakness.We genetically tested 11 family members in the family line, and the proband's father, uncle, and two cousins were all detected with heterozygous mutations at the site. These family members all have similar clinical manifestations of distal bilateral upper extremity weakness with muscle wasting.The daughter of the proband is a carrier of the MYOT gene mutation and has not yet shown corresponding clinical symptoms. According to the clinical characteristics and genetic mode of patients in this family, as well as the muscle pathological changes and genetic

test results of the proband, myofibrillary myopathy caused by MYOT mutation can be diagnosed. We review the relevant literature on MFMs, at present, a total of 70 cases of myofibrillary myopathy caused by MYOT mutations have been reported abroad, the age of onset is 35-78 years old, the clinical manifestations are mainly chronic progressive limb weakness, most patients are mainly distal muscle weakness, which can be accompanied by peripheral neuropathy and myocardial involvement, a small number of patients have sensory symptoms, muscle pain or spasm, and respiratory muscle and gastrointestinal smooth muscle involvement.Only one case of MYOT gene mutation related to muscular dystrophy and postoperative respiratory failure has been reported in China, and no myofibrillary myopathy caused by MYOT mutation have been reported in the literature.

Conclusions: Myofibrillary myopathy caused by MYOT gene mutation is a rare autosomal dominant disease, and patients in this family all present with progressive distal limb muscle weakness, muscle MRI shows that the anterior calf group muscles are mainly involved, and muscle biopsy finds borderline vacuoles as its main pathological feature.This family is the largest family of myofibrillary myopathy caused by MYOT gene mutations reported in China, and the c.680_683del we detected is a new mutation type of MYOT, which further expands the gene mutation lineage of myofibrillary myopathy.

Diagnosis of Pediatric Neuromuscular diseases in Thailand

Oranee Sanmaneechai,Pimchanok Kulsirichawaroj
Faculty of Medicine Siriraj Hospital Mahidol University

Introduction: Clinical data on the occurrence and frequency of inherited neuromuscular disorders (NMD) in the population of Thailand is scarce.
Objective: This study aims to provide the diagnosis of pediatric-onset hereditary NMD in Thailand.
Methods: Clinical data and diagnosis of patients in a pediatric multidisciplinary neuromuscular clinic at Siriraj hospital, the largest tertiary referral hospital, over a 17-year period (2005–2022) were retrospectively reviewed. Diagnosis was made base on clinical history and confirmatory genetic testing.
Results: A total of 312 patients were diagnosed with 36 different disorders encompassing 9 classes of NMD. In this cohort, 86.9% of patients were diagnosed with muscular dystrophies, motor neuron diseases, and hereditary neuropathies. Forty-two percent diagnosed with Duchenne and Becker muscular dystrophy (DMD/BMD). Spinal muscular atrophy (SMA) was the second most frequently diagnosed NMD (20.8% of patients) which classified to 5q SMA type 1 (15 patients), type 2 (36 patients), type 3 (12 patients), and non-5q SMA (2 patients). A highly heterogeneous presentation of NMD was notably identified. The least common disorders (3.5% of patients) involved metabolic and mitochondrial myopathies, muscle channelopathies, and other NMD.
Conclusions: Our study indicates a significant healthcare burden of NMD in Thailand, a major challenge for multidisciplinary approach and a variety of NMD treatments in the pipeline. This report calls for a national or regional NMD patient registry.

A patient diagnosed with anti-synthetase syndrome in the presence of autophagic vacuoles with sarcolemmal features

NACHUAN CHENG,MINGSHI GAO,DONGYUE YUE,CHONGBO ZHAO,WENHUA ZHU
Huashan Hospital, Fudan University

A 65-year-old woman was admitted to the hospital with the complaint of "hyperCKemia for 1.5 years and proximal lower limb weakness for more than 1 year".
On October 2021, she began to have persistent thigh muscle myalgia and found her creatine kinase (CK) level was elevated to 1400 U/L. After 1 week of anti-inflammatory treatment, her CK level dropped to 700 U/L and the myalgia was relieved. Since January 2022, the patient developed proximal lower limb weakness, manifested as weakness in squatting, difficulty in going up and down stairs, and prone to falling when walking. At that time, she found her CK level was 700 U/L and was diagnosed with "myositis" in the local hospital. She received oral glucocorticoids, had her lower limb weakness significantly improved, and the drug was discontinued 2 months later.In January 2023, she developed lower limb weakness again, lost 5 kg weight in the past year, and came to our hospital. she had no exercise intolerance, dysphagia, dyspnea, tendon contractures, muscle atrophy, or sensory abnormalities.
On examination, the muscle strength of her neck and proximal upper and lower limbs were decreased (left/right Medical Research Council grade: neck flexors 3+, shoulder abductors 4+/4+, elbow flexors 5/4+, hip flexors 4+/4+, hip extensors 3+/4, knee flexors 4/4), whereas others were normal.
Laboratory investigation revealed that her CK level was 201 U/L, lactate dehydrogenase (LDH) level was 233 U/L and erythrocyte sedimentation rate (ESR) was 50 mm/h. Myositis-specific antibody test was positive for anti-PL-12 and Ro-52. Chest CT showed interstitial inflammatory changes in both lungs and lung function showed mild restrictive pulmonary ventilation dysfunction. Magnetic resonance imaging of the lower limbs showed significant edema of both thigh and calf muscles without obvious muscle atrophy and fat. Electromyography showed fibrillation potentials and small, short, polyphasic, and early-recruited motor unit action potentials (MUAPs) in proximal and distal lower limb muscles, suggesting a myopathic pattern, along with diffuse brief myotonic potentials.
Muscle biopsy showed that many muscle fibers had significantly increased basophilic granules and some fibers had vacuoles, which were strongly positive for Periodic acid–Schiff (PAS) and Acid Phosphatase (ACP). Immunohistochemistry showed that the vacuolar membrane was positive for dystrophin and dysferlin staining, suggesting the sarcolemmal features. In addition, there are individual necrotic and regenerating muscle fibers.

Plateaus and reversals evaluated by different methods in patients with limb-onset amyotrophic lateral sclerosis

Nan Hu[1],Dongchao Shen[2],Xunzhe Yang[2],Liying Cui[2],Mingsheng Liu[2]
Peking Union Medical College Hospital

Objective: To determine the difference in frequency of amyotrophic lateral sclerosis (ALS) reversals and plateaus in limb-onset patients evaluated with different methods.

Methods: One hundred and eighteen patients with limb-onset ALS were prospectively recruited. ALS Functional rating scale-revised (ALSFRS-R) score, total Medical Research Council (MRC) muscle strengthscore and clinical global impression (CGI) score were followed up every three months for at least 1 year. The changes between two follow-up points in scores were analyzed.

Results: Reversal and plateau in ALSFRS-R score were detected in 26.14% patients between initial and 3-month, 21.19% between 3-month and 6-month, 23.73% between 6-month and 9-month, 19.49% between 9-month and 12-month, respectively. For total MRC muscle score, the percentages were 28.81%, 21.19%, 16.95%, 13.56%, respectively. For CGI score, the percentages were 74.57%, 64.41%, 66.10%, 66.95%, respectively. There was significant difference in the frequency of plateau or reversal between ALSFRS-R scale and total MRC scale over 3-month interval visit ($P < 0.05$), while no significant difference was revealed between CGI scale and ALSFRS-R scale or total MRC scale. The frequency of reversal and plateau were 8.47% at 6-month, 4.24% at 9-month, 3.34% at the last follow-up in both ALSFRS-R score and total MRC score, respectively.

Conclusion: Plateaus and reversals in ALSFRS-R score, total MRC score and CGI score are not uncommon in limb-onset patients during follow-up. The combination of ALSFRS-R score and total MRC score could better reflect the relentless progression of ALS. The importance of long-interval follow-up should be stressed in clinical practice.

Facial onset sensory and motor neuronopathy (FOSMN syndrome): Cases series and systematic review

Nan Hu,Lei Zhang,Xunzhe Yang,Hanhui Fu,Liying Cui,Mingsheng Liu
Peking Union Medical College Hospital

Objective: To provide new and comprehensive evidence for diagnosis and management of FOSMN syndrome.

Methods: We reviewed our database to identify patients with FOSMN syndrome. Online database including PubMed, EMBASE, and OVID were also searched for relevant cases.

Results: We identified a total of 71 cases, including 4 cases from our database and 67 ones from online searching. A predominance of male was observed [44 (62.0%)] with median onset age of 53 (range: 7-75) years old. The median (range) disease duration was 60 (3-552) months at the time of the visit. The initial symptoms could be sensory deficits in face (80.3%) or oral cavity (4.2%), bulbar paralysis (7.0%), dysosmia (1.4%), dysgeusia (4.2%), weakness or numbness of upper limbs (5.6%), or lower limbs (1.4%). Abnormal blink reflex was presented in 64 (90.1%) patients. CSF tests showed elevated protein level in 5 (7.0%) patients. Six (8.5%) patients had MND-related gene mutation. Five (7.0%) patients showed transient responsiveness to immunosuppressive therapy, then deteriorated relentlessly. Fourteen (19.7%) patients died, with an average survival time of around 4 years. Among them, five patients died of respiratory insufficiency.

Conclusion: The age of onset, progress of disease course, and prognosis of FOSMN syndrome could be varied significantly. The prerequisites of diagnosis were progressive and asymmetric lower motor neuron dysfunction, with sensory dysfunction which usually showed in face at the onset. Immunosuppressive therapy could be tried in some patients with suspected inflammatory clues. In general, FOSMN syndrome tended to be motor neuron disease with sensory involvement.

Split hand in amyotrophic lateral sclerosis: A systematic review and meta-analysis

Nan Hu[1],Jingyi Wang[2],Mingsheng Liu[1]
Peking Union Medical College Hospital

Objective: To investigate the frequency of split hand (SI) and its diagnostic performance in amyotrophic lateral sclerosis (ALS).

Methods: PubMed, EMBASE, OVID and other databases were searched systematically up to March 2021 for relevant reports about the split hand syndrome. Two reviewers screened and selected the titles and abstracts of the studies independently during the database searches and performed full-text reviews and extracted available data. In our study, AACMAP was calculated by AACMAP = APBCMAP/ADMCMAP and split-hand index (SI) was calculated by SICMAP = (APBCMAP × FDICMAP)/ADMCMAP. The mean differences (MD) in APB/ADMCMAP and SICMAP between patients with ALS and control group were calculated (APB the abductor pollicis brevis muscle; ADM the abductor digiti minimi muscle; CMAP compound muscle action potentials). Meta-analysis was performed to determine summary sensitivity, specificity, and area under the curve (AUC) with 95% confidence intervals (CI) for SICMAP.

Results: Pooled results of five studies including 339 patients showed that 50% (95%CI: 35%-65%) of patients with ALS presented split hand. APB/ADMCMAP in patients with ALS was significantly lower than healthy population (MD: -0.38, 95%CI: -0.48, -0.28). SICMAP in patients with ALS was significantly lower than healthy controls (MD: -5.87, 95%CI: -6.28, -5.46) and neuromuscular controls (MD: -5.60, 95%CI: -5.78, -5.42). Receiver operating characteristic curve analysis showed that the AUC was 0.860 [95%CI: 0.808, 0.911] for SICMAP. The sensitivity and specificity for SICMAP were 78% and 81% (cut-off value: 5.2-11.8), respectively.

Conclusion: Half of ALS patients might show split hand sign. SICMAP could be a potential biomarker in the diagnosis of ALS.

The frequency of ALSFRS-R reversals and plateaus in patients with limb-onset amyotrophic lateral sclerosis: a cohort study

Nan Hu,Dongchao Shen,Xunzhe Yang,Liying Cui,Mingsheng Liu
Peking Union Medical College Hospital

Objective: Although amyotrophic lateral sclerosis (ALS) is a relentlessly progressive neurodegenerative disorder, ALS patients might show reversals or plateaus of ALS Functional rating scale-revised (ALSFRS-R) scores during follow-up, which might cast the doubt on the diagnosis. The study aims to determine the frequency of reversals and plateaus of ALSFRS-R score in patients with limb-onset ALS.

Methods: One hundred and fifty four patients with limb-onset ALS were prospectively recruited. ALSFRS-R scores were followed up every 3 months for at least 1 year. The changes between two follow-up points in ALSFRS-R score were compared.

Results: Totally 95 (61.7%) participants showed 85 times plateau and 69 times reversal in ALSFRS score during the 12-month follow-up when compared the ALSFRS-R score between two adjacent follow-up points. Reversal and plateau in ALSFRS-R score were detected in 31.8% patients between initial and 3 months, 18.8% between 3 and 6 months, 22.7% between 6 and 9 months, 22.7% between 9 and 12 months, respectively. When comparing with the ALSFRS-R score in the baseline, reversal and plateau in ALSFRS-R score were detected in 31.8% patients at 3 months, 14.9% at 6 months, 6.5% at 9 months, 5.8% at 12 months, respectively.

Conclusion: Plateaus and reversals in ALSFRS-R score were common in limb-onset ALS patients during follow-up. A relatively stable or reversal in the ALS-FRS-R score does not exclude the diagnosis of ALS. Limitations of ALSFRS-R score as an outcome parameter in clinical trial should be further evaluated.

Split Phenomenon of Fasciculation between Antagonistic Muscles in Amyotrophic Lateral Sclerosis: An Ultrasound Study

Nan Hu,Yi Li,Jingwen Liu,Liying Cui,Mingsheng Liu
Peking Union Medical College Hospital

Objective: Paresis of muscle groups in patients with amyotrophic lateral sclerosis (ALS) tends to present split phenomena. We explored the split phenomenon of fasciculation in multiple antagonistic muscle groups in ALS patients.

Methods: One hundred and forty ALS patients and 66 non-ALS patients were included from a single ALS center. Muscle ultrasonography (MUS) was performed to detect fasciculation in elbow flexor-extensor, wrist flexor-extensor, knee flexor-extensor, and ankle flexor-extensor. Split phenomena of fasciculation between different antagonistic muscle groups were summarized, and the possible influence factors were analyzed through stratified analysis.

Results: The frequency of split phenomenon of fasciculation intensity was significantly higher than those of muscle strength (26.1% vs. 7.1% for elbow flexor-extensor, 38.3% vs. 5.7% for wrist flexor-extensor, 37.9% vs. 3.0% for knee extensor-flexor, and 33.6% vs. 14.4% for ankle flexor-extensor) ($P < 0.01$). For muscles with 0-1 level of muscle strength (the Medical Research Council, MRC, score), significance difference in mean fasciculation intensity was observed only in ankle flexor-extensor. For muscles with 2-5 level of muscle strength, significant dissociation of fasciculation grade was common, especially among patients with slow rapid progression rate and both upper and lower motor neuron (UMN and LMN) involvement. As for non-ALS patients, no significant difference was observed in fasciculation intensity between antagonistic muscles.

Conclusion: Split phenomenon of fasciculation between antagonistic muscles was common and relatively specific in ALS patients. Muscle strength, progression rate, and UMN involvement were influence factors of the split phenomenon of fasciculation intensity.

Pattern of paresis in amyotrophic lateral sclerosis: A cohort study

Nan Hu,Yi Li,Jingwen Niu,Liying Cui,Mingsheng Liu
Peking Union Medical College Hospital

Objective: Paresis of muscle groups in patients with amyotrophic lateral sclerosis (ALS) tends to present split phenomena. We explored the dynamic changes of split phenomenon in multiple antagonistic muscle groups among ALS patients.

Methods: One hundred and twenty limb-onset ALS patients were followed up regularly with an interval of 3 months. Two clinicians collected the muscle strength of elbow extensor-flexor, wrist flexor-extensor, knee extensor-flexor and ankle flexor-extensor individually. Split phenomena of muscle strength between different antagonistic muscle groups were summarized, and the possible influence factors were analyzed through stratified analysis.

Results: Significant differences in muscles strength were observed between flexors and extensors of elbow, wrist, knee and ankle ($P < 0.05$). The frequency of split phenomenon of elbow extensor-flexor was 15.1%, 13.8%, 19.1%, 17.8%, 12.5% at the baseline, 3-month, 6-month, 9-month and 12-month follow-up points, respectively. For wrist flexor-extensor, the frequency was 20.8%, 18.2%, 18.6%, 19.9%, 20.4%, respectively. For knee extensor-flexor, the frequency was 3.0%, 8.0%, 7.6%, 8.4%, 8.9%, respectively. For ankle flexor-extensor, the frequency was 8.8%, 9.2%, 10.9%, 15.4%, 15.7%, respectively. For muscles with 3-4 level of muscle strength, significant dissociation of muscle strength was common, especially among patients with slow rapid progression rate.

Conclusion: Split phenomenon of muscle strength between antagonistic muscles was common in limb-onset ALS patients. Muscle strength and progression rate were influence factors of the split phenomenon. As the disease progressed, the frequency of split phenomenon gradually increased, and might then slowly decreased.

Proposed protocol for fasciculation detection by muscle ultrasound in amyotrophic lateral sclerosis

Nan Hu[1],Jing Fan[1],Yi Li[3],Jingwen Niu[1],Lei Zhang[1],Yuzhou Guan[1],Liying Cui[2],Mingsheng Liu[1]
1. Peking Union Medical College Hospital
2. The first affiliated hospital, Zhejiang university

Objective: To provide a feasible protocol for detecting fasciculation by MUS in clinical practice and investigate potential diagnostic value of fasciculation among ALS patients.
Methods: The study comprised 149 ALS patients and 54 non-ALS patients, all underwent MUS on selected muscle groups in bulbar, cervical, thoracic and lumbosacral regions. The intensity of fasciculation was divided into five grades based on firing frequency and number in the involved muscle groups. The fasciculation diagnostic score was defined according to the diagnostic indicators with high specificity for ALS.
Results: Detection rate of fasciculation were highest in the lumbosacral (970/1622, 59.81%) and cervical (841/1516, 55.47%) muscle groups, followed by the thoracic muscles (148/548, 34.31%), and bulbar muscle groups (102/652, 15.64%) among ALS patiens ($p<0.05$). The detection of fasciculation in bulbar and thoracic muscle groups and detection of high-grade fasciculation in cervical and lumbosacral muscle groups were highly specific among ALS patients. For fasciculation diagnostic score, ROC analysis showed that the AUC was 0.961 (95%CI 0.927-0.996). The optimal cut-off value was 1 point with 95.77% of sensitivity and 88.89% of specificity.
Conclusions: Fasciculation was most often detected in lumbosacral and cervical muscle groups, followed by thoracic muscle groups, and least common in bulbar muscle groups. The detection of fasciculation in bulbar and thoracic muscle groups and high-grade fasciculation in cervical and lumbosacral muscle groups have high specificity for the diagnosis of ALS, which should be the main targets during MUS examination. Totally 13 muscle groups were recommended for routine fasciculation detection for each patient.

Clinical value of ultrasonography in evaluating diaphragmatic function in patients with amyotrophic lateral sclerosis

Wenjuan Liu,Weijiang Ding
The Second Affiliated Hospital of Nanchang University

Objective: To investigate the characteristics, related factors and clinical value of ultrasonic evaluation of diaphragm function in amyotrophic lateral sclerosis (ALS).

Methods: 36 patients with ALS (study group) and 25 healthy subjects (control group) were enrolled in the study. All subjects underwent diaphragm ultrasonography (DUS) evaluation. DUS was performed to record diaphragm thickness and diaphragmatic excursion. Demographic characteristics, pulmonary function test and the revised ALS functional rating scale (ALSFRS-R) were improved in the study group. The differences in DUS indexes between the study group and the control group and the differences between the mild ALS group and the control group and the non-mild ALS group were compared. The differences in ALSFRS-R score, DUS and pulmonary function indexes between the spinal onset ALS group and the bulbar onset ALS group were compared. The related factors of DUS indexes in the study group were analyzed. The DUS indexes of the study group were analyzed by clinical prediction with the ROC curve.

Results: (1) Study group compared with the control group, the diaphragm thickness at inspiration tidal volume (Tdi-rest), the maximum end-inspiratory diaphragm thickness (Tdi-ins), the difference between thickness during full inspiration and thickness during full expiration (Δins-exp) ($P < 0.001$), diaphragm thickening fraction (ΔTdi) ($P < 0.001$) and diaphragmatic excursion during quiet breathing (DE-quiet) ($P < 0.013$) in the study group were significantly lower than those in the control group. The ratio between Tdi_x0002_rest and Tdi-ins(ΔTmax) ($P=0.016$) increased significantly. The maximum end_x0002_expiratory diaphragm thickness (Tdi-exp) and diaphragmatic excursion during forced breathing (DE-max) did not decrease significantly ($P > 0.05$). (2) The mild ALS group was compared with the healthy control group, ΔTdi, Δins-exp decreased significantly ($P < 0.05$). There was no significant difference in other DUS indexes ($P > 0.05$); Tdi_x0002_rest, Tdi-ins, Δins-exp, ΔTdi, DE-quiet and DE-max in the mild ALS group were IVAbstract significantly higher than those in the non-mild ALS group ($P < 0.05$), ΔTmax was significantly lower than that in the non- mild ALS group ($P < 0.05$), and there was no significant difference in Tdi-exp between the two groups ($P > 0.05$). (3) There was no significant difference in ALSFRS-R score, DUS indexes and forced vital capacity (FVC) between the bulbar onset ALS group and the spinal onset ALS group ($P > 0.05$), but the maximal voluntary ventilation (MVV) decreased significantly ($P = 0.038$). (4) The related factor analysis of DUS indexes in the study group showed that Tdi-rest, Tdi-ins, Δins-exp, ΔTdi and DE-max were positively correlated with FVC, MVV, ALSFRS-R scores and the respiratory subscores. (5) The ROC curve analysis of

DUS index in the study group showed that Tdi-rest（AUC=0.840, P=0.001）, Tdi-ins（AUC=0.811, P=0.003）, Δins-exp（AUC=0.901, P＜0.001）, ΔTdi（AUC=0.814, P=0.002）, DE-max（AUC=0.844, P=0.001）had high accuracy in monitoring pulmonary insufficiency.

Conclusion: There are some changes in diaphragm function under ultrasound in patients with early mild ALS, and diaphragm thickness and diaphragm mobility are positively correlated with pulmonary function indexes (FVC, MVV) and ALSFRS-R score. Diaphragm ultrasound can be an effective method to monitor pulmonary insufficiency in patients with ALS.

Autophagic vacuolar myopathy involving the phenotype of spinocerebellar ataxia type 3

Jingjing Li,Yun Peng,Jincai Tang,Menghua Li,Min Zhu,Meihong Zhou,Pu Fang,Daojun Hong
The First Affiliated Hospital of Nanchang University

Spinocerebellar ataxia type 3 (SCA3) is a form of autosomal dominant cerebellar ataxia with a wide range of clinical manifestations, including ataxia and pyrami_x0002_dal and extrapyramidal signs. A few SCA3 patients have been noticed to be predisposed to the development of inclusion body myositis. It is still unknown whether muscle can be primarily involved in the pathogenesis of SCA3. This study reported an SCA3 family in which the index patient initially presented with parkinsonism, sen_x0002_sory ataxia, and distal myopathy but the absence of cer_x0002_ebellar and pyramidal symptoms. The clinical and electrophysiological studies implied a possible combina_x0002_tion of distal myopathy and sensory–motor neuropathy or neuronopathy. MRI muscle showed selective fat infifil_x0002_tration and absence of denervated edema-like changes, indicating the distal muscle weakness had a myopathic origin. Muscle pathology showed the myopathic involve_x0002_ment, besides neurogenic involvement, characterized by chronic myopathic changes with multiple autophagic vacuoles. Genetic screening revealed expanded CAG of 61 repeats in the ATXN3 gene, which showed co_x0002_segregation in the family. Besides the neurogenic origin, the myopathic origin may be partly attributed to the limb weakness of SCA3 patients, which expands the spectrum of the clinical manifestation of SCA3.

Combination of Neuromuscular Ultrasound with Nerve Conduction Studies Help Identify Treatment-responsive Lower Motor Neuron Syndrome

Lei Zhang,Jingwen Niu,Liying Cui,Mingsheng Liu
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Introduction: Identification of treatment-responsive lower motor neuron syndrome (TR-LMNS) is warranted, since effective treatments are available and the prognosis differs from that of amyotrophic lateral sclerosis (ALS).

Methods: Between January 2019 and May 2022, 102 consecutive treatment-naive LMNS patients suspected of MMN, pure motor CIDP or ALS with initial LMN presentation were recruited. Nerve and muscle ultrasound studies and NCS were conducted in all patients at baseline. Relevant diagnostic investigations were performed if clinical warranted. The proposed ultrasound evidence of TR-LMNS were: (1) nerve enlargements at ≥1 of the predetermined sites; (2) without fasciculations of high intensity in any of the predefined muscle groups. Final diagnoses were made by experienced physician after a prolonged followed-up period (≥ 12 months).

Results: Ultrasound evidence of TR-LMNS were found in 23 patients, and helped identify 6 additional treatment-responders without electrodiagnostic evidence of demyelination. In the present study, the sensitivity and specificity of NCS were 56.3% and 100%, respectively. When combining NCS, nerve ultrasound and muscle ultrasound, the sensitivity and specificity were 93.8% and 88.4%, respectively.

Conclusion: Neuromuscular ultrasound studies are supplementary modalities to NCS, and combined use of the above techniques might improve detection of treatment responders in LMNS patients.

Neuronal intranuclear inclusion disease: pathology study of small nerve fibers in skin

Wotu Tian,Yuwen Cao,Yunhua Yue,Li Cao,Xinghua Luan
Department of Neurology, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University School of Medicine

Introduction: To explore and analyze the clinical and the pathological characteristics of small fibers in skin of neuronal intranuclear inclusion body disease (NIID).
Methods: Clinical data were collected from NIID patients. Skin biopsies taken from the distal lateral calf were obtained, and immunohistochemistry staining were performed. Intraepidermal nerve fiber density (IENFD) was quantified with protein gene product 9.5 (PGP9.5) and growth-associated protein 43 (GAP-43).
Result: We enrolled 4 sporadic patients (2 males, 2 females), with the average age of onset at 54.5 years old (range from 44 to 67). None of them had diabetes or abnormal glucose tolerance. Case 1 had limb numbness and weakness, with chronic sensory and motor axonal damage upon electrophysiological examinations，without DWI high-intensity signal along the corticomedullary junction. Case 2 and Case 3 had tremor or rigidity of limbs. Case 4 was characterized by recurrent nausea and vomiting and cognitive impairment (MMSE=3). Case 2, 3 and 4 had bilateral subcortical linear hyperintensities on DWI, with or without decreased perfusion in white matter, with abnormal GGC repeat expansions in the 5' region of the NOTCH2NLC, with 108/18 (Case 1), 133/22 (Case 2), 206/18 (Case 3), 115/8 (Case 4). Intranuclear inclusions were identified with anti-P62 in fibroblasts and endothelial cells for all cases. IENFD for PGP9.5 and GAP-43 staining were significantly lower than healthy control according to EU standards (PGP9.5 staining: 6.3 (male)~7.9 (female) /mm, GAP-43 staining: 14.17 ± 5.49 /mm; P<0.0001). Case 1 had 1.89/mm (PGP9.5) and 0/mm (GAP43). Case 2 had 3.35/mm (PGP9.5) and 1.21/mm (GAP43). Case 3 had 1/mm (PGP9.5) and 0/mm (GAP43). Case 4 had 1.92/mm (PGP9.5) and 0/mm (GAP43).
Conclusions: The study of small fiber is an important extension and necessary supplement of peripheral nerve pathology, which is often involved in neurodegenerative disorders. Here, four NIID patients with different phenotypes had peripheral nerve damage, involving small nerve fibers. IENFD may become a biological marker for evaluation or early screening in NIID. In-depth research on a larger sample size will reveal the correlations between small fiber lesions and genotypes.

Muscular tuberculosis with lower extremity muscular masses as the initial presentation: clinicopathological analysis of two cases and review of the literature

Xiao-wei Zhu,Xing-hua Luan,Kai-li Jiang,Chao Zhang,Shi-hua Liu,Li Cao,Ping Zhong,Zhi-yan Liu
Department of Neurology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine

Introduction: Tuberculosis (TB) is a public health problem that mostly affects people in developing countries. TB presenting as a soft-tissue mass is rare, usually seen in muscular tuberculosis (MT) patients.
Methods: In this study, we present the clinical, radiographic, pathological features of 2 cases and retrospectively evaluated additional 28 patients who were diagnosed with MT.
Results: Patients occurred more in males (60.9%) than females (39.1%) with a male: female ratio of 1.6:1. The average age was 38.9 years and 30.1 years, respectively. MT usually present with painful or painless muscular nodules of lower limbs. Imaging findings, including ultrasound, CT and MRI could identify lesions and locate biopsy locations. The most typical histopathological feature of MT is granulomatous inflammation with caseous necrosis and epithelioid granulomata. Acid-fast bacilli stain and polymerase chain reaction (PCR) assays are helpful to identify tubercle bacillus.
Conclusion: We described 2 MT cases with lower extremity muscular masses as the initial presentation. Results suggest that muscle biopsy and pathological analysis remain necessary for the diagnosis. Most of patients could be cured with standardized antitubercular therapy.

Novel heterozygous MYOT mutation causing myofibrillar myopathy 3 with a mild late onset phenotype

Jialong Zhang[1],Xingyu Xia[1],Mingshi Gao[2],Chong Sun[1],Lulu Wang[1],Chongbo Zhao[1],Wenhua Zhu[1],Jianying Xi[1]

1. Huashan hospital, Fudan university

2. Department of Pathology, Huashan Hospital, Fudan University

Background: Myofibrillar myopathies (MFMs) are a group of muscular dystrophies with shared morphological features. Myofibrillar myopathy 3, a subset of MFMs, is caused by heterozygous mutations in MYOT gene located on chromosome 5q31.2. However, the full landscape of pathogenic mutations within this gene remains insufficiently characterized.

Methods: Two patients diagnosed with myofibrillar myopathy 3 were subjected to clinical evaluation, muscle MRI, electrophysiological study, and muscle biopsy. Genomic DNA was extracted and whole exome sequencing (WES) was performed. Sanger sequencing was used to confirm the heterozygous mutation in the MYOT gene.

Results: Both patients showed progressive weakness in lower limbs, difficulty with mobility tasks, with no significant upper limb weakness or discomfort. Creatine kinase levels were in the normal range in patient 1, but elevated in patient 2. Both patients revealed normal NCV studies and myogenic changes in electromyography. Muscle MRI of lower limbs revealed significant atrophy and fatty infiltration in the vastus intermedius and vastus medialis of the thigh, as well as the medial head of gastrocnemius and soleus in the calf. Muscle biopsy of Patient 1 demonstrated rimmed vacuoles, eosinophilic inclusions and cytoplasmic bodies in muscle fibers. These pathological features were not observed in Patient 2, and neither patient exhibited evidence of granulofilamentous material or Z-line disorganization. WES identified a heterozygous variant (c.116C>G; p.S39C) in MYOT gene in both patients and Sanger sequence confirmed the variant. Since the same missense change at the same amino acid residue, c.116C>T (p.S39F) was previously determined as a pathogenic mutation, we consider both patients harbored the novel mutation (c.116C>G; p.S39C) in MYOT, leading to the diagnosis of MFM3.

Conclusions: Here we reported a novel mutation associated with myofibrillar myopathy 3, expanding the mutation spectrum of MFM3. Both patients a mild phenotype with late onset and further researches are needed to uncover genotype and phenotype correlation.

Impact of demographic factors, comorbidities and co-medication on progression and survival in a large Chinese ALS cohort

Nan Hu,Jianfeng Ding,Jing Fan,Lei Zhang,Dongchao Shen,Xunzhe Yang,Liying Cui,Mingsheng Liu
Peking Union Medical College Hospital

Objective: To clarify the impact of specific risk/protective factors on the disease progression and survival in a large population of Chinese sporadic ALS(sALS) patients.

Methods: We investigated a cohort of 937 sALS patients pro- and retrospectively. Uni- and multivariate regression analysis were performed to analyze the influence of demographic factors, comorbidities and medication on the progression and survival of ALS.

Results: Our results showed younger age of onset ($p<0.05$), long diagnostic delay ($p<0.001$) and intake of Riluzole ($p<0.001$) were significantly related to low progression rate and long survival time. History of smoking ($p<0.05$) and bulbar onset ($p<0.001$) were risk factors for rapid progression and poor prognosis. Baseline ALSFRS-R score ($p<0.001$) and total MRC score ($p<0.05$) were positively related to mean survival time of included patients. Neither comorbidities nor intake of antihypertensive drugs, antidiabetics, and statins as dependent variables showed considerable influence on ALS progression or survival.

Conclusion: Our study revealed early onset and long diagnostic delay were indicators of slow progression and long survival. Smoking and bulbar onset were risk factors for poor prognosis and abstaining from smoking was beneficial to patients with ALS in improving median survival time. Long-term intake of Riluzole should be recommended for affordable patients.

Impacts of serum biomarkers regarding glucose, lipid and protein on progression and survival in a Chinese ALS cohort

Nan Hu,Jing Fan,Lei Zhang,Dongchao Shen,Xunzhe Yang,Liying Cui,Mingsheng Liu
Peking Union Medical College Hospital

Objective: To explore the impacts of nutritional biomarkers regarding glucose, protein and lipid on ALS progression and survival in a cohort of Chinese ALS patients.

Methods: A total of 191 ALS patients were included in our analysis. Pearson correlation was employed to analyze the relationships between baseline serological and clinical variables. Uni- and multivariate analysis were performed to analyze the influence of nutritional biomarkers on the progression and survival of ALS. A p-value of less than 0.05 was considered to be statistically significant.

Results: Hyperglycemia (around 1/6) and hyperlipidemia (1/5-1/3) were common among ALS patients while protein deficiency was not predominant. Serum TC ($p=0.026$) and LDL-C ($p=0.044$) was negatively related to baseline ALSFRS-R score, while serum PA was positively associated with baseline ALSFRS-R score ($p=0.018$). Serum levels of TC ($p=0.041$), apoB ($p<0.001$), Lp (a) ($p=0.002$) and FFA ($p=0.049$) were negatively associated with baseline FVC%. None of studied biomarkers showed significant relationship with ALS progression or survival time, except for serum level of Lp(a) had a weakly positive correlation to ALS progression rate after backward selection ($p=0.048$).

Conclusion: Serum biomarkers of glucose, lipid or protein might only have a weak relationship with autonomous function and respiratory function status, but have no significant impact on the progression or overall survival of ALS. More studies were needed to provide guidance of nutritional management and diet recommendation for ALS patients.

CAG Repeat Expansion in THAP11 Is Associated with a Novel Spinocerebellar Ataxia

Cuijie Wei[1],Dandan Tan[1],Zhao Chen[2],Yu Huang[3],Jianwen Deng[4],Jingjing Li[5],Yidan Liu[1],Xinhua Bao[1],Jin Xu[7],Zhengmao Hu[8],Suxia Wang[7],Yanbin Fan[1],Yizheng Jiang[8],Ye Wu[1,6],Yuan Wu[1],Shuang Wang[1],Panyan Liu[2],Yuehua Zhang[1,6],Yuwu Jiang[1,6],Hong Zhang[9],Daojun Hong[10],Nanbert Zhong[11],Hong Jiang[2,8,12,13,14],Hui Xiong[1,6]

1. Department of Pediatrics, Peking University First Hospital, Beijing, P.R. China
2. Department of Neurology, Xiangya Hospital, Central South University, Changsha, P.R. China
3. Department of Medical Genetics, School of Basic Medical Sciences, Peking University, Beijing, P.R. China
4. Department of Neurology, Peking University First Hospital, Beijing, P.R. China
5. GrandOmics Biosciences, Beijing, P.R. China
6. Beijing Key Laboratory of Molecular Diagnosis and Study on Pediatric Genetic Diseases, Beijing, P.R. China
7. Center of Ultrastructural Pathology, Lab of Electron Microscopy, Peking University First Hospital, Beijing, P.R. China
8. Key Laboratory of Hunan Province in Neurodegenerative Disorders, Central South University, Changsha, P.R. China
9. Institute of Cardiovascular Sciences and Key Laboratory of Molecular Cardiovascular Sciences, Peking University Health Science Center, Beijing, P.R. China
10. Department of Neurology, The First Affiliated Hospital of Nanchang University, Nanchang, P.R. China
11. New York State Institute for Basic Research in Developmental Disabilities, Staten Island, New York, USA
12. National Clinical Research Center for Geriatric Diseases, Central South University, Changsha, P.R. China
13. National International Collaborative Research Center for Medical Metabolomics, Central South University, Changsha, P.R. China
14. Department of Neurology, The Third Xiangya Hospital, Central South University, Changsha, P.R. China

Background: More than 50 loci are asso- ciated with spinocerebellar ataxia (SCA), and the most frequent subtypes share nucleotide repeats expansion, especially CAG expansion.

Objective: The objective of this study was to confirm a novel SCA subtype caused by CAG expansion.

Methods: We performed long-read whole-genome sequencing combined with linkage analysis in a five- generation Chinese family, and the finding was validated in another pedigree. The three-

dimensional structure and function of THAP11 mutant protein were predicted. Poly- glutamine (polyQ) toxicity of THAP11 gene with CAG expansion was assessed in skin fibroblasts of patients, human embryonic kidney 293 and Neuro-2a cells.

Results: We identified THAP11 as the novel causative SCA gene with CAG repeats ranging from 45 to 100 in patients with ataxia and from 20 to 38 in healthy control subjects. Among the patients, the number of CAA inter- ruptions within CAG repeats was decreased to 3 (up to 5–6 in controls), whereas the number of 30 pure CAG repeats was up to 32 to 87 (4–16 in controls), suggesting that the toxicity of polyQ protein was length dependent on the pure CAG repeats. Intracellular aggregates were observed in cultured skin fibroblasts from patients. THAP11 polyQ protein was more intensely distributed in the cytoplasm of cultured skin fibroblasts from patients, which was replicated with in vitro cultured neuro-2a transfected with 54 or 100 CAG repeats.

Conclusions: This study identified a novel SCA subtype caused by intragenic CAG repeat expansion in THAP11 with intracellular aggregation of THAP11 polyQ protein. Our findings extended the spectrum of polyQ diseases and offered a new perspective in understanding polyQ-mediated toxic aggregation.

The collapse of muscle cell tension in alpha-dystroglycanopathies with hypoglycosylation of alpha-DG is caused by reduced B3GALNT2 enzyme activity and enhanced sulfation of matriglycans by CHST10

Xiaona Fu[1],Hui Wang[2],WenJia Chai[2],XiaoYu Chen[3],Danyu Song[3],Wei Wang[2],Jingwei Zhong[2],Zhimei Liu[1],Hui Xiong[3],Fang Fang[1],Xiaotun Ren[1],Jingang Gui[2]

1. 1. Department of Neurology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

2. Key Laboratory of Major Diseases in Children, Ministry of Education, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

3. Department of Pediatrics, Peking University First Hospital, Beijing, China

Introduction:

B3GALNT2 mutations cause alpha-dystroglycanopathies characterized by muscular dystrophy, brain malformations, and developmental delay. This study investigated the clinical features and molecular mechanisms of B3GALNT2 mutations in Chinese patients.

Methods:

Five Chinese patients with B3GALNT2 mutations were recruited. Patient-derived fibroblast cell lines were cultured for experiments. RNA extraction, allele-specific PCR, minigene construction, WGA pull-down, immunoblot, laminin overlay, immunofluorescence, mRNA array analysis, B3GALNT2 protein expression, purification, enzyme activity analysis, and statistical analysis were performed.

Results:

The clinical data revealed a spectrum of phenotypes among the patients with B3GALNT2 mutations. In silico analysis predicted that the identified mutations would disrupt the function of B3GALNT2 protein. The fibroblast cell lines derived from patient biopsies exhibited altered B3GALNT2 expression compared to controls. The minigene assays demonstrated aberrant splicing patterns. The WGA pull-down and immunoblot analysis indicated abnormal glycosylation patterns in the patient samples. Laminin overlay and immunofluorescence staining revealed impaired α-dystroglycan-laminin interaction. Enzyme activity analysis revealed reduced activity in mutant recombinant B3GALNT2 protein. mRNA array analysis unveiled up-regulated CHST10 gene expression associated with B3GALNT2 mutations.

Conclusions:

This study provides clinical and molecular insights into B3GALNT2 mutations in Chinese patients. Mutations disrupt B3GALNT2 function, causing glycosylation defects, impaired interaction, and dysregulated gene expression. Findings contribute to understanding the pathogenic mechanisms of this rare disorder.

Muscle RING finger-1 is required for skeletal muscle regeneration by regulating myoblast proliferation and differentiation

Mengge Yang,Huajie Gao,Bitao Bu
Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology

Background: Our previous study observed prominent accumulation of MuRF-1 in regenerating myofibers in multiple muscular diseases; however, how MuRF-1 plays roles during myogenesis is still unclear. This study was designed to further explore the underlying mechanisms of MuRF-1 involved in myogenesis.

Methods: Human myoblasts were employed to evaluate the roles of MuRF-1 in myogenesis. MuRF-1 expression during myogenesis was firstly detected in vitro. Then, knockdown of MuRF-1 gene was achieved using short interfering RNA (siRNA) technique, and myoblast proliferation and differentiation were assessed by flow cytometry, using real-time quantitative Polymerase Chain Reaction (RT-qPCR), Western blot (WB) and immunofluorescent staining. Finally, we examined the MuRF-1 and related molecules in muscle biopsies from patients with immune-mediated necrotizing myopathy (IMNM), dermatomyositis (DM), dysferlinopathy and controls.

Results: MuRF-1 expression was found to be upregulated during myogenesis. Depletion of MuRF-1 by siRNA inhibited myoblast proliferation, possibly associated with suppressed cell cycle protein Cyclin A expression and DNA synthesis. MuRF-1 knockdown significantly inhibited myoblasts differentiation and myotube formation, and the expression of myogenic transcription factor MyoG was detected to be decreased dramatically. Cyclin A and MyoG expression were also significantly upregulated in IMNM, DM and dysferlinopathy muscles. Furthermore, double IF staining showed prominent colocalization of MuRF-1 and MyoG in regenerating myofibers.

Conclusions: MuRF-1 is required for skeletal myogenesis by regulating myoblast proliferation and differentiation, which may contribute to muscle injury repair. These findings challenge the mainstream view that MuRF-1 plays as a muscle atrophy-related marker.

A novel knockout mouse model for LAMA2-related muscular dystrophy: damage of blood brain barrier and impaired muscle cytoskeleton resulted in short lifespan

Dandan Tan[1,3],Yidan Liu[1],Huaxia Luo[1],Qiang Shen[2],Hong Zhang[2],Hui Xiong[1]

1. Peking University First Hospital

2. Institute of Cardiovascular Sciences and Key Laboratory of Molecular Cardiovascular Sciences, Peking University Health Science Center

3. Department of Neurology, the First Affiliated Hospital of Nanchang University

Introduction: Laminin α2, encoded by the LAMA2 gene, attaches with laminin β1 and γ1 chains to form laminin-α2β1γ1, which is a main component of extracellular matrix in the basement membrane of skeletal muscle and blood-brain barrier. However, the underlying pathogenesis of muscle damage and brain abnormalities in LAMA2-related muscular dystrophy (LAMA2-MD) remains unclear. In this study, we analyzed the brain and muscle transcriptome data of a novel mouse model of LAMA2-CMD, dyH/dyH, to explore the pathogenesis.

Methods: The brain and muscle data differences between dyH/dyH and wild-type mice at 2-week-old detected by single-cell RNA sequencing, RNA sequencing, Immunofluorescence and western blot were analyzed.

Results: We discovered that laminin α2 was primarily expressed on the brain cortical surface. In contrast, Lama2 was selectively and highly expressed in vascular and leptomeningeal fibroblasts, as well as vascular smooth muscle cells, with a small amount of expression in astrocytes. Our novel Lama2 knockout mouse model (dyH/dyH) revealed significant differences in cell-cell interactions among these cell types, suggesting that laminin α2 deficiency might disrupt gliovascular basal lamina assembly. Moreover, our transcriptomic study revealed damage to the muscle cytoskeleton and impaired muscle development in dyH/dyH mice, which contributed to severe dystrophic symptoms and muscle pathology changes.

Conclusion: Our findings shed light on the mechanisms underlying muscular dystrophy and brain abnormalities in LAMA2-MD. Understanding these processes may offer valuable insights for developing potential therapeutic strategies to address the challenges posed by LAMA2-related disorders.

Dystrophin expression and epigenetic drug treatment restore the dysregulated gene expressions in XLDCM patient-derived cardiomyocytes disease model

Jeffrey Lui[1],Anna Hing Yee Law[1],Sheng Zhu[1],Stephen Yin Cheng[1],Yiu Fai Cheung[1],Hung Fat Tse[2],Godfrey Chi Fung Chan[1],Sophelia Hoi-Shan Chan[1]

1. The University of Hong Kong

2. Division of Cardiology, Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, HKSAR

X-linked dilated cardiomyopathy (XLDCM), caused by DMD mutation, is characterized by early onset of severe heart failure with no or minimal skeletal muscle weakness. Without heart transplantation, this disease results in premature death. We previously established an XLDCM patient-specific induced pluripotent stem cell (iPSC)-derived cardiomyocytes (CMs) disease model to study the pathophysiological mechanism, and the impacts of mutation correction and drug therapy. We observed that DMD gene correction by CRISPR-Cas9 in XLDCM iPSC-CMs restored dystrophin expression and remediate calcium handling defects. We also found that the application of Trichostatin A (TSA, a pan histone deacetylase inhibitor, an epigenetic drug) improved XLDCM iPSC-CMs calcium handling. To investigate the transcriptomic differences underlying the cardiac pathology in XLDCM and the transcriptional changes mediated by DMD correction and TSA treatment, we performed RNA-seq on healthy control, XLDCM, DMD corrected and TSA-treated XLDCM iPSC-CMs. A transcriptomic analysis revealed that the genes responsible for cardiac contractility and calcium handling were dysregulated in XLDCM iPSC-CMs. However, when the DMD mutation was corrected, or the cells were treated with TSA, these gene expressions were restored to normal levels. Additionally, genes related to extracellular matrix (ECM) and cell adhesion were largely dysregulated in XLDCM iPSC-CMs but were also restored after DMD mutation correction. Interestingly, a significant amount of ECM and cell adhesion genes were only enriched in the CMs derived from DMD corrected iPSCs, suggesting that these corrected cells may have a compensatory mechanism to modify their own micro-environment for improved cardiac muscle function. In **conclusion**, this study indicates that restoring the dystrophin expression and treatment with an epigenetic drug improve the XLDCM disease phenotype in iPSC-CMs by restoring dysregulated gene expressions.

DMD gene correction and drug therapies to rescue the dysregulated calcium handling gene in patient-specific in vitro cardiomyocyte disease model of X-linked dilated cardiomyopathy

Yin CHENG[1],Hing Yee LAW[1],Sheng ZHU[1],Jeffrey LUI[1],Tsun Yui CHAN[1],KM NG[2],Ngar Yun POON[3,4,5],Yiu Fai CHEUNG[1],Hung Fat TSE[2],Chi Fung CHAN[1],Hoi Shan CHAN[1]

1. The University of Hong Kong, Queen Mary Hospital, HKSAR
2. Division of Cardiology, Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, HKSAR
3. Department of Medicine and Therapeutics, The Chinese University of Hong Kong, HKSAR
4. Hong Kong Hub of Paediatric Excellence (HK HOPE), Hong Kong Children's Hospital, HKSAR
5. Centre for Cardiovascular Genomics and Medicine, Lui Che Woo Institute of Innovative Medicine, The Chinese University of Hong Kong, HKSAR

X-linked dilated cardiomyopathy (XLDCM) is a lethal disease of dystrophinopathy caused by DMD mutation. Currently, there are no effective treatments. Previous studies have suggested that abnormal calcium influx and disrupted calcium handling in the cardiomyocytes are a direct consequence of an altered dystrophin-glycoprotein complex in dystrophinopathy, leading to cardiac cell damage. Membrane stabilizers have shown that dystrophin protects against stress-induced mechanical damage to the cell membrane, and stabilizing damaged portions of these membranes can prevent calcium overload and heart muscle cell death. Additionally, histone deacetylases inhibitors have been found to help calcium balance through handling of calcium modulation.

We aim to establish an XLDCM patient induced pluripotent stem cells (iPSCs) derived cardiomyocytes as a disease model to study the underlying pathophysiological mechanisms, and to study the potential therapeutic effect of mutation correction and drug screening using this established patient-derived iPSC disease model. We established an XLDCM induced pluripotent stem cell (iPSC) disease model from an XLDCM patient and an isogenic DMD gene-corrected line with CRISPR-Cas9, and a healthy control for the generation of cardiomyocytes (CMs). We performed drug screening by applying Poloxamer 188 and Trichostatin A to this established disease model.

We found the established XLDCM patient-derived iPSC-CMs exhibited dystrophin deficiency, membrane instability, abnormal calcium handling, and reduced natriuretic peptides expression. The mutation correction reversed the pathologies. Treatment of XLDCM iPSC-CMs with Poloxamer 188 and Trichostatin A also improved membrane stability and rescued the dysregulated calcium handling without affecting dystrophin expression.

Our current study demonstrated the importance of dystrophin restoration and restoration of calcium handling in the therapeutic pathway for XLDCM related to DMD mutation.

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原因不明的呼吸衰竭或者呼吸功能障碍[1]

- 出现咳嗽无力、活动后憋喘、端坐呼吸及夜间睡眠呼吸障碍等典型呼吸系统症状
- FVC低于预计值的80%
- 仰卧位FVC较直立位FVC下降10%以上
- 实验室检查提示膈肌受累

中轴肌和/或近端肢带肌无力[1]

- 出现仰卧起坐、上下楼梯及下蹲后起立困难，跑跳能力差等典型肌无力症状
- 肌电图检查显示肌源性损害
- 肌肉影像学检查提示肌肉受累

强直脊柱或脊柱弯曲畸形[1,2]

- 约1/3的庞贝病患者出现脊柱侧弯
- 可出现驼背、双肩不等高、双侧肩胛骨不对称、腰部不对称、脊柱前倾、骨盆倾斜等症状

原因不明的CK升高[1]

- 存在高CK血症（在成人晚发型庞贝病的早期，高CK血症可能是唯一可以检测到的异常）

原因不明：在常规检查后仍无法找到诱因；FVC：用力肺活量；CK：血清肌酸激酶

晚发型庞贝病延迟诊断现象普遍，推荐疑似患者尽早进行酶活性和基因检测，以明确诊断[1,3-5]

晚发型庞贝病若未能及时治疗，使用轮椅和辅助通气的需求逐年增加，呼吸衰竭是常见死因[6]

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【性状】本品为白色或类白色冻干块状物或粉末。复溶后，应为可能含有颗粒物的澄明、无色至淡黄色的液体。

【适应症】用于庞贝病（酸性α-葡萄糖苷酶[GAA]缺乏症）患者的治疗

【不良反应】在临床试验中，阿糖苷酶α最常见的不良反应（≥5%）是超敏反应（更多详尽内容请参见说明书）。

【警告】速发过敏反应，超敏反应和免疫介导反应及心肺衰竭风险。

- 有些患者在阿糖苷酶α输注期间以及输注后出现危及生命的速发过敏反应和严重超敏反应，其表现为呼吸窘迫、缺氧、呼吸暂停、呼吸困难、心动过缓、心动过速、支气管痉挛、喉咙痛紧感、低血压、血管性水肿（包括舌或颈肩肿胀、眶周水肿和面部浮肿）、荨麻疹等，还有些患者在接受阿糖苷酶α治疗后出现免疫介导反应，其表现为蛋白尿、肾病综合征以及坏死性皮肤病变，因此，在阿糖苷酶α输注期间以及输注后必须密切监测患者，并做好应对速发过敏反应和超敏反应的措施，告知患者有关速发过敏反应、超敏反应和免疫介导反应的体征和症状，并告知患者在出现这些体征和症状时应立即就医（参见【注意事项】）。
- 伴有心脏或呼吸系统功能受损的婴儿型庞贝病患者可能存在因为输液导致体液过多而使心脏或呼吸系统损害程度发生严重且急剧加重的风险，因此需要额外监测（参见【注意事项】）。

【注意事项】在注射用阿糖苷酶α输注期间以及输注后3小时内，有些患者会出现速发过敏反应和超敏反应。如果出现上述情况，必须立即停止注射用阿糖苷酶α输注，并给予适当的医学治疗（更多详尽内容请参见说明书）。

【禁忌】无

【贮藏】2-8°C保存

【包装】1瓶/盒；10瓶/盒 玻璃瓶（I型玻璃），带有瓶塞（硅化丁基橡胶）

【有效期】36个月

【批准文号】药品批准文号：国药准字SJ20150049

【生产企业】Genzyme Ireland Limited

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MAT-CN-2320031　审批日期：2023年9月

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4

快速起效,**4周**提升SMN蛋白2倍[5-7]
4项国际临床研究,纳入广泛的SMA患者[8-11]
累积**4年+**疗效与安全性数据[12]

6

全身获益—满足患者**6大治疗需求**[13-17]:

- ↑**改善**主要运动功能
- ↑**改善**呼吸/进食功能
- ↑**改善**独立生活能力
- ↓**更低**不良事件发生率
- ↓**更低**治疗脱落率
- ↓**更低**药物蓄积风险

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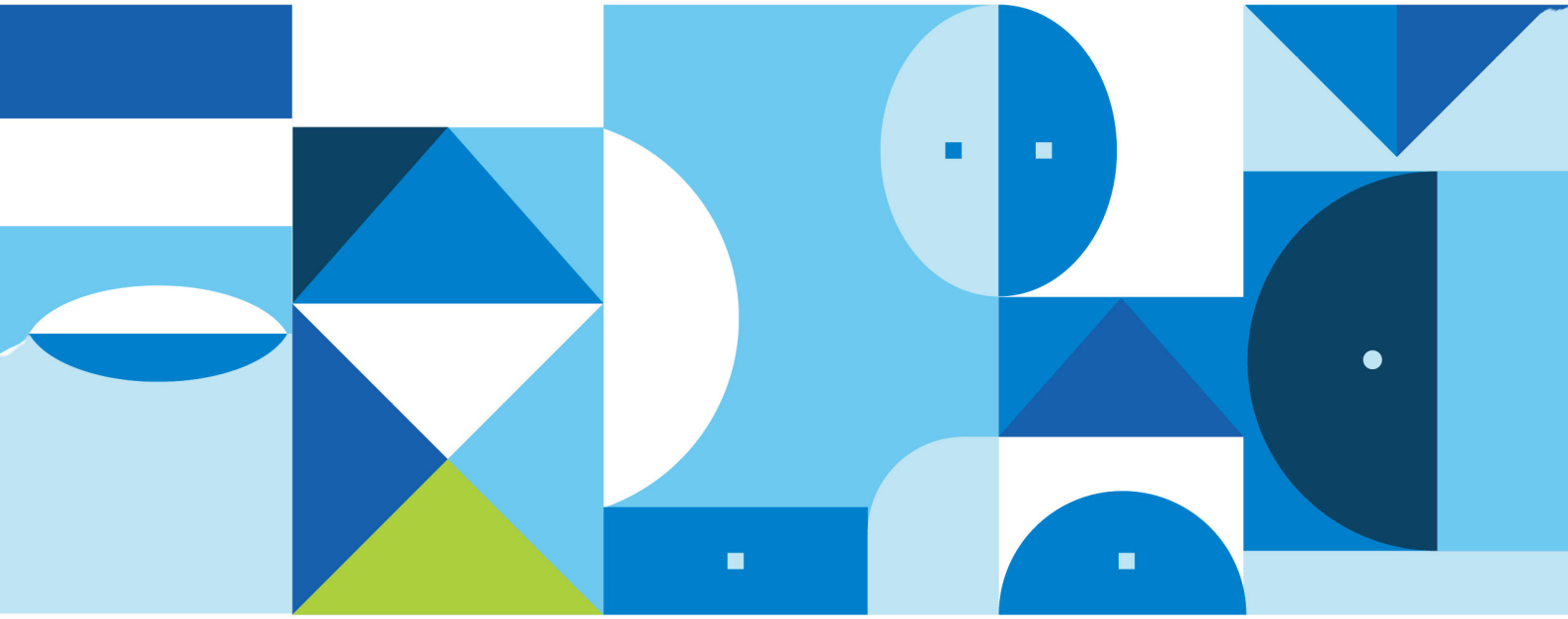

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