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Oral Presentation
Poster Presentations

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contents

Oral Presentation

ID:32

Therapeutic reduction of neurocan in murine intracerebral hemorrhage lesions promotes oligodendrogenesis and functional recovery

Hongmin Li[1,2,3,4],Samira Ghorbani[3,5],Olayinka Oladosu[3],Ping Zhang[6],Yunyan Zhang[3],Chang-Chun Ling[6],Voon Yong*[3],Mengzhou Xue[1,2]

1. Department of Cerebrovascular Diseases, The Second Affiliated Hospital of Zhengzhou University; Zhengzhou, Henan, China
2. Academy of Medical Science, Zhengzhou University; Zhengzhou, Henan, China
3. Hotchkiss Brain Institute and Department of Clinical Neurosciences, University of Calgary; Calgary, Canada
4. 首都医科大学附属北京友谊医院
5. Department of Biology, University of Toronto Mississauga; Mississauga, Canada
6. Department of Chemistry, University of Calgary; Calgary, Canada

Objective: Intracerebral hemorrhage (ICH) causes prominent local deposition of extracellular matrix molecules, particularly the chondroitin sulphate proteoglycan member neurocan. In tissue culture, neurocan inhibits adhesion and process outgrowth of oligodendrocytes, which are early steps in myelination. However, whether the elevated neurocan has functional consequences for ICH in vivo, and can be therapeutically targeted to facilitate recovery, are unknowns.

Methods: Mice were retro-orbitally injected with adeno-associated virus (AAV) to reduce neurocan deposition after ICH induction by collagenase. Other groups of ICH mice were treated with vehicle or a drug that reduces chondroitin sulphate proteoglycans (CSPGs) synthesis, 4-4-difluoro-N-acetylglucosamine (difluorosamine). Behavioral tests were conducted at multiple time points. Brain tissues were investigated for expression of neurocan by immunofluorescence microscopy and western blot analysis. Brain cryosections were also stained for microglia/macrophage phenotype, oligodendrocyte lineage cells and neuroblasts by immunofluorescence microscopy. CX3CR1CreER:Rosa26TdT (Ai9) mice with ICH were employed for aging comparison experiments. Tissue structural changes were assessed using brain magnetic resonance imaging (MRI).

Results: AAV-reduction of neurocan increased oligodendrocyte numbers and functional recovery in ICH. The small molecule inhibitor of CSPG synthesis, difluorosamine, lowered neurocan levels in lesions and elevated numbers of oligodendrocyte precursor cells, mature oligodendrocytes, and SOX2+ nestin+ neuroblasts in the perihematomal area. Difluorosamine shifted the degeneration-associated functional state of microglia/macrophages in ICH towards a regulatory phenotype. MRI analyses showed better fiber tract integrity in the penumbra of difluorosamine mice. These beneficial difluorosamine Results were achieved with delayed (2 or 3 days) treatment after ICH.

Conclusion: Reducing neurocan deposition following ICH injury is a therapeutic approach to promote histological and behavioral recovery from the devastating stroke.

Key Words: Extracellular matrix; neurocan; chondroitin sulphate proteoglycans; oligodendrogenesis; functional recovery; intracerebral hemorrhage.

ID:37

Metabolic regulation of B cell cytokine responses in multiple sclerosis

Rui Li*1,Hulun Li2,Ying Fu1,Amit Bar-Or3

1. 福建医科大学

2. 哈尔滨医科大学

3. University of Pennsylvania

Objective: Among key antibody-independent B-cell functions is their capacity for context-dependent secretion of distinct cytokine profiles that shape local immune responses, which have now been implicated in the pathophysiology of multiple sclerosis (MS). Surprisingly, little is known about the mechanisms involved in the regulation of B-cell cytokine expression. Our goal here is to investigate fundamental mechanisms underlying regulation of the balance between B-cell pro- and anti-inflammatory cytokine responses and their impact on CNS inflammation.

Methods: Cytokine capture assays were used initially to purify cytokine-defined human B cell populations ex-vivo, followed by unbiased RNA sequencing that revealed transcriptomic differences between IL-10+ and GM-CSF+ human B cells . Seahorse assay was used to measure B cell OXPHOS. Cytokines from B cells were detected by either ELISA or FACS. Access to samples from a Phase I BTKi study in healthy controls provided in vivo confirmation that BTK inhibition could modulate B cell pro-inflammatory cytokine responses. Finally, we used experimental autoimmune encephalomyelitis (EAE) to explore the impact of B-cell OXPHOS or P2RX7 modulation on neuroinflammation in vivo.

Results: We find that B-cell cytokine production is metabolically regulated both in vitro and in vivo, with particular involvement of mitochondrial respiration (OXPHOS), and that distinct modes of B-cell activation shift their metabolic state, regulate the extent of ATP release by the B cells, and trigger the coordinated and modular regulation of ATP-pathway molecular machinery that enables ATP and its metabolites to function as a '4th signal', reciprocally modulating the balance between pro- and anti- inflammatory cytokine expression. Inhibition of either B-cell OXPHOS or ATP signaling could attenuate CNS inflammation in vivo, as well as restore the balance of B-cell cytokine responses in MS. Furthermore, we demonstrated that BTK inhibition, an emerging B-cell-targeting autoimmune disease therapeutic approach, could modulate B cell cytokine responses through decreasing B-cell OXPHOS.

Conclusion: Together, our study reveals a fundamental mechanism involving metabolic regulation of B-cell cytokine responses and points to non-depleting therapeutic strategies that restore the B-cell cytokine balance in MS by targeting B-cell metabolism.

Key Words: Multiple Sclerosis, B cells, Metabolism, Cytokine, OXPHOS

ID:38

Extramedullary neutrophil generation in lung promotes stroke-associated pneumonia

kaibin shi*1,2,Nuo Cheng3,Ying Zhang2,Wenyan He1,Fu-Dong Shi1,3

1. Beijing Tiantan Hospital, Capital Medical University; Chinese Institutes for Medical Research, Beijing.
2. Chinese Institues for Medical Research, Beijing
3. Tianjin Medical University General Hospital

Objective: Pneumonia is a common and devastating complication in patients with stroke, yet prophylaxis use of antibiotics fails to prevent stroke-associated pneumonia, suggesting non-infectious components underlying the pathogenesis. Acute brain injury often triggers profound alterations in peripheral organs. Whether stroke induced a quick non-sterile change in the lung and its contribution to stroke-associated pneumonia is unknown.

Methods: Single cell sequencing of bronchoalveolar fluid harvested from patients with acute ischemic stroke within 24 hours of symptom onset was performed to characterizing the acute alterations in lung microenvironment post stroke. Murine ischemic stroke model induced by middle cerebral artery occlusion was used to elucidate the mechanisms underlying acute pulmonary alteration and its relationship to stroke-assocaited pneumonia.

Results: By adopting single cell sequencing of bronchoalveolar fluid harvested from patients with acute ischemic stroke within 24 hours of symptom onset, we identified a large number of neutrophils accumulated in the bronchoalveolar fluid, with enhanced pro-inflammatory and pro-permeability features. Of interest, one third neutrophils in bronchoalveolar fluid are immature neutrophils. Depletion of neutrophils, or blockade of interleukin-1β and vascular endothelial growth factor α, mitigated acute inflammatory response in lung and reduced the risk of pneumonia in a murine ischemic stroke model induced by middle cerebral artery occlusion. Lineage tracing of hematopoietic stem and progenitor cells (HSPC) showed that extramedullary myelopoiesis in the lung tissue replenished focal neutrophil pool in the acute phase of stroke. Parabiosis demonstrated that HSPCs in the lung are mainly motivated from bone marrow. CCR2+ HSPCs are the most expanded progenitor populations in the bone marrow and migrate to the lung mediated by CCL2. Pharmacological blocking of CCR2 significantly inhibited mobilization of HSPCs and subsequent neutrophil generation and prevented stroke-associate pneumonia.

Conclusion: Our study identified acute extramedullary myelopoiesis in the lung causes acute sterile inflammation which renders the lung prone to stroke associated pneumonia, suggesting early anti-inflammatory treatment as a potential approach to prevent this fatal complication in stroke patients.

Key Words: Extramedullary myelopoiesis, neutrophil, pneumonia, stroke

ID:59

Brain Lesion Characteristics in Chinese MS Patients: A 7T-MRI Cohort Study

Shuzhen Guan1,Yu-Jing Li1,Lei Su2,Zhe Zhang2,Chenyang Gao1,Ai Guo2,Mengting Zhang2,Xiaoyu Shi2,Xinyao Liu2,Tian Song2,Wangshu Xu2,Huabing Wang2,Joseph Kuchling3,Jing Jing2,De-Cai Tian2,Yaou Liu2,Yunyun Duan2,Friedemann Paul3,Fu-Dong Shi*1,2

1. Department of Neurology, Tianjin Medical University General Hospital, Tianjin, China
2. Tiantan Neuroimaging Center of Excellence, China National Clinical Research Center for Neurological Diseases, and Departments of Neurology, Radiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China;
3. Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine and Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

Objective: Prevalence, susceptibility genes, clinical and radiological features may differ across different ethnic groups of multiple sclerosis (MS). Our aim is to characterize brain lesions in Chinese patients with MS by 7T-MRI.

Methods: MS participants were enrolled from the ongoing cohort of China National Registry of Neuro-Inflammatory Diseases (CNRID). A 7T-MRI of the brain was performed. Each lesion was evaluated according to a standardized process. Central vein sign (CVS) and paramagnetic rim lesion (PRL) were identified. Additionally, the characteristics of lesions at both patient-level and lesion-level are summarized based on other literature on 7T-MRI.

Results: We included 120 MS patients. Their mean (SD) age was 34.6 (9.4) years. The ratio of female-to-male was 1.7:1. The mean disease duration of patients with MS was 5.5 ± 6.1 years. The median EDSS score was 2 (range, 0-8). A total of 8502 lesions were identified. The median lesion count was 44.5 (IQR, 18-89) (Range, 2-370). The median (IQR) percentage for these special locations are as follows: cortical lesions (CL) was 2.7% (0-5.7%), juxtacortical lesions was 16.2% (7.8%-25.7%), periventricular lesions was 30.2% (17.2%-38.7%), and infratentorial lesions was 5.8% (0.4-11.9%). CL occurred in 70 (58%) patients, accounting for only 443 (5%) of the total lesions. Of the 443 CL, 309 (69.8%) were leukocortical lesion. CVS appeared in 5392 (63%) lesions from 117 (98%) patients. 1792 (21%) lesions and 104 (87%) patients had paramagnetic rim.

Conclusion: Our study elaborated the lesion features of Chinese patients with MS based on 7T-MRI. Lesion burden is heavy in Chinese patients with MS. The median lesion count and proportion of PRL are high. The reported heavy burden calls for ramping up regional and global efforts to care for MS patients. The management and research of Chinese population with MS needs to be further strengthened.

Key Words: Multiple Sclerosis, 7T-MRI, China

ID:67

Microglia regulates seizure activity via SPP1-MCRIP1 Axis in mouse models of status epilepsy

Yingying Chang1,Zhuoran Zhang1,Shihe Jiang2,Shuzhen Guan1,Wei-Na Jin*1,2,Fu-Dong Shi1,2

1. Department of Neurology, Tianjin Medical University General Hospital, Tianjin, China
2. China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Objective: Status epilepticus (SE) is an intricate neuroinflammatory disorder that markedly impairs the patients' quality of life of and places a heavy society burden. Despite serving as the brain's initial defense mechanism following injury, the role of microglia in SE remains poorly understood. This study seeks to elucidate the spatial and temporal characteristics of neural injury in SE and explore potential immune interventions by targeting microglial activity.

Methods: Immunostaining and flow cytometry were used to evaluate immune cell infiltration in the brains of SE mice. Subsequent to targeted microglia depletion with PLX3397, alterations in epileptic behavior and neural network dynamics were tracked using two-photon microscopy.

The secreted phosphoprotein 1 (SPP1) gene was knockout using AAV-SPP1 plasmid, and its impact on seizure activity and brain immune responses was evaluated through behavioral tests, immunofluorescence, and Fluoro-Jade C (FJC) staining. Co-immunoprecipitation (CO-IP) and proteomics were conducted to identify potential proteins interacting with SPP1. Western blot analysis was employed to confirm the signaling pathways regulated by SPP1. Furthermore, the impact of inhibiting ERK activation with Mirdametinib on seizure severity was examined.

Results: Microglia activation was predominantly observed in the cortex, hippocampus, and thalamus. Depletion of microglia using PLX3397 exacerbated seizure severity, indicating a protective role. Spatial transcriptomics analysis revealed a significant increase in SPP1 expression in these brain regions. Knockout of SPP1 led to reduced seizure activity and neuronal damage, accompanied by a decrease in anti-inflammatory cytokines. Co-immunoprecipitation and proteomics experiments confirmed the interaction between SPP1 and MAPK Regulated Corepressor Interacting Protein 1 (MCRIP1). Western blot analysis further verified that SPP1 binding to MCRIP1 inhibits the activation of ERK signaling pathway. Treatment with mirdametinib notably reduced seizure severity and spike activity in SE mice while also increasing the level of anti-inflammatory cytokines.

Conclusion: This study highlights the protective role of SPP1-producing microglia and its regulation of SE through SPP1-MCRIP1-ERK axis. These Results offer a more profound understanding of the immune processes involved in SE and pinpoint potential therapeutic target.

Key Words: Status epilepticus (SE), Microglia, Secreted phosphoprotein 1 (SPP1), MAPK Regulated Corepressor Interacting Protein 1 (MCRIP1)

ID:77

The Blood-brain Immune Interface in COVID-19

Zhaoqi Yan[1,2],Jae Kyu Ryu[1,2,3],Mauricio Montano[4,5],Elif G Sozmen[1,2,3],Karuna Dixit[1,2],Rahul K. Suryawanshi[4],Warner C Greene[4,5,6,7],Katerina Akassoglou*[1,2,3]

1. Gladstone Institute
2. Center for Neurovascular Brain Immunology at Gladstone and UCSF
3. Department of Neurology, Weill Institute for Neurosciences, University of California, San Francisco
4. Gladstone Institute of Virology
5. Michael Hulton Center for HIV Cure Research at Gladstone
6. Department of Medicine, University of California, San Francisco
7. Department of Microbiology and Immunology, University of California, San Francisco

Objective: Life-threatening thrombotic events and neurologic symptoms are prevalent in COVID-19 and persistent in Long COVID patients suffering from post-acute sequelae of SARS-CoV-2 infection. Despite the clinical evidence, the underlying mechanisms of coagulopathy in COVID-19 and its consequences in inflammation and neuropathology remain poorly understood, and treatment options are insufficient. Fibrinogen, the central structural component of blood clots, is abundantly deposited in the lungs and brains of COVID-19 patients, correlates with disease severity, and is a predictive biomarker for post-COVID cognitive deficits.

Methods: We combined plasma clot formation assay, fibrinogen peptide array, spike-binding epitope mapping, peptide alanine scanning, in vitro functional assay to study fibrin and SARS-CoV2 Spike interaction. SARS-CoV-2 Beta and Delta variants were used as mouse models of COVID-19 infection, and multi-pronged approaches were conducted to characterize lung and neuro-pathologies, including 3D imaging of solvent-cleared organs (3DISCO), immunostaining, and bulk RNA-seq. Quantitative mass spectrometry phosphoproteomics and kinase activity analysis were used to determined protein phosphorylation and kinase-substrate relationships.

Results: We found that fibrin binds to the SARS-CoV-2 spike protein, forming proinflammatory blood clots that drive systemic thromboinflammation and neuropathology in COVID-19. Key pathologies in the lung induced by SARS-CoV-2 infection, including macrophage infiltration, alveolar hemorrhage, oxidative stress, and fibrosis, are significantly reduced in fibrinogen-deficient mice and *Fgg*γ390–396A mice, which express mutant fibrinogen that retains normal clotting function but lacks the γ390–396 motif for binding to the receptor CD11b–CD18. Fibrin activates macrophages through its inflammatory domain in the lung, while suppressing natural killer (NK) cells upon SARS-CoV-2 infection. Unbiased transcriptomics and phosphoproteomics revealed that fibrin suppressed NK-mediated cytotoxicity and cytokine production, and downregulated protein phosphorylation related to NK activation. Depletion of NK1.1+ cells abolished the protection provided by fibrinogen depletion. Moreover, fibrin promotes neuroinflammation and induces innate immune activation in the brain in different models of COVID-19 with or without neuroinvasion. The monoclonal antibody 5B8, targeting the inflammatory fibrin domain, provides protection from microglial activation, neuronal injury, demyelination, as well as from thromboinflammation in the lung after infection.

Conclusion: Our data demonstrated fibrin drives inflammation and neuropathology in SARS-CoV-2 infection, and fibrin-targeting immunotherapy may represent a therapeutic intervention for patients with acute COVID-19 and long COVID.

Key Words: Fibrinogen; Neuropathology; COVID-19; Microglia; NK cell; Bulk RNA-seq; Phosphoproteomics; Anti-fibrin immunotherapy

ID:134

Targeting cGAS-STING Innate Immunity for the Treatment of Age-Related Macular Degeneration

Lili Gong*,Xiangyu Ge,Xingfei Zhu,We Liu
中山大学中山眼科中心

Objective: The cGAS-STING pathway is an innate immune signaling pathway that senses cytosolic DNA. Our recent studies have shown that STING expression is increased in the retina and retinal pigment epithelium (RPE) of patients with dry age-related macular degeneration (AMD), accompanied by increased chromatin accessibility. In mouse models of oxidative damage or light-induced damage, cGAS-STING signaling is activated in the retina, and the STING inhibitor C176 can protect the retina from oxidative damage. This study aims to elucidate the protective effects and mechanisms of inhibiting STING transcription or knocking out the STING gene in the retina of mice under pathogenic stimuli of dry AMD.

Methods: Light damage (15,000 lumens, 2 hours) or sodium iodate-induced oxidative damage was used to induce damage in photoreceptors or RPE, respectively. Retinal morphology and structure were observed through HE staining, immunofluorescence staining, OCT, and fundus photography. Transcriptomic and intercellular communication analyses were performed using bulk RNA sequencing or single-cell RNA sequencing. Retinal function was assessed using ERG and optomotor response testing.

Results: RNA-seq analysis revealed that the epigenetic regulator protein BRD4 promotes the expression of cGAS and STING. Drug screening identified that competitive inhibitors and degradation inhibitors of BET can inhibit STING expression by regulating the accessibility of the STING gene under light and oxidative damage, thereby protecting retinal structure and function. Additionally, the commonly used ophthalmic anti-inflammatory drug methotrexate can downregulate gene expression by promoting heterochromatin enrichment of the cGAS and STING promoters, thereby inhibiting retinal and RPE inflammation through the suppression of cGAS-STING signaling. STING is primarily expressed in retinal microglia, and knocking out STING can reduce retinal neurodegeneration and microglial activation caused by light damage , oxidative stress as well as ischemia-reperfusion injury.

Conclusion: The cGAS-STING pathway may play a critical role in various neurodegenerative eye diseases and retinal inflammation. Targeting this pathway could offer new therapeutic strategies for blinding retinal diseases such as AMD, glaucoma, and diabetic retinopathy.

Key Words: cGAS-STING, microglia, PROTAC, retina

ID:137

sTIM-3 alleviates EAE by dampening NLRP3 inflammasome activation via interacting with ASC

Xiaodi Zhang,Pin Wang,Lifen Gao*

免疫学系

Objective: This study aimed to investigate the potential role of soluble T cell immunoglobulin and mucin-domain containing-3 (sTIM-3) in the regulation of the NLRP3 inflammasome, a multi-protein complex critical in innate immune response and inflammatory diseases.

Methods: In this study, PEMs, BMDMs and THP1 cells were included to assay the effect of sTIM-3 on NLRP3 inflammasome activation. The production of pro-inflammatory cytokines IL-1β and IL-18 in the supernatants of above cells stimulated with LPS and ATP with or without the presence of sTIM-3 was examined by ELISA. Cleaved caspase-1 and IL-1β were detected by western blot, and ASC specks were determined by IFA. Co-IP and confocal Imaging were performed to confirm the interaction of sTIM-3 and ASC. In vivo studies were conducted to evaluate the effect of sTIM-3 on septic shock and experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis (MS). Additionally, the correlation of sTIM-3 levels with clinical parameters was analyzed in MS patients.

Results: The results showed that sTIM-3 inhibits NLRP3 inflammasome activation, acompanied by decreased IL-1β, IL-18, low levels of cleaved caspase-1 and IL-1β, as well as less ASC specks. Mechanistically, we found that sTIM-3 could interact with ASC but not NLRP3, caspase-1, NEK7. Notably, sTIM-3 interacted with ASC to inhibit its oligomerization and NLRP3 inflammasome activation. In vivo, sTIM-3 was effective in alleviating the severity of septic shock and EAE by inhibiting NLRP3 inflammasome activation. In MS patients, higher sTIM-3 levels were associated with lower disease severity, less demyelination, and a negative correlation with the Multiple Sclerosis Walking Scale-12, suggesting a protective role of sTIM-3 in MS progression.

Conclusion: The finding identifies sTIM-3 as a promising therapeutic agent for treating a range of inflammatory diseases driven by excessive NLRP3 inflammasome activation, which offers novel insight for further exploration of sTIM-3 as a potential biomarker and therapeutic target in inflammatory diseases.

Key Words: sTIM-3, ASC, NLRP3 Inflammasome, Sepsis, Multiple Sclerosis

Poster Presentations

ID:33

Uncovering the Potential role of Mitochondrial Genes in Myasthenia Gravis and its Subgroups Based on A Mendelian Randomization Study

Jingluan Tian,Ying Zhou,Xinyi Xiao,Hansi Liang,Xin Wang,Yanzheng Gu,Zhe Lei,qun Xue*

苏州大学附属第一医院

Objective: Myasthenia gravis (MG) is a B cell- and T cell-mediated autoimmune neuromuscular disorder with the high heterogeneity. Mitochondria perform diverse vital multifunction and is closely related to MG. The mitochondrial function in MG warrants further study.

Methods: Based on the three principals, we conducted mendelian randomization (MR) study to evaluate the genetically causal relationship between mitochondrial genes and MG, as well as its subgroups. The transcriptome analysis including the different expression genes, GOKEGG enrichment pathway, and Cox logistic were performed in the Xiantao academic platform using TCGA-THYM datasets. The protein and protein interaction network model were analysis in the STRING and Cytoscape. Human MitoCarta3.0 datasets were used to summary the mitochondrial pathway. The expression of mitochondrial proteins SOD2 and GRPEL1 in the thymus tissue were assessed by immunohistochemistry.

Results: The MR study demonstrated that mitochondrial genes GRPEL1, REXO2, CA5A, SLC25A18, MRM3 and SCO1 were increasing risk factors to MG or LOMG development. SIRT5, NFU1 and DLD were protective factors to MG or EOMG. In addition, SOD2 and COX7A1 were negative associated with EOMG. PDK1 might play the opposite effect to EOMG and LOMG. Most of these genes were linked to thymoma or its histological type and immune cells infiltration. PPI analysis indicated that SOD2 were the core genes in the metabolism-related pathways. Moreover, COX logistic regression manifested that SOD2 and GRPEL1 were related to the overall survival of thymoma. Meantime, immunohistochemistry validation in thymus tissues confirmed both SOD2 and GRPEL1 were differently expression among thymoma-associated MG group, thymic hyperplasia-associated MG group and thymic cyst group.

Conclusion: The MR study demonstrated that mitochondrial genes GRPEL1, REXO2, CA5A, SLC25A18, MRM3 and SCO1 were increasing risk factors to MG or LOMG development. SIRT5, NFU1 and DLD were protective factors to MG or EOMG. In addition, SOD2 and COX7A1 were negative associated with EOMG. PDK1 might play the opposite effect to EOMG and LOMG. Most of these genes were linked to thymoma or its histological type and immune cells infiltration. PPI analysis indicated that SOD2 were the core genes in the metabolism-related pathways. Moreover, COX logistic regression manifested that SOD2 and GRPEL1 were related to the overall survival of thymoma. Meantime, immunohistochemistry validation in thymus tissues confirmed both SOD2 and GRPEL1 were differently expression among thymoma-associated MG group, thymic hyperplasia-associated MG group and thymic cyst group.

Key Words: Myasthenia Gravis, SOD2, GRPEL1, mitochondrial protein, Mendelian Randomization Study

Presenting Type: Oral or Poster

ID:42

Amyloid-β-related Angiitis: a Case Report and Characteristics

Yingzhe Shao,Li Yang*
Tianjin Medical University General Hospital

Objective: Amyloid-β-related angiitis is a rare disease, and data regarding its characteristics is scant.

Methods: A case of amyloid-β-related angiitis diagnosed by pathology is reported.

Results: A 60-year-old right-handed female presented with headache for three years, enunciation unclear for two years and dizziness for three days. She had type 2 diabetes for three years. There was no history of smoking, drinking, hypertension or exposure to toxic chemicals or drugs. And it was no obvious abnormalities in personal history, marriage and family history. At admission she presented dysarthria, memory decay and cognitive impairment. The Mini-Mental State Examination (MMSE) is 23 and the Montreal Cognitive Assessment (MoCA) is 13. And other physical examination was unremarkable. Laboratory tests during hospitalization are generally normal.

The Magnetic Resonance Imaging (MRI) Results demonstrated lesion in the left temporal, occipital lobe, right frontal lobe and bilateral basal ganglia with involvement of gray and white matter. The lesion was characterized by hyperintense on FLAIR and T2 weighted imaging (T2WI). The lesion in the left temporal lobe and right frontal lobe was abnormal contrast enhancement. And there was cerebral microbleeds on susceptibility weighted imaging (SWI).

Considering that there was multiple mass like lesion with enhancement, a biopsy was performed. Hematoxylin-eosin and immunohistochemical staining showed vascular wall damage, inflammation with granuloma formation consisting of lymphocytes and macrophages and multiple cerebral microbleeds. There was prominent immunoreactivity against amyloid-β (4G8) and less against amyloid-β (6E10) in the cerebral vessel wall. The pathological diagnosis of the patient was amyloid-β-related angiitis (ABRA).

We used intravenous methylprednisolone (500mg×5days) and gradually reduced the dosage. The patient's headache, dizziness and dysarthria improved significantly, and the lesion in the left temporal lobe and right frontal lobe significantly decreased compared to before treatment. The patient was discharged from the hospital with prednisolone (60mg), and she still had cognitive impairment.

Conclusion: Amyloid-β-related angiitis result from spontaneous autoimmune inflammation against amyloid in the vessel wall. Common clinical symptoms include cognitive behavioural abnormalities, focal neurological deficits, seizures, or unusual headaches. MRI is an important diagnostic tool, which shows hyperintensities on T2WI or FLAIR images with gadolinium enhancement. On SWI, a majority of the patients have the presence of microbleeds at cortico-subcortical junction. Brain biopsy remains the definitive standard. Vascular or perivascular inflammation and amyloid deposition within the affected vessels at histopathologic examination is the characteristic manifestation. Treatment strategies include steroids and other immunosuppressant therapy. Most patients respond well to therapy.

Key Words: Amyloid-β-related angiitis; Brain biopsy; Pathology

ID:45

Formyl Peptide as A Potential Biomarker for Neurodegeneration in Multiple Sclerosis

Zichun Xiao1,2,Fudong Shi*1,2,3,4

1. 天津医科大学总医院
2. 天津市神经病学研究所
3. 首都医科大学附属北京天坛医院
4. 国家神经系统疾病临床医学研究中心

Objective: Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) and a major cause of disability among young adults. Neurodegeneration is a driving force on the progression of MS, and its monitoring or treatment is an unmet need in clinic.

Methods: The Methods employed a comprehensive mechanistic exploration, which involved conducting immunofluorescence staining of human brain slices to analyze the expression and distribution of FPR1, and utilizing enzyme-linked immunosorbent assay for quantifying FPR1 ligand levels in blood samples obtained from patients and healthy individuals. The induction of experimental autoimmune encephalomyelitis (EAE) in both wild-type and gene knockout mice was carried out via MOG35-55 immunization, followed by an evaluation of FPR1 expression, distribution, and immune cell infiltration in the central nervous system using immunofluorescence and flow cytometry. Additionally, single-cell sequencing was employed to identify differentially high-expressed genes and assess functional enrichment. In vitro experiments were also conducted to analyze the expression of ROS, proinflammatory cytokines, and cell apoptosis.

Results: In this study, we found that the neurodegeneration is accompanied with cell necrosis in the CNS lesion of MS patients, leading to an increased levels of necrotic cells derived mitochondrial formyl peptide (mtFP) in the peripheral blood and cerebrospinal fluid in patients. Meanwhile, the mtFP receptor-formyl peptide receptor 1 (FPR1) -is specifically upregulated in the CNS of MS, but not in parallel controls or Alzheimer's disease, another kind of neurodegeneration disease. By further assessing the potential link between mtFP/FPR1 and MS progression and neurodegeneration,We found that MS patients display significantly elevated levels of mtFP in blood both during acute attacks ($n = 77$, 42.68 ± 3.64 vs. 16.05 ± 2.4 pg/ml, $P < 0.0001$) and disease remission ($n = 86$, 38.45 ± 2.51 vs. 16.05 ± 2.4 pg/ml, $P < 0.0001$). In the experimental autoimmune encephalomyelitis (EAE) mouse model of MS, genetic elimination of FPR1 reduced the production of reactive oxygen species and the antigen presentation capacity of microglia and macrophages, attenuating neurodegeneration within the CNS.

Conclusion: Collectively, our study has uncovered mtFP is as a potential new biomarker predicting the neurodegeneration in MS.

Key Words: Multiple sclerosis, neurodegeneration, demyelination

ID:46

cGAS-STING-IFN-I Signaling Pathway Promots Autoreactive T cells and Aggregates Neuromyelitis Optica Spectrum Disorder

Xiao-Shan Du,Tian-Xiang Zhang,Xue Gao,Chao Zhang,Fu-Dong Shi*
天津医科大学总医院

Objective: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease characterized by anti-aquaporin 4 (AQP4) antibody-mediated astrocyte damage and subsequent demyelination. The abnormal type I interferon (IFN-I) production influences the differentiation of B cells and T cells, and exacerbates the disease in NMOSD patients. This study aims to examine the contributions of IFN-I to NMOSD, its molecular mechanisms, and clinical implications.

Methods: We used single-cell RNA sequencing data analysis to illustrate the responses of cGAS-STING-IFN-I signaling pathway in myeloid cells in both the periphery and central nervous system (CNS) in NMOSD patients. NMO-IgG intracerebral injection mouse model (NMO-IgG model) and Th17-AQP4p135-153 specific passive transfer mouse model (Th17-AQP4 model) were established to verify the activation of the IFN-I signaling. The STING-/- mice and STING inhibitor H-151 were used to observe the effects of inhibiting the signaling pathway on the NMO-IgG mouse model.

Results: Here, we have identified robust activation of the cGAS-STING-IFN-I signaling pathway in myeloid cells in both the periphery and CNS. Upregulations of cGAS-STING-IFN-I pathway in microglia were observed in NMO-IgG model and Th17-AQP4 model. STING deficiency alleviated pathology in NMO-IgG model and markedly ameliorated the clinical manifestations in the Th17-AQP4 models and subsequent IFN-I activity in microglia. Notably, ablation of STING markedly reduced the activation of AQP4-specific Th17 cells and B cells, as well as astrocyte damage caused by their infiltration into the CNS. Further, treatment with STING inhibitors could alleviate the severity of the disease.

Conclusion: These findings uncover the cGAS-STING-IFN-I pathway in promoting autoreactive T cells and provide preclinical evidence inhibition of this pathway is a new therapeutic revenue for NMOSD.

Key Words: neuromyelitis optica spectrum disorders; type I interferon; Innate immune response; T cells

ID:48

Inhibition of LCP1 in monocytes and macrophages from the ischemic brain hemisphere downregulated cell lipid metabolism

Yan Wang*

Peking University Third Hospital

Objective: Ischemic stroke poses a significant health burden with limited treatment options. Lymphocyte Cytosolic Protein 1 (LCP1) facilitates cell migration and immune responses by aiding in actin polymerization, cytoskeletal rearrangements, and phagocytosis. We have demonstrated that the long non-coding RNA (lncRNA) Maclpil silencing in monocyte-derived macrophages (MoDMs) led to LCP1 inhibition, reducing ischemic brain damage. However, the role of LCP1 of MoDMs in ischemic stroke remains unknown.

Methods: We investigated the impact of LCP1 on ischemic brain injury and immune cell signaling and metabolism. Utilizing the high-dimensional CyTOF technique, we demonstrated that knocking down LCP1 in MoDMs led to a reduction in neuroinflammation and attenuation of lymphopenia, which is linked to immunodepression. It also showed altered immune cell signaling by modulating the phosphorylation levels of key kinases and transcription factors, including p-PLCg2, p-ERK1/2, p-EGFR, p-AKT, and p4E-BP1 as well as transcription factors like p-STAT1, p-STAT3, and p-STAT4. Further bioinformatic analysis indicated that Akt and EGFR are particularly involved in fatty acid metabolism and glycolysis.

Results: We found that knockdown of LCP1 in MoDMs demonstrated robust protection against ischemic infarction and improved neurological behaviors in mice.Indeed, single-cell sequencing analysis confirmed that enrichment of fatty acid and glycolysis metabolism in Lcp1high monocytes/macrophages. Furthermore, Lcp1high cells exhibited enhanced oxidative phosphorylation, chemotaxis, migration, and ATP biosynthesis pathways. In vitro experiments confirmed the role of LCP1 in regulating mitochondrial function and fatty acid uptake.

Conclusion: These findings contribute to a deeper understanding of LCP1 in the context of ischemic stroke and provide valuable insights into potential therapeutic strategies targeting LCP1 and metabolic pathways, aiming to attenuating neuroinflammation and lymphopenia.

Key Words: Ischemic stroke, Macrophages, Lipid metabolism, Neuroinflammation

ID:50

Clock gene regulates molecular profiles associated with intracerebral hemorrhage

Suliman Khan,Mengzhou Xue*

The Second Affiliated hospital of Zhengzhou University

Objective: To investigate the association of circadian rhythms (Clock gene) with the onset, recovery, and progression of intracerebral hemorrhage (ICH); To understand the Clock gene mediated regulation of molecular and immunological changes in ICH micemodel.

Methods: The ICH model was induced by injecting type VII collagenase into the striatum region of C57BL/6 mice under stereotactic system guidance. Sleep analysis and wheel run activity were performed to assess the role of circadian rhythm disruption after ICH. The neurological functions were assessed through the Focal deficit neurological test and Corner turn test. The H&E stain was used to observe neuronal degeneration and hematoma size induced by ICH brain injury. MPO was observed by immunohistochemical staining. TUNEL staining was used to quantify the apoptosis neurons. MRI scan was used to observe the size and physiology of ICH hematoma.

Results: Disruption of circadian clock caused the alteration of genes associated with neurological disease in different brain regions of mice, indicating that circadian clock disruption increases the risk of neurological diseases. In addition, key regulatory genes are associated with key biological pathways and functions including immunological responses. Transcriptome profiling revealed differential expression of key regulatory genes associated with common neurological diseases such as Alzheimer's disease, Parkinson disease and meningitis in striatum, hippocampus, and hypothalamus of ICH animal model. In addition, genes related to circadian clock such as Clock, Per1, Per2, Per3, and Cry1 were also found to be dysregulated and altered, indicating that ICH can disrupt the circadian clock machinery. Sleep piezoelectric test Results revealed that ICH caused a decrease in sleep bout number during daytime and increased the length of sleep bout during nighttime. The wheel run activity test Results indicated that ICH significantly increased the period (longer free period), while under light condition (LL) ICH mice showed a long period of about 27.5 h unlike control mice, which lost rhythm.

Conclusion: Results based on behavioral tests, MRI scans, Hematoxylin and Eosin (H&E) staining, Immunohistochemical and Immunofluorescent staining Results showed that in the case of Clock KO condition, the severity of ICH was increased and the recovery from ICH was delayed as compared to ICH model of wild type mice.

Key Words: Intracerebral Hemorrhage; circadian clock; Clock gene; immune regulations

ID:55

Tumefactive Demyelination as the First Presentation of MOG Ab-Associated Disease

Huihui Xue1,linjie zhang2,yuan qi2,cuiyun sun2,li yang2,chunsheng yang*2

1. 天津医科大学

2. 天津医科大学总医院

Objective: Tumefactive brain lesions are a rare presentation of myelin oligodendrocyte glycoprotein-associated disease (MOGAD). They must be differentiated from brain tumors, neuromyelitis optica spectrum disorders (NMOSD), and multiple sclerosis (MS). This case report highlights the clinical, radiological, and histological features of a patient with MOGAD-associated tumefactive brain lesions, underscoring the importance of accurate diagnosis and treatment.

Methods: A 45-year-old woman with a known history of hypertension was admitted to the hospital after experiencing progressive limb weakness, slow mental responses, and aphasia over a period of three weeks. Notably, there was no prior history of infections, fever, or recent vaccinations. An MRI of the brain revealed a mass and associated edema localized in the left frontal lobe. To further investigate the lesion, a brain biopsy was performed, which showed perivascular lymphocyte infiltration, focal myelin loss, and preserved axons, all of which are suggestive of tumefactive demyelination. Immunohistochemical staining and PET-CT scans were conducted, and both serum and cerebrospinal fluid (CSF) were tested for MOG antibodies, along with oligoclonal band analysis.

Results: The biopsy and immunohistochemical analysis indicated demyelination, and PET-CT supported this diagnosis. The patient's serum MOG Ab titer was 1:320, and CSF MOG Ab was 1:1, confirming MOGAD. Oligoclonal bands were negative, and other possible diseases were excluded. After treatment with high-dose intravenous methylprednisolone (IVMP), the patient experienced complete remission of symptoms, and MRI showed significant reduction of lesions. Tocilizumab was prescribed to prevent relapse.

Conclusion: Tumefactive demyelination lesions can manifest in MOGAD. Radiological and pathological evaluations are essential for diagnosis and differentiation from other diseases. These lesions respond well to intravenous methylprednisolone (IVMP), and early treatment may improve prognosis and help avoid severe outcomes.

Key Words: Myelin oligodendrocyte glycoprotein associated disease (MOGAD), tumefactive demyelination, intravenous methylprednisolone (IVMP)

ID:63

The Impact of Phytosomal Curcumin Supplementation on Glial Activation and Neuroinflammatory Markers on a Mouse Model of Chronic Neuroinflammation

Anushka Chatterjee,Ingrid Wagnon,Lillian Jabur,Natalie Mikhael,Minjet Hwang,Ilaria Rossetti,Anandwardhan Hardikar,Mugdha Joglekar,Gerald Muench,Erika Gyengesi*

Western Sydney University

Objective: Chronic neuroinflammation is a pathological hallmark for neurodegenerative disorders triggered by internal or external stimuli leading to altered central nervous system (CNS) homeostasis, production of proinflammatory cytokines, chronic glial activation, overexpression of neuroinflammatory markers and protein misfolding. This multifaceted nature of neurodegenerative disorders demands therapeutic strategies which will have an impact on the cellular and molecular phenotype without causing deleterious effects. Therefore, in this study, we explored a highly bioavailable phytosomal curcumin formulation in a mouse model of chronic neuroinflammation (GFAP-IL6).

Methods: A comprehensive approach combining mass spectrometry analysis of the plasma concentration of curcumin followed by transcriptomic analysis of the cerebellum, hippocampus, amygdala and prefrontal cortex and immunohistochemistry along with stereology was employed to investigate the effect of curcumin supplementation on neuroinflammatory markers and glial activation on mice at 9 months age.

Results: Phytosomal curcumin diet was able to interfere with the neuroinflammatory pathways by downregulating the mRNA levels of pro-inflammatory markers P2rx7 and Nfkb1 in the hippocampus as compared to the animals on control diet. In female GFAP-IL6 mice, the amygdala was the region that curcumin feeding had the greatest impact with genes such as Aif1, C3, Nfkb1, S100a10, Tmem119 being downregulated. Curcumin diet also had a positive impact on the glial activation with lower microglial numbers in the cerebellum along with lower microglial and astrocyte numbers in the hippocampus as compared the mice on control diet.

Conclusion: Our study on phytosomal curcumin supplementation in GFAP-IL6 mice mostly showed positive effects on neuroinflammatory markers and glial cells therefore making it a therapeutic potential against chronic neuroinflammation either by reversing or slowing down the neuroinflammatory process.

Key Words: chronic neuroinflammation, glial activation, phytosomal curcumin, neuroinflammatory markers

ID:69

GFAP-positive Extracellular Vesicles Modulate the Natural Killer Cell- Mediated Immunity in Glioblastoma

NADIAH ABU*,Johannes Jun Wei Low,Bee Hong Soon
UNIVERSITI KEBANGSAAN MALAYSIA

Objective: Glioblastoma (GB) is an aggressive brain cancer with poor prognosis, characterized by immune tolerance and a complex immunosuppressive tumor microenvironment. Extracellular vesicles (EVs), nano-sized vesicles released by all cells, including GB cells, are implicated in tumor immunity. This study aims to investigate the role of GB-derived EVs in immune modulation especially in antibody-dependent cytotoxicity.

Methods: Autoantibody profiling was conducted using serum from GB patients (n=10) and healthy controls (n=5) via the

i-Ome Array platform. Two autoantigens were selected for further validation on EVs. EVs were isolated from serum

samples of GB patients (n=18), healthy controls (n=35), and GB cell lines (n=4) using size exclusion columns. Characterization of EVs was performed using flow cytometry, nanoparticle tracking analysis, and transmission electron microscopy. Autoantigen validation was conducted via bead-based flow cytometry. A modified antibody-dependent cytotoxicity (ADCC) assay with natural killer (NK) cells and EVs was performed using the xCELLigence RTCA platform at various effector-to-target ratios.

Results: Autoantibody profiling revealed 16 differentially expressed autoantibodies ($p<0.05$, $logFC>0.5$) in GB patients serum, including anti-GFAP and anti-HSP90AA1. EV characterization showed that EVs from GB patients, healthy controls, and cell lines expressed tetraspanins (CD63, CD9), were <200nm in size, and had a rounded morphology. GFAP was significantly expressed on GB patients and the U251MG cell line EVs, while HSP90AA1 showed no significant difference. In the ADCC assay, GFAP-positive EVs from the U251MG cell line acted as decoys for GFAP antibodies, enabling immune escape from NK cell toxicity at a 10:1 effector-to-target ratio.

Conclusion: Preliminary findings suggest that GFAP is upregulated in GB-derived EVs, which may facilitate immune escape by competitively binding GFAP antibodies, thereby reducing NK cell-mediated cytotoxicity. EVs may play a significant role in immune modulation in GB patients.

Key Words: glioma, exosome, antibody

ID:70

Premature Thymic Involution in MS and Other Autoimmune Diseases: a Hospital-Based Radiographic Observational Analysis

Xiaoyu Huang[1],Haoxiao Chang[2],Junqiang Yan[2],Anxin Wang[2],Ningning Wang[2],Peng Liu[4],Yemin Shi[5],Xin Zhao[1,3],Xue Xia[2],Shiyi Yin[2],De-Cai Tian[2],Kaibin Shi[2],Xinli Wang[2],Yuan Cai[7],Ganqin Du[2],Wenhao Huang[2],Guoyan Qi[4],Xinghu Zhang[2],Zhang Zhang[6],Wei-Na Jin[2],Fu-Dong Shi*[1,2]

1. Tianjin Medical University General Hospital
2. Department of Neurology, China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University
3. Department of Neurology, The First Affiliated Hospital, College of Clinical Medicine, Henan University of Science and Technology
4. Center of Treatment of Myasthenia Gravis, People's Hospital of Shijiazhuang, Hebei Medical University
5. Beijing Academy of Artificial Intelligence
6. Department of Radiology, Tianjin Medical University General Hospital
7. Department of Medicine & Therapeutics, The Chinese University of Hong Kong

Objective: To characterize the feature of thymic in multiple sclerosis and other autoimmune diseases and investigate the correlation between thymic character and active T cells.

Methods: In this hospital-based, multicenter observational study, a semi-automatic auxiliary algorithm was employed to characterize the thymic in 16 autoimmune diseases by retrospectively examining chest computed tomography (CT) images of 2655 patients and 2874 health control from 4 institutions in China. A thymic scoring system with a four-point scale (0-3) was used to evaluate thymic fatty replacement, based on the ratio of fatty and soft tissues. Baseline information on the demographic, clinical, and potential risk factors was collected. Multivariable linear regression and logistic regression analysis were conducted to estimate the thymic character, with age, sex, BMI, smoking, chronic disease, malignant tumor, allergy, radiation, and current infection as covariates. To gain a better understanding of the association between thymic character and output active T cells, 80 individuals with myasthenia gravis who had a CT done routinely were prospectively enrolled and their peripheral blood was taken for flow cytometry experiments.

Results: Thymic of autoimmune diseases patients demonstrate a unique morphological characteristic with respect to higher trapezoidal proportions, larger bilobed size, and reduced density, in comparison to healthy controls. When evaluated using thymus scoring, autoimmune disease patients displayed a greater proportion of complete fatty replacement (score 0) and mainly fatty thymus (score 1). It is evident that all sixteen autoimmune diseases demonstrate a consistent trend of exacerbated age-dependent thymic involution than health control. The proportion of active T cells and double negative T cells in MG are found to be significantly associated with thymus density in FCM tests.

Conclusion: A radiographic auxiliary algorithm by using chest CT images uncovers the general thymic character of autoimmune diseases patients. The premature thymic involution and the connection between thymic character and active T cells proportion could offer a novel and all-encompassing explanation of the pathogenesis of autoimmune diseases, with self-tolerance being lost as a result of thymic defect.

Key Words: Premature thymic involution ; Radiographic observational analysis ; Active T cells ; Autoimmune diseases

ID:71

Integrating single-cell RNA-seq transcriptomics reveal shared characteristics of regulatory T lymphocytes among Systemic lupus erythematosus, Multiple sclerosis and Primary Sjögren's syndromes

Haonan Guan1,2,3,4,5,Yang Liu4,Zhilin Chang3,4,5,Yingying Chang3,4,Tian Lan3,4,5,6,Weina Jin*1,2,4,5,6

1. 郑州大学第三附属医院
2. Zhengzhou University
3. Center for Neurological Diseases
4. China National Clinical Research Center for Neurological Diseases
5. Beijing Tiantan Hospital
6. Capital Medical University

Objective: Autoimmune diseases constitute a group of disorders characterized by immune-mediated attacks on the body's own organs. It is hypothesized that there may be similarities in peripheral immune transcriptomics across various autoimmune diseases, potentially linked to abnormal immune responses in patients with autoimmune diseases. This study aims to analyze the transcriptional profiles of immune cell composition, genes, and signaling pathways in the peripheral blood of individuals with three common autoimmune diseases: systemic lupus erythematosus (SLE), multiple sclerosis (MS), and primary Sjögren's syndrome (pSS).

Methods: We analyzed single-cell RNA sequencing data from peripheral blood mononuclear cells derived from 17 patients (7 with SLE, 5 with MS, and 5 with pSS), alongside 15 healthy controls, utilizing the Seurat software package (version 4.4.0) within R studio. Subsequent investigations were carried out on these cells to explore differences and associations across the three autoimmune diseases, by comparing changes in the composition of immune cell populations, distinctive genes, and signaling pathways. The scRNA-seq data for SLE, MS and pSS were sourced from the Gene Experession Omnibus(GEO)

Results: After quality control on the ScRNA-seq data, low-quality cells and doublets were filtered out. The analysis yielded 37,586 cells from 5 healthy controls and 35,108 cells from 7 SLE patients, 14,047 cells from 5 healthy controls and 22,967 cells from MS patients, and 23,274 cells from 5 healthy controls and 26,988 cells from pSS patients. Examination of cell clusters based on gene expression revealed a decreased proportion of peripheral blood T cell clusters across all three diseases. Differential gene analysis of T cells revealed 117 shared genes. Pathway enrichment analysis of these genes highlighted enrichment in pathways such as infection, immune response, and NF-kappa B pathways. Subsequent analysis of T cell clusters showed an increased proportion of regulatory T (Treg) cells. Further differential gene and pathway enrichment analysis of Treg cells identified four shared genes (RPS26, GIMAP4, GIMAP7, VIM) and highlighted the disease-specific characteristics of each of the three diseases.

Conclusion: Our data elucidate the evolving composition of immune cell populations in the peripheral blood of individuals with three autoimmune diseases: SLE, MS and pSS. The identification of commonly expressed genes (GIMAP4, GIMAP7) in regulatory T cells suggests promising targets for therapeutic intervention across these diseases

Key Words: systemic lupus erythematosus, multiple sclerosis, multiple sclerosis, DEG, scRNA-seq, regulatory T cells.

ID:72

Treatment strategy towards myasthenia gravis with GAD65-IgG associated neurological disorders

Xiao-Na Xu,Wen-Jun Luo,Hui-Ning Li,Chun-Sheng Yang*
Tianjin Medical University General Hospital

Objective: The report aimed to investigate the clinical manifestations of, therapeutic strategy for, and underlying mechanisms in a patient with myasthenia gravis (MG), glutamic acid decarboxylase 65 (GAD65) antibody-associated neurological disorders, and type B2 thymoma.

Methods: The diagnostic procedures included antibody testing (cell- and tissue-based assays) and cranial imaging examinations. Hematoxylin-eosin staining and immunohistochemistry were used to make a pathological diagnosis of the patient's anterior mediastinal tumor. Additionally, we conducted a literature review relevant to this case.

Results: A 50-year-old woman with early-onset, acetylcholine receptor antibody-positive, generalized MG received intravenous methylprednisolone (IVMP), immunoglobulin, and tacrolimus. She experienced remarkable clinical improvements in chewing and swallowing. However, approximately two weeks later, she was admitted to the emergency room because of a disturbance of consciousness, which manifested as a stuporous and apathetic state. GAD65 antibodies were detected in the patient's serum and cerebrospinal fluid by cell-based assays, binding to the granular layer of monkey cerebellum slides. She improved considerably after treatment with efgartigimod alfa, high-dose IVMP, and rituximab. Two months later, the patient underwent resection of the anterior mediastinal tumor through an extended thymectomy. A diagnosis of type B2 thymoma (pathological stage I, according to the Masaoka classification) was established. Immunohistochemistry suggested that GAD65 was expressed by fibrocytes rather than by tumor cells. To date, the patient has not experienced recurrence of the neurological symptoms.

Conclusion: There is no defined therapy for myasthenia gravis with GAD65-IgG associated neurological disorders. Thymomas trigger several changes that influence immune tolerance, which remains a major puzzle. Nevertheless, early and efficient immunotherapy is important and may be associated with better outcomes. We believe that this report provides novel insights into the diagnosis and therapy for this disease.

Key Words: myasthenia gravis, GAD65 antibody, efgartigimod alfa, thymoma, autoimmune

ID:74

Real-World Practice of Satralizumab Treatment in Neuromyelitis Optica Spectrum Disorder among Chinese Population: A Prospective Case Series

Shengfei Hu,rui Li*

The Third Affiliated Hospital of Sun Yat-sen University

Objective: Objective: Satralizumab is a novel biological agent that prevents the recurrence of neuromyelitis optica spectrum disorder (NMOSD) by targeting the IL-6 receptor (IL-6R) and blocking its related signaling pathways. However, real-world data on the effectiveness and safety of satralizumab in NMOSD remain limited, moreover, potential biomarkers for treatment response are yet to be explored. This study aims to analyze the clinical immune responses of patients treated with satralizumab, providing insights into its mechanism of action, identifying potential biomarkers for therapeutic response, and assisting in developing personalized clinical decision-making.

Methods: Methods: This study prospectively collected data from nine NMOSD patients treated with satralizumab. Evaluations were conducted at screening and at 1, 2, 3, 4, 5, 6, 9, 12, and 24 months post-treatment, assessing relapse occurrence, Expanded Disability Status Scale (EDSS) scores, complete blood count, liver and kidney function, and IgG levels. Peripheral blood biomarker analysis was also performed on a subset of patients.

Results: Results: A total of nine female patients were enrolled in the study. The average age at the initiation of satralizumab was 40 years, with a mean disease duration of 7.89 years. The mean annualized relapse rate (ARR) for the two years prior to treatment was 1.1, and the average pre-treatment EDSS score was 3.72. The mean follow-up period was 19.67 months. During treatment with satralizumab, eight patients did not experience a relapse. One patient relapsed one month after starting treatment, primarily presenting with decreased vision, but had no further relapses. The average EDSS score at the last follow-up was 3.61. Four experienced lymphopenia and leukopenia. Peripheral blood biomarker analysis was performed on four patients. In three patients whose disease remained stable, levels of AQP4-IgG, GFAP, NfL, Th17 cells ratio, and CD27+CD38+CD19+ cells ratio showed a downward trend during satralizumab treatment. In the patient who relapsed during treatment, levels of GFAP, AQP4-IgG, Th17 cells, and CD27+CD38+CD19+ cells increased after relapse and decreased when the disease stabilized again, whereas NfL levels increased after relapse without subsequent decline. There were no clear trends in the serum levels of IgG, TREM2, IL6, or IL6Ra among the four patients.

Conclusion: Conclusion: Real-world data from a Chinese population demonstrate the favorable efficacy and safety profile of satralizumab. Satralizumab may exert immunomodulatory effects by influencing various protein molecules and lymphocyte subpopulations. Levels of AQP4-IgG, GFAP, NfL, Th17 cells ratio, and CD27+CD38+CD19+ cells ratio may serve as potential biomarkers reflecting therapeutic response.

Key Words: Neuromyelitis Optica Spectrum Disorder, satralizumab, biomarker

ID:75

Brain Characteristics in Patients with Myelin Oligodendrocyte Glycoprotein Antibody-associated Disorder by 7.0 T MRI

Zhihui Qi[1],Lei Su[1,2],Joseph Kuchling[3],Chenyang Gao[1,2],Thoralf Niendorf[3],Carsten Finke[3],Zhe Zhang[2],Ai Guo2,Jing Jing[2],De-Cai Tian[2],Yu-Jing Li[1],Mengting Zhang[2],Xiaoyu Shi[2],Xinyao Liu[2],Huabing Wang[2],Yaou Liu[2],Claudia Chien[3],Michael Levy[4],Yunyun Duan[2],Friedemann Paul[3],Fu-Dong Shi*[1,2],Zhihui Qi

1. 天津医科大学总医院

2. Tiantan Neuroimaging Center of Excellence, China National Clinical Research Center for Neurological Diseases, and Departments of Neurology, Radiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

3. Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine and Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

4. Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Objective: The diagnosis of Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) can radiographically mimic multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). The disease is hallmarked with cortical lesion (CL), central vein sign (CVS), and paramagnetic rim lesion (PRL) having not yet been well-established in MOGAD.

Methods: We have characterized 45 patients with MOGAD using 7.0 Tesla (7T) MRI at 2 academic research hospitals in China and Germany. 7T MRI, laboratory, and clinical data were collected. The classification of CLs, the proportion of CVS, and the phase shifts of lesions on susceptibility weighted imaging were analyzed.

Results: Of the 45 patients enrolled with MOGAD, 282 lesions were identified. We further identified 31(11%) CLs including leukocortical, intracortical, and subpial type of cortical lesions, in which intracortical lesions (16/31, 52%) were frequently involved. CVS was detected in 53(19%) lesions of 21(47%) patients; while multiple veins sign (MVS) showed in 154(55%) lesions of 30(67%) patients. The number (3.4±5.7 vs. 1.2±1.9, p= 0.0163) and percentage (55% vs. 19%, $p < 0.0001$) of MVS lesions for each MOGAD patient were higher than those of CVS. Eight patients (18%) had 39(14%) lesions of hypointense signal with paramagnetic phase, showing nodule and irregular border in appearance.

Conclusion: In our observational MOGAD cohort, all three types of CLs were recognized with intracortical lesions being the most common. The number and proportion of lesions with MVS were higher than those with CVS. Lesions with paramagnetic phase were rare and non-rim in appearance. These findings provide a better understanding of the underlying pathology of MOGAD and will help in the distinction of MOGAD from other demyelinating disorders.

Key Words: MRI; Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)

ID:78

Effectiveness and Safety of Glucocorticoids Bridging Rituximab in Neuromyelitis Spectrum Disorder

Jia Liu,Chunyang Wang,Xue Gao,Yi Shen,Jing Pan,Shu Yang,Moli Fan,Dongmei Jia,Chao Zhang*

天津医科大学总医院

Objective: Anti-CD20 monoclonal antibody rituximab have been widely used to prevent relapses in patients with neuromyelitis optica spectrum disorder (NMOSD), but data on early use of oral prednisone overlapping with rituximab for effective reduction of relapses are limited. In this study, we evaluated the long-term efficacy of oral prednisone bridging rituximab therapy in NMOSD patients with anti-aquaporin-4 antibody (AQP4-IgG).

Methods: We collected the medications and disease activities in patients with AQP4-IgG+ NMOSD patients in this retrospective study. Time to first relapse was evaluated after starting stable doses of prednisone and/or initiating rituximab. We compared the efficacy and safety of different doses of prednisone with sequential rituximab treatment in NMOSD.

Results: 211 patients fulfilled the inclusion criteria for the study, including 91 patients who were treated with prednisone monotherapy and 120 patients who were treated with prednisone bridging rituximab. In total, 59.3% (54/91) of patients in the prednisone monotherapy group experienced new relapses. The proportions of patients with relapses were different in the subgroups of prednisone monotherapy, with 100% (23/23) in the group of dose ≤ 5mg/d, 64.1% (25/39) in the group of doses 7.5-10mg/d, and 20.7% (6/29) in the group of dose ≥ 12.5mg/d. 24.2% (29/120) of patients in the prednisone bridging rituximab group experienced relapses. Bridging rituximab regimen significantly reduced the risk of relapses compared to prednisone monotherapy (hazard ratio: 0.24, 95% CI: 0.15-0.38, $p < 0.0001$). Patients with prolonged usage of prednisone tapering (6-12 months) had a significant reduction in the relapse risk compared to those with prednisone tapering 3-6 months (hazard ratio: 0.3119, 95% CI: 0.09125-1.066, $p = 0.0264$). The most common adverse events were hyperlipidemia in the prednisone monotherapy group (17.6%) and infections in the prednisone bridging rituximab group (25.8%).

Conclusion: Prednisone bridging rituximab therapy is associated with the reduced relapse risk in patients with AQP4-IgG+ NMOSD, especially when the bridging time is over 6 months.

Key Words: Bridging; Rituximab; Relapse; NMOSD

ID:81

Epidemiology, prevalence and temporal trend of incidence of NMOSD at Penang Island, Malaysia, and a review of worldwide prevalence and genetic associations

Jyh Yung Hor*1,Chee Keong Wong1,Yin Yin Tan1,Syafiq Idris1,Najihah Khalid1,Yi Ping Ong1,Thien Thien Lim2,On behalf of the Penang NMOSD Study Group1

1. Department of Neurology, Penang General Hospital, Penang, Malaysia
2. Department of Neurology, Island Hospital, Penang, Malaysia

Objective: Unlike multiple sclerosis that is more prevalent in populations with European ancestry, NMOSD appears to be more prevalent among populations with non-European ancestry, suggesting certain degree of genetic predisposition. We investigated the epidemiology, prevalence and incidence of NMOSD at the multi-racial Penang Island, Malaysia, located at the equatorial South East Asia. Studying the temporal trend of incidence (new cases) in a specified population may provide insights into "genetic vs. environmental" risk factors of the disease.

Methods: (1) A population-based study was carried out where hospitals with neurology service (adult and paediatric) (n=6) at Penang Island participated. Patients fulfilling the 2015 IPND criteria and were AQP4-IgG+ were included, and their demographic and clinical data were collected. (2) Population-based prevalence/incidence studies and genetic studies of NMOSD worldwide were reviewed.

Results: A total of 79 patients were identified, with 38 patients were residents of Penang Island [32 Chinese (East Asian ancestry) and 6 Malays (Austronesian ancestry)]. There was no resident patient among the small population with South Asian ancestry. Female:male ratio was >9:1, and patients invariably relapsed if without appropriate maintenance immunosuppressant. On prevalence day (31 Dec 2023), the prevalence was 6.96/100,000 among Chinese, and 1.57/100,000 among Malays, despite living in the same environment. For incident cases from 2012-2023, the annual incidence was 4.40/million among Chinese, and 1.65/million among Malays. Over 12 years, the temporal trend of incidence (new cases) appeared relatively stable, apart from a slight increase after universal COVID19 vaccination during 2021-2023.

Conclusion: Based on our and other population-based studies, there was differential prevalence of NMOSD in populations with different ancestries – Black African (up to 10/100,000), East Asian (~6/100,000), Austronesian (~2/100,000), European (~1.5-2/100,000), and South Asian (~1/100,000). No latitude gradient was observed unlike that seen in multiple sclerosis. The incidence (new cases) appeared relatively stable over time, except for a slight increase post-universal vaccination. Genetic studies in various populations identified several different HLA risk and protective alleles. Current data suggest that genetic predisposition may play an important role in NMOSD disease prevalence, and vaccination may be a minor trigger for NMOSD onset in at-risk population.

Key Words: NMOSD, AQP4, epidemiology, population study, genetics, vaccination

ID:83

Lactylation mediates MEK1 activation, which in turn activates STAT6, promoting the polarization of microglia towards an anti-inflammatory state.

Ling Xin,tao yan*

tianjin medical university general hosiptal

Objective: This study aims to elucidate the molecular mechanism by which lactylation modification of lysine at position 97 of the MEK1 protein kinase promotes its phosphorylation, facilitating interaction with and activation of STAT6. This, in turn, promotes the polarization of microglia toward an anti-inflammatory state, thereby improving stroke recovery. At the molecular level, lactylation connects lactate, a metabolic byproduct, with cellular functions through a mechanistic pathway. This research is expected to enhance understanding of post-stroke pathological processes related to anaerobic glycolysis and microglia, providing new insights into the immune regulation mechanisms of the central nervous system and offering novel strategies for treating neuroinflammation and neurodegenerative diseases.

Methods: C57 male mice will be used to establish a photochemical (PT) ischemic stroke model. Proteomic mass spectrometry will verify lactylation modifications and identify differentially modified proteins. MEK1 lactylation will be confirmed via immunoprecipitation, Western blotting, and immunofluorescence. Mice will be divided into four groups: sham surgery, stroke, post-stroke lactate intervention, and post-stroke lactate with MCT inhibitor 7ACC2. Behavioral assessments, TTC staining, laser speckle imaging, and inflammation markers will evaluate recovery. Immunoprecipitation will assess lactylation-related proteins and pathways.

In vitro experiments using the BV2 microglial cell line will investigate how exogenous lactate affects MEK1 lactylation, phosphorylation, STAT6 activity, MAPK signaling, inflammation, and microglial polarization. Mutant virus transfection and co-immunoprecipitation will validate the mechanisms involved.

Results: Proteomic mass spectrometry data showed that the majority of proteins in mice exhibited upregulated lactylation modifications. Notably, lysine at position 97 of the MEK1 protein displayed a 2.12-fold increase in lactylation modification. Molecular docking further confirmed that lactate molecules could be captured by MEK1. Immunoprecipitation validated that MEK1 indeed underwent lactylation, and both stroke and exogenous lactate addition elevated MEK1 lactylation and phosphorylation levels. After mutating the lysine at position 97, MEK1 lactylation significantly decreased, and phosphorylation was abolished, indicating that MEK1 activation may be linked to lactylation at lysine 97.

Additionally, we observed an interaction between MEK1 and STAT6, and lactate supplementation promoted STAT6 activation, a result also confirmed by in vitro kinase assays. In vitro experiments demonstrated that lactate improved the behavioral scores of mice, reduced the infarct volume, enhanced blood supply, increased lactylation modification levels, decreased the secretion of inflammatory factors, and promoted microglial polarization toward an anti-inflammatory phenotype.

Conclusion: Lactate promotes MEK1 lactylation and phosphorylation, which in turn activates STAT6 and drives microglial polarization toward an anti-inflammatory state, ultimately improving post-stroke outcomes.

Key Words: microglia, MEK1, STAT6, lactylation, stroke

ID:85

Group 2 innate lymphoid cells instruct meningeal myelin-reactive T cells to augment neuroinflammation

Huachen Huang*
天津医科大学总医院神经所

Objective: Multiple sclerosis (MS) is an autoimmune disorder characterized by the activity of autoreactive T cells within the central nervous system (CNS).

Methods: In this study, we demonstrate that group 2 innate lymphoid cells (ILC2s), primarily located in the meninges, play a significant role in driving the pathogenesis of experimental autoimmune encephalomyelitis (EAE), a murine model for MS.

Results: Single-cell sequencing and flow cytometry analysis reveal meninges ILC2s could activate and expand myelin-specific T cells via MHC-II-mediated antigen presentation. Genetic deficiency or antibody ablation of ILC2s restricts neuroinflammation and demyelination in EAE model. Furthermore, enhanced MHCII activity and antigen-presentation are observed in females versus males in both EAE mice and MS patients, which may contribute to sex-dimorphic EAE susceptibility.

Conclusion: These observations reveal a previously unrecognized role of meninges-resident ILC2s in the augmentation of neuroinflammation, targeting meningeal ILC2s presents a novel avenue to treat MS and other autoimmune disorders in CNS.

Key Words: Group 2 innate lymphoid cells, Multiple sclerosis, Antigen presentation, Neuroinflammation

ID:88

CD22 blockade exacerbates neuroinflammation in neuromyelitis optica spectrum disorder

Yali Han*, 文君 张
天津医科大学神经病学研究所

Objective: Neuromyelitis optica spectrum disorder (NMOSD) is an autoantibody-triggered central nervous system (CNS) demyelinating disease that primarily attacks the spinal cord, optic nerves and brainstem. Among the first responders to CNS injury, microglia are prominent player that drives NMOSD lesion formation. However, the key molecular switches in control of the detrimental activity of microglia in NMOSD are poorly understood. CD22 governs the activity of innate and adaptive immunity. In this study, we therefore investigated to what extent and by what mechanisms CD22 may modulate microglia activity, neuroinflammation and CNS lesion formation.

Methods: We investigated the potential effects and mechanisms of CD22 blockade on microglia activity, leukocyte infiltration and CNS demyelination in a mouse model of NMOSD induced by injection of NMOSD patient serum-derived AQP4-IgG and human complement.

Results: In humans and mice, we found that CD22 was mainly expressed in B cells and microglia, along with a decrease of CD22 expression in NMOSD versus controls. In NMOSD mice, antibody blockade of CD22 led to enlarged CNS lesion, astrocyte loss and demyelination. This was accompanied by enhanced inflammatory activity and phagocytosis in microglia. Further, the detrimental effects of CD22 blockade were alleviated in NMOSD mice subjected to microglia depletion or depletion of peripheral Gr-1+ myeloid cells, suggesting the involvement of microglia and peripheral Gr-1+ myeloid cells. In contrast, depletion of B cells did not alter the detrimental effects of CD22 blockade in NMOSD. Additionally, CD22 blockade also led to reduced expression of phosphorylated SYK and GSK3β in NMOSD. Notably, the detrimental effects of CD22 blockade were diminished in NMOSD mice receiving a phosphorylated SYK inhibitor R406.

Conclusion: Our findings revealed a previously unrecognized role of CD22 as a key molecular switch that governs the detrimental effects of microglia and Gr-1+ myeloid cells in NMOSD, which paves the way for future design of immune therapy for NMOSD.

Key Words: CD22, microglia, neuroinflammation, neuromyelitis optica spectrum disorders, demyelination

ID:90

EFHD1 Expression Correlated with Aging-related Mitochondrial Dysfunction and Predicted Prognosis in Atherosclerosis Plaque

Lin Wang1,Tao Yan*1,Yuxiu Han2,Yu Qiao1,Zhi Qi1,Wei Zhang1,Ling Xin1,Mingjing Yu1

1. 天津医科大学总医院

2. 天津医院

Objective: Atherosclerosis (AS) is prevalent among the elderly population and poses a significant global health burden. However, the precise underlying mechanisms linking aging and mitochondrial dysfunction in AS remain unclear.

Methods: Through comprehensive utilization of databases including GEO, MitoCarta, MSigDB, and HAGR, we employed various bioinformatics Methods to explore the possible function of EFHD1. This included the functional enrichment analysis, immune cell infiltration, and the lncRNA-miRNA-EFHD1 network. The validity of EFHD1 was confirmed using additional datasets and through Receiver Operating Characteristic (ROC) curve evaluation. Lastly, we conducted Western Blot and real-time quantitative PCR to confirm EFHD1 expression in AS models. In vitro studies were carried out to assess the potential role of EFHD1 in the THP-1 cell line after knocking down EFHD1.

Results: Totally seven genes associated with aging and mitochondrial function (ALDH3A2, UCP1, BCL2, EFHD1, AHCYL1, HTRA2, and ALDH9A1) were discovered in AS, with EFHD1 identified as the principal hub gene. Immune infiltration analysis indicated that EFHD1 was negatively associated with MDSC, activated B cells, and natural killer cells. An evident decline in EFHD1 was noted in unstable or advanced plaques compared to stable or early plaques, accompanied by significant AUC values of 0.917 (GSE100927) and 0.933 (GSE41571). Moreover, we recorded a reduction in EFHD1 expression in AS tissues and macrophages treated with oxidized low-density lipoprotein (ox-LDL). Following the silencing of EFHD1, TNF-α and IL-1β decreased, while ALODA, PKM2, MMP-9, JAK2, and STAT3 levels were upregulated. Furthermore, levels of ATP and reactive oxygen species (ROS) were diminished, while calcium ions and mitochondria levels remained unchanged.

Conclusion: Our research revealed a reduction in EFHD1 expression within atherosclerotic tissues, suggesting its potential role in inflammation and mitochondrial energy metabolism as a key regulator of the calcium signaling pathway. This discovery offers possible advancements in the early diagnosis and treatment strategies for AS.

Key Words: Atherosclerosis;Aging; Mitochondria Dysfunction;EFHD1;GEO;Calcium Signaling Pathway

ID:91

Characterization of Bone Marrow and Peripheral B/T Subpopulations and Clonality in NMOSD Patients

Han Jin,Qiang Liu*

Tianjin Medical University General Hospital

Objective: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease hallmarked by the presence of antibodies against water channel aquaporin-4 (AQP4). Current therapeutic strategies focus on immunosuppression and B cell depletion. This study aims to investigate the clonal landscape of lymphoids in NMOSD patients with active and remitting/relapsing stages after B-cell targeted treatment with rituximab.

Methods: A total of 26 sex- and age-matched participants were recruited in this study, including eight controls, seven active NMOSD, and eleven post-treatment patients (six remitting and five relapsing). Mononuclear cells from bone marrow and peripheral blood were collected and sequenced by single-cell RNA and BCR/TCR V(D)J sequencing. More than 15,000 B cells and 95,000 T cells were analyzed for subtype identification, clonal expansion, and B-T cellular interactions for the comparison between different disease courses.

Results: The clonality of B cells and plasma cells was increased in active patients versus controls, and in relapsing versus remitting patients. The clonal expansion was mostly identified in plasma cells, which was higher in bone marrow versus blood. Treatment of rituximab significantly reduced clonal expansion and inhibited somatic hypermutation in both B cells and plasma cells. Similarly, the lowest T cell clonal expansion was observed in remitting patients, with $CD8^+$ effector, memory, and KIR+ T cells as the major sources of T cell clones. Gene set enrichment analysis suggested that both CD4+ and CD8+ T cells were inhibited after rituximab treatment, whereas during disease relapsing, they were more activated.

Conclusion: This study suggests that expanded clonality can be observed in both B cells and T cells in NMOSD patients with active and relapsing stages. The interactions between B cells and T cells in bone marrow need to be further investigated so as to identify novel immunosuppressive therapeutic targets.

Key Words: NMOSD, clonal expansion, B cell, T cell

ID:92

Exploring the pathogenesis and treatment of cerebral small vessel cognitive impairment based on the theory of " "Brain Collaterals-Xuanfu-Domination of Life Activities"

Shifan Tu*,xiaolu huang
陕西中医药大学

Objective: Enriching and expanding the understanding of CSVCI pathogenesis from the microscopic structure level of traditional Chinese medicine. Provide ideas for understanding and treating CSVCI.

Methods: This article is based on the theory of "Xuanfu Brain Network Divine Mechanism", relying on Xuanfu, taking Brain Network as an opportunity, using Divine Mechanism as a bridge, and combining with the pathological characteristics of CSVCI, it explores the pathogenesis and prevention laws of CSVCI from a new perspective. It summarizes that in the early stage of CSVCI, due to insufficient spleen and kidney function, lack of nourishment in Xuanfu, and insufficient brain network, Divine Mechanism is lost, and CSVCI disease is blocked by phlegm and blood stasis for a long time. Xuanfu is blocked and the meridians are blocked, and the operation of Divine Mechanism is unfavorable.Based on this, corresponding treatment Methods are given for the basic principles of Su Ben Peiyuan and Kai Xuan Chang Luo.

Results: Xuanfu is the gateway of the veins, the veins are the channels for the operation of qi and blood, and the brain-Xuanfu is the bridge between the essence, qi, blood, jin liquid and the divine machine. The author believes that CSVCI is nothing more than the two ends of the virtual and the real, and its core pathogenesis is "Xuanluo depression", the deficiency, the viscera is not nourished, the qi and blood metaplasia are not sourced, the Xuanfu is lost, and the veins are not nourished, so that the divine machine is not used, and the real one, the phlegm and stasis are pulsating, the Xuanfu is occluded, and the veins are stagnant, resulting in the failure of the divine machine. The treatment should be based on "opening the Xuan Xuan" and at the same time cooperating with the method of replenishing deficiency and laxative. Combined with clinical syndrome differentiation, the flexible use of Xinxuan Divergent Medicine, Insect Channeling Medicine, combined with blood circulation and stasis medicine, phlegm and dampness medicine, and tonic medicine to open Xuan Changluo to provide ideas for the TCM differentiation and treatment of CSVCI.

Conclusion: Cerebral small vessel cognitive impairment (CSVCI) is a cognitive disorder caused by the occurrence of small vessel lesions in the brain. Its pathogenesis, diagnosis, and treatment are hot and difficult topics in clinical research. The pathogenesis of CSVCI is not yet clear, and no specific drugs have been found to treat CSVCI. Traditional Chinese medicine has been effective in treating CSVCI, with a good prognosis and significant improvement in patients' quality of life. This article is based on the theory of "Xuanfu Brain Network Divine Mechanism", relying on Xuanfu, taking Brain Network as an opportunity, using Divine Mechanism as a bridge, and combining with the pathological characteristics of CSVCI, it explores the pathogenesis and prevention laws of CSVCI from a new perspective. It summarizes that in the early stage of CSVCI, due to insufficient spleen and kidney function, lack of nourishment in Xuanfu, and insufficient brain network, Divine Mechanism is lost, and CSVCI disease is blocked by phlegm and blood stasis for a long time. Xuanfu is blocked and the meridians are blocked, and the operation of Divine Mechanism is unfavorable. Based on this, corresponding treatment Methods are given for the basic principles of Su Ben Peiyuan and Kai Xuan Chang Luo, enriching and expanding the understand-

ing of CSVCI pathogenesis from the microscopic structure level of traditional Chinese medicine. Provide ideas for understanding and treating CSVCI.

Key Words: Cerebral small vessel disease; Cognitive impairment; Brain network; Xuanfu; Divine machine; Traditional Chinese Medicine Treatment;

ID:95

Proteomics analysis of immune response-related proteins in Guillain-Barr´ e Syndrome (GBS) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Yujing Li*,Xueyu Zhang,Wenjun Zhang,Yali Han,Minshu Li,Jianli Zhao,Jie Wu,Xiaowen Li,Jing Xu
天津医科大学总医院

Objective: The Objective is to characterize differentially expressed proteins (DEPs) in Guillain-Barr´e Syndrome (GBS) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) through high-throughput analysis, both of which are rare neurological disorders characterized by immune-mediated damage to peripheral nerves. Few studies have focused on immune-response proteins, We aims to identify significantly different serum immune-response proteins in patients with CIDP and GBS. The findings of this research have the potential to contribute to further studying the pathogenesis of CIDP and GBS.

Methods: Serum samples were obtained from 11 healthy controls (HCs), 21 patients diagnosed with GBS, and 19 patients diagnosed with CIDP. Peripheral venous blood was collected from each participant, the serum will undergo the ganglioside antibodies testing process. Each sample was subjected to analysis using the Immune-Response Proteins panel of Olink Proteomics Analysis. We utilize Volcano plots, heatmaps, KEGG enrichment pathways to show our outcomes. Pearson's correlation was conducted to analyze the correlation between DEPs and clinical indicators from patients.

Results: In the comparison between CIDP and GBS groups, up-regulation of ITM2A and down-regulation of NTF4 were observed. Comparing GBS with healthy control group revealed 18 up-regulated proteins and 4 down-regulated proteins. Similarly, comparing CIDP with the healthy control group identified 15 up-regulated proteins and 4 down-regulated proteins. Furthermore, DEPs enrichment analysis was conducted to gain insights into the potential functions of proteins exhibiting variable expression levels, NF-kappa B signaling pathway is important. Additionally, the correlation between clinical characteristics and DEPs were uncovered.

Conclusion: In conclusion, DEPs associated with immune responses were detected in the serum of individuals diagnosed with GBS, CIDP, and healthy controls. Importantly, the DEPs have significant potential to advance our understanding of the pathogenesis in these debilitating neurological disorders.

Key Words: Chronic inflammatory demyelinating, polyneuropathy, Guillain-Barr´ e syndrome, Olink, Immune response-related protein proteins

ID:98

Microglia Senescence Influences Neuroinflammation and Neurodegeneration in aging brain

Tian Lan1,Ting Pan1,2,Hao-Nan Guan1,2,Shi-He Jiang1,Tian Yang1,Wei-Na Jin*1,2

1. 首都医科大学附属北京天坛医院

2. The Third Affiliated Hospital of Zhengzhou University, Zhengzhou University, 100 Science Avenue, Zhengzhou, Henan, China

Objective: Aging is one of the most important risk factors leading to the development of diseases in various body organs, and the senescence of immune function is an important factor in inducing or aggravating aging-related diseases. It is hypothesized that microglia in the aging brain act as the driver to promote the immune activation and inflammatory factor release, triggering neuroinflammation and causing neuronal damage and synaptic plasticity decline in hippocampal region, ultimately leading to cognitive impairment. This study aims to provide new ideas and directions to improve the nervous system's function by remodeling the brain's microenvironment via targeting the senescence of microglia and improving the inflammatory environment.

Methods: We used single-cell spatial transcriptomics combined with proteomics to characterize the spatial and molecular features of senescence of microglia in the hippocampus of the young and old people. Then we focused on the molecular basis of aging microglia regulating neuroinflammation and injury of nerve by immunofluorescence and flow cytometry. And by drug inhibition to delete senescent hippocampal cells in the old mice, in order to evaluate the function of neurovascular unit, synaptic plasticity and cognitive function, and ultimately to explore the strategy of targeting microglia senescence to improve the immune microenvironment and neural function in the brain.

Results: We found that the distance of senescent microglia appeared in the hippocampal region of aged mice and showed senescence-related inflammatory features. High expression of the TREM2 receptor may be related to the activation of senescent microglia. It was also found that these microglia co-located with neurons in the hippocampus of the elderly, which may affect the function of hippocampal neurons and cognitive function in the elderly. The human brain spatial transcriptome further confirmed a significant increase in glial cells around neurons, and the differentially expressed gene spectrum is predominantly rich in various neurodegenerative diseases. It is speculated that glial cell-neuron interactions may influence the course of neuro-degeneration. The most significantly down-regulated gene we found was TMEM74, which may be associated with reducing microglia autophagy and maintaining the number of aging microglia and pro-inflammatory capacity.

Conclusion: Our data elucidate microglia senescence influences neuroinflammation and neurodegeneration in aging brain. Neuronal damage and synaptic plasticity in the hippocampus, ultimately result in cognitive dysfunction.

Key Words: aging, immuno-senescence, microglia, neuroinflammation, neurodegeneration, neuroimmunology

ID:101

Which reason played the major role and pushed the manifestation progression in this encephalitis?

Shipeng Guo*

Affiliated Hospital of Guizhou Medical University

Objective: After the global COVID-19 pandemic, there have been a few case reports about encephalitis with SARS-CoV-2, more bewildered, some of these cases combined another pathogen, which made symptoms complicated.Here, we reported a case of SARS-CoV-2-associated encephalitis with a history of tuberculous to provide reference for its pathogenesis.

Methods: We describe the clinical details of a male patient with encephalitis,who has a history of tuberculosis, with SARS-CoV-2 ssRNA detected in his CSF.

Results: A 48-year-old math teacher was admitted to neurological department on account of continuous mental disorders, raving, and hyposomnia for 4 days with afebrile,accompanied by slow response, visual hallucinations, and flu-like symptoms, and the symptoms worsened with time.He had been diagnosed with tuberculosis at 20 and 1 years ago, respectively, with irregular anti-TB therapy.Physical examination,he showed emotional euphoria, unresponsiveness, irrelevancy, free movement of four limbs, Kernig's sign (-), Brudzinski's sign (-). Blood investigation showed an normal white cell count, neutrophil dominant(81.2%), relatively decreased lymphocytes(9.5%), and the increased erythrocyte sedimentation rate(57mm/h) and C-reactive protein(64.2mg/L) . Lymphocyte subsets(PCS /uL):B (CD19+#) 78 ↓ , total T (CD3+#) 452 ↓ ,NK (CD16+56+#) 69 ↓ , killer T (CD3+CD8+#) 150 ↓ , adjuvant T (CD3+CD4+#) 294 ↓ . The patient was negative for Tumor markers,anti-nuclear antibodies,Autoimmune encephalitis antibodies and other autoantibodies suggestive of demyelinating disease.Chest CT scan showed old lesions in the upper lobe of the left lung.Brain MRI showed T2-weighted hyperintensity in the left parietal lobe, right temporoparietal junction, and bilateral paraventricular junction without enhancement, consistent with chronic infectious lesions. Analysis of the patient's CSF showed normal glucose, protein, interleukin-6 concentrations, and cell counts. SARS-CoV-2 ssRNA was detected in throat swabs and CSF. The patient's pathogenetic condition substantially relieved after intravenous low-dose steroids and oral Nirmatrelvir Tablets/Ritonavir Tablets for 5 days.At the same time, due to preventing TB recrudescing, the patient confirmed taking Isoniazid, Pyrazinamide, Ethambutol Hydrochlroide and Rifampicin.On the follow up, his throat swabs and CSF were re-tested for SARS-CoV-2 ssRNA, and the Results were negative.

Conclusion: The observation that the patient contracted COVID-19 during a period of low prevalence implies a potential similarity in pathogenesis to previously reported cases, suggesting that individuals with chronic viral or bacterial infections (e.g., human immunodeficiency virus, chronic hepatitis B or C, and tuberculosis) are prone to developing encephalitis associated with COVID-19.Its pathogenesis may be related to tuberculosis interfering with the immune system.

Key Words: Encephalitis,SARS-CoV-2,Tuberculosis,Mental disorders

ID:102

Histidine-rich glycoprotein modulates neutrophils and thrombolysis-associated hemorrhagic transformation

Xianli Song,Yuexin Zhao,Rongrong Liu,Wei Jiang*

Jing-jin Neuroimmne Center; Tianjin Medical University General Hospital

Objective: To investigate the role of histidine-rich glycoprotein (HRG) in mitigating tissue plasminogen activator (tPA)-induced hemorrhagic transformation (HT) in patients with acute ischemic stroke (AIS) by modulating neutrophil activity. Our aim is to gain deeper insights into HRG's function in the immune response following thrombolytic therapy and assess its potential in reducing thrombolysis-related adverse effects.

Methods: Plasma samples from AIS patients undergoing tPA treatment were analyzed using high-throughput mass spectrometry to screen for differentially expressed proteins, with a particular emphasis on HRG expression. In a subsequent validation study involving 157 AIS patients, HRG levels were further confirmed using enzyme-linked immunosorbent assay (ELISA). Additionally, in vitro experiments were conducted to investigate HRG's effects on tPA-induced neutrophil death (NETosis), inflammatory cytokine production, and blood-brain barrier (BBB) permeability. A mouse model of ischemic stroke was utilized to assess HRG's protective role against HT resulting from delayed thrombolysis. Further exploration of HRG's functional mechanism was conducted through HRG siRNA knockdown and neutrophil depletion experiments.

Results: Following tPA thrombolytic therapy, HRG levels in plasma were significantly elevated within 1 hour. However, no significant increase in HRG was observed in patients who ultimately developed HT. In vitro experiments revealed that HRG significantly inhibited tPA-induced NETosis and the activation of pro-inflammatory signaling pathways in neutrophils. Furthermore, HRG reduced the neutrophils' capacity to migrate across the BBB. Mouse experiments demonstrated that HRG decreased hemorrhage volume, improved neurological function, and reduced neutrophil infiltration into the brain after delayed thrombolytic therapy. Additionally, HRG siRNA knockdown experiments exacerbated HT development, while neutrophil depletion or NETosis inhibition significantly alleviated HT.

Conclusion: This study demonstrates that the elevation of HRG levels following tPA treatment can regulate neutrophil immune activity, inhibit neutrophil infiltration, and dampen excessive immune activation, thereby reducing the risk of tPA-related HT and potentially extending the thrombolytic time window. HRG emerges as a promising target for predicting and managing HT, although further research is necessary to fully elucidate its underlying mechanisms.

Key Words: tPA Histidine-rich glycoprotein Hemorrhagic transformation Ischemic stroke Neutrophil

ID:104

Cortical Microhemorrhage Presentation of Small Vessel Primary Angiitis of the Central Nervous System

Ai Guo1,Zhe Zhang2,Ge-hong Dong3,Lei Su4,Chenyang Gao4,Mengting Zhang1,Xiaoyu Shi1,Huabing Wang1,Xinghu Zhang1,De-Hong Lu3,Ying Fu5,Jing Jing1,2,Fu-Dong Shi1,4,Decai Tian*1

1. Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
2. Tiantan Neuroimaging Center of Excellence, China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
3. Department of Pathology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China;
4. Department of Neurology, Tianjin General Hospital, Tianjin, China
5. Department of Neurology and Institute of Neurology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China

Objective: Primary angiitis of the central nervous system (PACNS) is a rare vasculitis restricted to the brain, spinal cord, and leptomeninges. This study aimed to describe the imaging characteristics of patients with small vessel PACNS (SV-PACNS) using 7 T magnetic resonance imaging (MRI).

Methods: This ongoing prospective observational cohort study included patients who met the Calabrese and Mallek

criteria and underwent 7 T MRI scan. The MRI protocol includes T1-weighted magnetization-prepared rapid gradient echo imaging, T2 star weighted imaging, and susceptibility-weighted imaging. Two experienced readers independently reviewed the neuroimages. Clinical data were extracted from the electronic patient records. The findings were then applied to a cohort of patients with large vessel central nervous system (CNS) vasculitis.

Results: We included 21 patients with SV-PACNS from December 2021 to November 2023. Of these, 12 (57.14%) had cerebral cortical microhemorrhages with atrophy. The pattern with microhemorrhages was described in detail based on the gradient echo sequence, leading to the identification of what we have termed the "coral-like sign." The onset age of patients with coral-like sign (33.83 ± 9.93 years) appeared younger than that of patients without coral-like sign (42.11 ± 14.18 years) ($P = 0.131$). Furthermore, the cerebral lesions in patients with cortical microhemorrhagic SVPACNS showed greater propensity toward bilateral lesions ($P = 0.03$). The coral-like sign was not observed in patients with large vessel CNS vasculitis.

Conclusion: In conclusion, the coral-like sign represents a notable imaging feature of SV-PACNS. Although coral-like sign may be observed in other small vessel diseases, their detection should prompt clinicians to consider SV-PACNS in differential diagnosis.

Key Words: Small Vessel Primary Angiitis of the Central Nervous System, cortical microhemorrhage

ID:105

Central vein sign and trigeminal lesions of multiple sclerosis visualised by 7T MRI

Jing Jing1,Zhe Zhang1,Lei Su2,Chenyang Gao2,Ai Guo1,Xinyao Liu1,Huabing Wang1,Xinghu Zhang1,Yaou Liu3,Giancarlo Comi4,Emmanuelle Waubant5,Fu-Dong Shi1,2,Decai Tian*1

1. Departments of Neurology, Tiantan Neuroimaging Center of Excellence, China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

2. Department of Neurology, Tianjin Medical University General Hospital, Tianjin, China.

3. Department of Radiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

4. Department of Neurology, Institute of Experimental Neurology, Vita-Salute University and San Raffaele Scientific Institute, Milan, Italy.

5. UCSF MS Center, San Francisco, California, USA.

Objective: Although trigeminal nerve involvement is a characteristic of multiple sclerosis (MS), its prevalence across studies varies greatly due to MRI resolution and cohort selection bias. The mechanism behind the site specificity of trigeminal nerve injury is still unclear. We aim to determine the prevalence of trigeminal nerve involvement in patients with MS in a consecutive 7T brain MRI cohort.

Methods: This observational cohort originates from an ongoing China National Registry of Neuro-Inflammatory Diseases. Inclusion criteria were the following: age 18 years or older, diagnosis of MS according to the 2017 McDonald criteria and no clinical relapse within the preceding 3 months. Each participant underwent 7T MAGNETOM Terra scanner (Siemens, Erlangen, Germany), using a 32-channel phased array coil at Beijing Tiantan Hospital. T1-weighted magnetisation-prepared rapid acquisition gradient echoes, fluid-attenuated inversion recovery (FLAIR) and fluid and white matter suppression images were used to identify lesions. FLAIR* and T2* weighted images were used to identify central vein sign (CVS) within the trigeminal lesions.

Results: 120 patients underwent 7T MRI scans between December 2021 and May 2023. 19/120 (15.8%) patients had a total of 45 trigeminal lesions, of which 11/19 (57.9%) were bilateral. The linear lesions extended along the trigeminal nerve, from the root entry zone (REZ) (57.8%, 26/45) to the pontine-medullary nucleus (42.2%, 19/45). 26.9% (7/26) of the lesions in REZ showed a typical central venous sign.

Conclusion: In this 7T MRI cohort, the prevalence of trigeminal nerve involvement was 15.8%. Characteristic CVS was detected in 26.9% of lesions in REZ. This suggests an inflammatory demyelination mechanism of trigeminal nerve involvement in MS.

Key Words: MRI; MULTIPLE SCLEROSIS.

ID:108

Neuronal regulated cell death in aging-related neurodegenerative diseases: key pathways and therapeutic potentials

Run Song1,2,Junqiang Yan*1,Shiyi Yin1

1. 河南科技大学第一附属医院

2. 首都医科大学附属北京天坛医院国家神经疾病临床医学研究中心

Objective: In this article, we aim to explore recent advancements in understanding seven forms of regulated cell death (RCD) and their involvement in age-related diseases, with a focus on neurodegeneration. We specifically examine how newly identified forms like ferroptosis, cuproptosis, and disulfidptosis contribute to cognitive decline and neurodegenerative disorders through mechanisms such as inflammation, oxidative stress, and protein aggregation. Furthermore, we delve into the key signaling pathways and crosstalk among these RCD types, identifying potential therapeutic targets that could help reverse aging processes and treat neurodegenerative conditions.

Methods: We conducted an electronic search of the PubMed database using search terms such as RCD, apoptosis, necroptosis, pyroptosis, cuproptosis, ferroptosis, and related neurodegenerative diseases (e.g., AD, PD, HD, ALS). Various combinations of these terms were used to ensure comprehensive coverage.Publications not meeting these criteria were excluded, with most of the included literature (around 70%) published between 2018 and 2023.

Results: We identified key mechanisms of both traditional and emerging RCD forms in age-related neurological diseases, with a focus on cuproptosis, ferroptosis, and disulfidptosis. Our findings highlight the coexistence and potential interconversion between ferroptosis and disulfidptosis, emphasizing the importance of timing in therapeutic interventions. Leveraging the interplay between these RCD pathways offers promise for developing treatments to mitigate neuronal aging and disease progression.

Conclusion: Precise characterization of RCD pathways and their intersections is essential for designing effective therapies, as compensatory mechanisms may complicate interventions. Our focus on regulated cell death in neurodegeneration underscores the need for further exploration of non-regulated or yet-undiscovered cell death forms. Developing reliable biomarkers for in vivo monitoring will be crucial for early diagnosis and tracking treatment responses in neurodegenerative diseases.

Key Words: apoptosis; autophagy; cuproptosis; disulfidptosis; ferroptosis; necroptosis; neurodegenerative disease; neurological aging diseases; PANoptosis; pyroptosis

ID:111

Compound 78c exerts a therapeutic effect in EAN

Xueyu Zhang,Yujing Li*,Jianli Zhao,Jie Wu,Xiaowen Li,Jing Xu
天津医科大学总医院

Objective: Guillain-Barré syndrome (GBS) is an acute immune-mediated inflammatory disorder of the peripheral nervous system, often characterized by muscle weakness or paralysis, with symptoms typically peaking within two weeks. Despite the effectiveness of intravenous immunoglobulin (IVIg) and plasma exchange (PE), GBS remains severe, with approximately 25% of patients requiring artificial ventilation and a mortality rate of 3-10%. New treatments are still needed. Although GBS is classified as an autoimmune disease, the underlying immune mechanisms and pathophysiology remain poorly understood. This study aims to elucidate the therapeutic effects and underlying mechanisms of Compound 78c, a specific CD38 inhibitor in experimental autoimmune neuritis (EAN) model.

Methods: We utilized a rat EAN model induced by P0 peptide. Following induction, we assessed clinical scores and administered Compound 78c at peak disease manifestation to evaluate its impact on symptoms. Concurrently, we analyzed electrophysiological parameters—including terminal latency, amplitude, and conduction velocity—using electromyography on sciatic nerves. Histological examinations via HE and LFB staining were performed on peripheral nerve tissues to determine whether these agents mitigated inflammatory cell infiltration and demyelination processes. Additionally, we investigated treatment effects on EAN-related inflammatory cell subtypes through immunofluorescence staining, flow cytometry further characterized alterations in various immune cell populations from spleen and bone marrow samples.

Results: The group treated with CD38 inhibitors exhibited lower clinical scores compared to the control group (Mean±SD of treatment vs control = 4.238±1.548 vs 5.762±1.583). Electromyographic Results indicated significant improvements in both amplitude (Mean±SD of treatment vs control = 17.50±2.931 vs 9.443±2.500) and conduction velocity (Mean±SD of treatment vs control = 69.00±6.573 vs 46.57±6.188). Pathological assessments revealed reduced degrees of inflammatory cell infiltration (Mean±SD of treatment vs control = 1764±272.2 vs 3360±431.4). However, demyelination was notably more pronounced within the modeling cohort as evidenced by elevated LFB scores (Mean±SD of treatment vs control = 0.5667±0.2944 vs 1.657±0.1512). Furthermore, flow cytometric analysis showed decreased cell numbers of CD38 positive cells within spleen and bone marrow samples from treated subjects and variable fluctuation profile of immune cells (T/B/NK/Macrophage cells).

Conclusion: In conclusion，CD38 inhibitors effectively ameliorate both clinical symptoms and electrophysiological impairments associated with EAN model rats while reducing inflammatory cell infiltration and altering the immune cell profile. This finding lays a foundation for further exploration.

Key Words: GBS、EAN、compound78c、CD38 inhibitor

ID:112

Microglial Replacement in the Aged Brain Restricts Neuroinflammation Following Intracerebral Hemorrhage

Wenyan Zhang[1],Xiuping Li[2],Xiaolin Gao[1],Mingming Liu[1],Zhaoli Han[3],Minshu Li[1],Ping Lei[3],Qiang Liu*[1]

1. Department of Neurology, Tianjin Neurological Institute, Tianjin Institute of Immunology, Tianjin Medical University General Hospital, Tianjin 300052, China.
2. Department of Neurology, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen 518035, China.
3. Department of Geriatrics, Tianjin Medical University General Hospital, Tianjin 300052, China.

Objective: Aged microglia display augmented inflammatory activity after neural injury. Although aging is a risk factor for poor outcomes after intracerebral hemorrhage (ICH) insults, the precise impact of aging-related alterations in microglia on neural injury remains poorly understood. This study was to investigate the impact of microglial replacement in the aged brain on neural injury.

Methods: Male C57BL/6 mice (16-20 months) were received vehicle or PLX3397 (290 mg/kg of chow) for 21 days to eliminate microglia. Followed by withdrawal for 21 days, ICH was induced by collagenase injection. The modified Neurologic Severity Score (mNSS), corner-turning test, and foot-fault test were performed at day 1 and day 3 after ICH. Brain water content was measured on day 3 after ICH. Immunostaining of ZO-1, claudin-5, NeuN, and Caspase-3 was to assess blood-brain barrier disruption and neuronal death after ICH. Flow cytometry was used to detect the counts of peripheral immune cells and cytokine production in brain and spleen.

Results: We found that replacement of microglia in the aged brain reduced neurological deficits and brain edema after ICH. Microglial replacement in aged brain attenuated blood-brain barrier disruption and neuronal death after ICH. Brain infiltration of leukocytes and inflammatory activity of microglia in the aged brain following ICH were suppressed by repopulated new microglial cells. Notably, newly repopulated microglia had reduced expression of IL-1β, TNF-α, and CD86, and upregulation of CD206 in response to ICH.

Conclusion: Our study reveals that microglial replacement in the aged brain attenuates neuroinflammation and brain injury after ICH, suggesting that it may be a promising candidate for preclinical ICH studies.

Key Words: microglial replacement; aged brain; neuroinflammation; intracerebral hemorrhage.

ID:113

Bone Marrow Granulopoiesis Fuels B Cell-mediated Central Nervous System Inflammation and Autoimmunity

Wenyan Zhang1,Handong Li1,Ting Li1,Chunsheng Yang1,Decai Tian2,Zhe Ruan3,Tingyu Yin1,Caiyun Qi1,Tongxiao Xu1,Wenyan He2,Meini Zhang4,Jie Zhou5,Ting Chang3,Qiang Liu*1

1. 天津医科大学总医院

2. China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China.

3. Department of Neurology, Tangdu Hospital, Air Force Medical University, Xi’ an, Shaanxi 710038, China.

4. Department of Neurology, First Hospital of Shanxi Medical University, Taiyuan, Shanxi 030001, China.

5. Tianjin Institute of Immunology, Department of Immunology, Tianjin Medical University, Tianjin 300070, China.

Objective: Neuromyelitis optica spectrum disorder (NMOSD) is a B cell-mediated autoimmune neurological disease. Evidence suggests that neutrophils are involved in the deleterious CNS inflammatory cascade in NMOSD. However, whether and how neutrophils shape B cell activity and AQP4-IgG production in NMOSD patients remains poorly understood. As the source of granulopoiesis and a central hub that governs immune homeostasis, bone marrow hematopoietic stem and progenitor cells (HSPCs) sense and orchestrate inflammation by increased proliferation and skewing toward particular cellular lineages. This study aims to address the mechanism of HSPCs response to B cell-mediated autoimmunity in NMOSD.

Methods: We conducted single-cell RNA-sequencing and BCR sequencing to characterize HSPCs and their downstream lineages in bone marrow samples obtained from NMOSD patients and controls. In addition, flow cytometry analysis was performed to measure the alteration of HSPCs. The potency of neutrophil augmenting B cell maturation and autoantibody production was verified by cell culture in vitro. An investigator-initiated, open-label, single-arm, phase 1/2 clinical trial was completed in Tianjin Medical University General Hospital and Tangdu hospital. This study is registered with ClinicalTrials.gov, NCT05154734.

Results: Single-cell RNA-sequencing and flow cytometry analysis demonstrated that bone marrow hematopoiesis was substantially skewed toward the granulocyte lineage in patients with NMOSD. The aberrant granulopoiesis was mediated by hyperactive JAK-STAT signaling in HSPCs and led to the augmented output of ISG15+ neutrophils that highly expressed B cell activating factor (BAFF). Communication between ISG15+ neutrophils and mature B cells enhanced. By quantifying the expression of BAFF among different cell types at the individual patient level, we found that neutrophils were also a major source of BAFF and linked to clonal expansion of bone marrow B cells in patients with NMOSD receiving rituximab who experienced relapse. Clinical trial demonstrated that targeting BAFF with belimumab, an FDA-approved monoclonal antibody, reduced NMOSD relapse, CNS lesions, and the AQP4-IgG titer.

Conclusion: Aberrant bone marrow granulopoiesis in patients with NMOSD leads to increased output of ISG15+ neutrophils, which drives the maturation of autoreactive B cells and the production of AQP4-IgG through BAFF production. Targeting aberrant bone marrow hematopoiesis may provide a new avenue to restrict detrimental CNS inflammation and autoimmunity in patients with NMOSD and perhaps other B cell-mediated autoimmune diseases.

Key Words: bone marrow; hematopoiesis; granulopoiesis; central nervous system; neuromyelitis optica spectrum disorder; neuroinflammation.

ID:114

A Real-World Comparative Study on The Efficacy and Safety of Tocilizumab and Rituximab in Patients with Neuromyelitis Optica Spectrum Disease and Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease

Lijie Zhu,Yao Shi,Yulin Li,Xiaona Xu,Jia Liu,Chao Zhang*
Tianjin Medical University General Hospital

Objective: Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are chronic inflammatory autoimmune diseases of CNS that cause blindness and paralysis, and now increasing evidence has shown that IL-6R blockade and B cell depletion are effective against them. However, studies directly comparing the effectiveness and safety of these treatments in patients with NMOSD and MOGAD are lacking. Therefore, this study aimed to evaluate the long-term clinical outcomes and treatment responses to IL-6R monoclonal antibody (mAb) tocilizumab and anti-CD20 mAb rituximab in patients with aquaporin-4 IgG–seropositive (AQP4-IgG+) NMOSD and MOGAD.

Methods: Between January 1, 2017 and January 1, 2022, we conducted a retrospective study of 163 patients with AQP4-IgG+ NMOSD and 26 patients with MOGAD. The analyses included individual relapses, annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS) score, and adverse events. Data were gathered using an electronic recording system, telephone follow-ups, and outpatient follow-ups.

Results: In patients with AQP4-IgG+ NMOSD, compared with prednisolone treatment, both tocilizumab and rituximab treatments significantly reduced the risk of relapse ($p < 0.001$), ARR ($p \leq 0.01$), and EDSS score ($p < 0.001$). There were no significant differences in relapse rate between tocilizumab and rituximab treatment. However, patients in the tocilizumab group (12/56, 21.4%) had lower adverse event rates than those in the rituximab group (33/81, 40.7%).Tocilizumab reduced the ARR ($p = 0.008$), and notably, improved EDSS score compared to prednisolone ($p = 0.001$), or rituximab ($p = 0.03$)in patients with MOGAD. However, no significant differences were detected on the relapses or ARR between rituximab and prednisolone treatments in MOGAD patients. And in terms of adverse events in MOGAD, there was no difference between tocilizumab and rituximab treatment groups.

Conclusion: Both tocilizumab and rituximab significantly reduced disease relapse and disability compared to prednisolone in NMOSD, and tocilizumab exhibited greater safety than rituximab. Compared to prednisolone or rituximab, tocilizumab demonstrated considerable efficacy with reduced relapse rates and improved EDSS scores in MOGAD. Larger randomized-controlled trials are warranted to compare the efficacy and safety between IL-6R inhibitors and B cell-depleting agents in NMOSD and MOGAD.

Key Words: tocilizumab , rituximab, NMOSD ,MOGAD ,efficacy, safety

ID:116

NEK2 Regulates B Cell Function and The Severity of Autoimmune Experimental Encephalomyelitis

Zhirui Liu,Si-Ting Wu,Tianxiang Zhang,Xiaoshan Du,Chao Zhang*

Tianjin Medical University General Hospital

Objective: Never in mitosis gene A (NIMA)-related kinase 2 (NEK2) is a member of serine-threonine kinase family that plays a pivotal role in cell cycle. The high expression of NEK2 correlates with B cell proliferation, which observed in multiple myeloma (MM) and diffuse large B-cell lymphoma. Abnormally increased immature B cells in transgenic mice with conditional overexpression of NEK2 in the B cell lineage suggesting its potential contribution to development and maturation of B cells. However, the role of NEK2 in regulating B cell immunity in autoimmune diseases is still unclear.

Methods: EAE was induced by injecting subcutaneously on each side of the spine at the femoral level with 100 μg of MOG35-55 peptide in CFA with 5 mg/mL Mycobacterium tuberculosis.Mice were administrated intraperitoneally with NEK2 inhibitor or vehicle every day after onset of EAE until mice euthanasia.NEK2 inhibitor(INH1) with 50μM was the optimal to inhibit function of B cells and was applied in subsequent in vitro experiments. Single-cell suspension of human periphery blood, mouse spleen tissue, or mouse brain and spinal cord tissues was prepared and stained with fluorochrome-conjugated antibodies.B cells were isolated by magnetic-activated cell sorting (MACS) method.Isolated human B cells were cultured in serum-free x-vivo 15 medium (Lonza) for 24h with treatment of INH1 or vehicle.Fluorescence-activated cell sorting (FACS) were applied to isolate mouse B cells and CD4+ T cells.Then,CD4+ T cells were co-cultured with B cells.Gene expression was determined by RT-PCR.

Results: NEK2 highly expressed in MS patients and its blockage induced reductions of expression of co-stimulatory molecular CD80 and CD86, proliferation and differentiation to ASCs and SWM in human B cells in vitro. Applying NEK2 inhibitor (INH1) in the experimental autoimmune encephalomyelitis (EAE) mice, they presented improved neurological function, rescued demyelination, and reduced CNS-infiltrated inflammatory cells compared to EAE mice treated with vehicle. Mass cytometry finds the NEK2 inhibition down-regulated the expression of co-stimulatory molecular and reduced the proportion of Th1 cells in CD4+ T cells. Flow cytometry confirmed the consistent results. Further investigations in vitro illuminated that blocking NEK2 reduced CD4+ T cell proliferation and differentiation to Th1 cells by inhibiting B-T cell interactions.

Conclusion: Altogether, we report an immunomodulatory role for NEK2 and provide a potential target of NEK2 in MS therapeutic investigation.

Key Words: NEK2, multiple sclerosis, experimental autoimmune encephalomyelitis, B cells

ID:118

Inhibition of DNMT3A Function Exacerbates Ischemic Stroke in Pregnant mice

Ting Pan[1,2],Tian Lan[2],Hao-nan Guan[1],Tian Yang[2],Wei-na Jin*[2]

1. The Third Affiliated Hospital of Zhengzhou University

2. Center for Neurological Diseases, China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, China.

Objective: DNA methylation plays a crucial role in both the pathogenesis and prognosis of stroke. However, the relationship between DNA methylation and stroke in pregnancy remains unclear. We employed the small molecule inhibitor RG108 to inhibit DNA methylation in both pregnant and non-pregnant MCAO female mice to investigate the effects and mechanisms that DNA demethylation influences ischemic stroke in pregnant females.

Methods: The RT-qPCR and western blot were performed to assess the expression and activity of the DNMT3A gene in the peripheral blood and brain tissues of both pregnant and non-pregnant female mice. Focal cerebral ischemia was induced by 60 min intraluminal occlusion of the middle cerebral artery (MCAO) by using filament cannulate into the left internal carotid artery and subsequently into the anterior cerebral artery in murine subjects of female mice at 7.5 days of pregnancy. 7T-MRI was scanned to evaluate the infarct volume of pregnant MCAO mice treated with RG108 drug compared to those without intervention. Additionally, laser speckle imaging was used to further observe cerebral blood flow alterations between these two groups of pregnant MCAO females, while motor coordination and balance abilities were assessed through a rotarod test for both two groups. Following this, we conducted flow cytometry analyses on immune cell populations such as lymphocytes and myeloid cells within the brain and peripheral blood to identify specific immune cell changes and migration patterns.

Results: Despite the decreased DNMT3A protein levels, there was an observed increase in DNMT3A mRNA and activity in the brain of pregnant MCAO mice as compared to sham control. The inhibition of DNMT3A activity through DNA methylase inhibitor RG108 treatment led to further enlargement in infarct volume, a decrease in cerebral blood flow, and worsened motor coordination deficits in pregnant MCAO mice. Furthermore, inhibition of DNMT3A activity with RG108 enhanced the infiltration of myeloid cells from the peripheral blood into the brain, involving neutrophils, macrophages and monocytes. Mechanistically, estrogen E2 stimulated DNMT3A in myeloid cells through interaction with the estrogen receptor (ER), leading to a shift in myeloid cell polarization towards an immunosuppressive state, indicating the anti-inflammatory effects of DNMT3A signaling.

Conclusion: Our data elucidate that inhibition of DNMT3A function exacerbates inflammatory brain injury during ischemic stroke and aggravates neuro-inflammation in pregnancy.

Key Words: DNA Methylase Inhibitor, RG108, DNA demethylation, DNMT3A, pregnant MCAO mice, MCAO

ID:119

Nomogram for the Prediction of Relapse Factors in Patients with Neuromyelitis Optica Spectrum Disorder during Rituximab Treatment

Yanning Huang[1,2,3],Wu Lei[1],Hui Sun[1],Sai Gao[1],Dehui Huang*[1],Xi Zhang[1,2]

1. Chinese PLA General Hospital

2. Nankai University

3. The First Affiliated Hospital of Guangxi Medical University

Objective: Develop a nomogram to analyse the factors influencing the relapse of neuromyelitis optica spectrum disorder (NMOSD) during rituximab (RTX) treatment.

Methods: A retrospective analysis of 214 NMOSD patients was performed, and 181 individuals with AQP4-IgG-seropositivity were selected. 32 patients who relapsed during RTX treatment were included, and 122 sets of lymphocyte subset monitoring data were collected. 110 sets of data were finally included and divided into relapse (n = 30) and nonrelapse (n = 80) groups depending on whether a relapse occurred between two adjacent RTX treatments. Logistic and LASSO regressions were used to identify the relevant factors influencing NMOSD relapse, and a nomogram was constructed. Receiver operating characteristic (ROC) curves were generated to evaluate the nomogram's differentiation, and the bootstrap method was utilized for internal validation. Calibration curve and decision curve analysis were also conducted.

Results: Comparisons of baseline data revealed differences in the RTX administration interval as well as CD3-CD19+ B lymphocyte and CD3-CD56+ NK cell levels. The RTX administration interval and the level of CD3-CD19+ B lymphocytes were independent variables influencing relapse. The nomogram had an area under the curve (AUC) of 0.71 and a 95% confidence interval (CI) of 0.58-0.83. The Hosmer-Lemeshow (H-L) goodness-of-fit test yielded a $\chi 2 = 11.80$ ($p = 0.16$). Decision curve analysis revealed that the model provided greater net benefits within the threshold probability range of 0.18-0.98.

Conclusion: The nomogram model developed in this study indicates that the RTX administration interval and CD3-CD19+ B lymphocyte levels independently influence NMOSD relapse, exhibiting good discriminative capability, consistency, and clinical benefits.

Key Words: NMOSD, RTX, nomogram, relapse, prediction

ID:120

Neuroprotective effect and mechanisms of MIP2 on secondary brain injury after Intracerebral hemorrhage in mice

Rabeea Siddique,Suliman Khan,Mengzhou Xue*
Second affiliated hospital of Zhengzhou university

Objective: To investigate the neuroprotective effect and mechanisms of action of inhibitory peptide MIP2 on ICH induced secondary brain injury in mice.

Methods: The experimental intracerebral hemorrhage (ICH) mouse model was induced by injecting bacterial collagenase-VII. The focal deficit neurological score and corner turn test was performed for neurobehavioral analysis. The H&E staining, Immunofluorescent staining, immunohistochemistry staining, TUNEL and EVAN's blue assay were performed. Western blot analysis was conducted to evaluate BBB permeability, apoptotic proteins detection, inflammatory proteins, and oxidative stress-related proteins expression after secondary brain injury.

Results: MIP2 (MyD88 adaptor-like inhibitory peptide) decreased hematoma volume and neurobehavioral function scores compared to the vehicle group. MIP2 treatment decreased the expression levels of MMP9 and elevated the expression of Blood brain barrier (BBB) tight junction proteins (ZO-1, Occludin, Claudin-5). Results based on EVAN's blue assay, ZO-1, vWF, and MMP9 positive cells indicated that MIP2 protected the BBB integrity. Immunofluorescent staining of Iba-1, MPO, and GFAP showed that MIP2 can potentially reduce the activation of microglia/macrophages, neutrophils, and astrocytes respectively. In response to the application of MIP2 the expression of the pro-apoptotic protein (Bax), and the number of TUNEL-positive cells was decreased, while the expression of anti-apoptotic protein (Bcl-2) was elevated. In addition, the expression of inflammatory proteins (MyD88, TLR4, TNF-α, IL-6, NF-kβ, iNOS) was mitigated by targeting the MyD88/TLR4 pathway.

Conclusion: MIP2 protected BBB integrity, alleviated the neuroinflammation, reduced apoptosis of neuronal cells, and oxidative stress-mediated damage on ICH-induced secondary brain injury via MyD88/TLR4 pathway, thus provided neuroprotective effects against ICH-induced brain damage. It is hypothesized that MIP2 can be used as an effective therapeutic option against ICH.

Key Words: Cerebral hemorrhage, Secondary brain injury, Neuroinflammation, MIP2, Molecular regulations

ID:121

Effects of mood stabilizers on transcriptome profiles of human neuronal and glial cell lines

Typhaine Chauveau,Mai Sakai,Uema Motone,Ono Chiaki,Kikuchi Yoshie,Hino Mizuki,Kunii Yasuo,Abe Takaaki,Hiroaki Tomita,Zhiqian Yu*,Hiroshi Komatsu,Saya Kikuchi

Tohoku University

Objective: Bipolar disorder (BD) is a unique disorder characterized by frequent alternating mood symptoms, depression and mania, affecting approximately 1.5% of the population and is often initially misdiagnosed. The highest rate of lifetime risk of completed suicide with BD is likely between 5-6% of the general population. Mood stabilizers are thus crucial in alleviating manic and depressive conditions and prevent relapses in bipolar disorder (BD) patients. While alterations in various cell types in the brain have been suggested to be involved in the pathogeneses of BD, the effect of mood stabilizers on each cell type has not been characterized.

Methods: The gene expression of four mood stabilizers, lithium (Li), valproate (VPA), carbamazepine (CBZ), and lamotrigine (LTG) treated human neuronal (SK-N-SH), oligodendroglial (OL), and astrocytic (U-87MG) cell lines, were analyzed by microarray and further compared with the genomic database of patients with BD.

Results: Four mood stabilizers differentially altered specific patterns of genes without commonly altered genes in the SK-N-SH, OL, and U-87MG. VPA commonly affected more genes among the three types of cells, while Li treatments showed limited effects on gene expression. Gene ontology analyses provide insights into the biological processes of altered genes affected by four mood stabilizers in neuronal and glial cells, resulting in tissue morphogenesis, metabolic process, cellular and apoptotic signaling pathways. In comparison with gene profiles from the postmortem dorsolateral prefrontal cortex of BD patients and blood leucocytes from unmedicated BD patients, several altered peripheral transcripts related to neuroinflammation, myelination and blood-brain-barrier integrity were identified that may reflect the efficacy of mood stabilizers in preventing recurrence of manic-depressive symptoms in BD.

Conclusion: The differential gene expression changes induced by mood stabilizers in neuronal and glial cells provide new insights into their pharmacological mechanisms. These findings may contribute to a more nuanced understanding of how mood stabilizers function at the molecular level in BD treatment.

Key Words: bipolar disorder, mood stabilizers, gene expression, glial cells, neurons

ID:124

Capillary Reduction Profoundly Promotes Tumorigenesis by Impairing T-cell Transport and Immune Surveillance

Zhiyao Lu,Lei Dong*
Nanjing University

Objective: Despite the consensus that angiogenesis is a necessary strategy for tumor development, antiangiogenic therapy's efficacy in overall survival benefits remains inconclusive, often resulting in relapses after several months in clinical follow-ups. While tumors require angiogenesis to meet their nutritional needs, the immune system relies on micro-vessels for immune surveillance. Effective T-cell attacks against immunogenic cells rely on systemic mobilization, including timely T-cell activation, recruitment, and rapid clonal expansion. We aim to investigate how and to what extent physiological capillary abundance would affect T-cell recruitment in cancer cell irritating conditions, and try further to quantificate the influence.

Methods: We first constructed spontaneous tumor models with genetically engineered mice, and observed cancer events in mice with various capillary abundance. Phenomenon was retested in metastasis models of different cancer cell lines. Meanwhile, we monitored local T-cell immune response during very early stage. Referring to the relationship, vascular intervention treatments were applied to regulate T-cell recruitment efficiency.

Results: We observed reduced tumorigenesis and enhanced T-cell delivery in mice with increased micro-vessel numbers, and vice versa. Quantitative analysis revealed a mathematical relationship between cancer risk and capillary abundance, showing that the change in tumor risk is inversely proportional to at least fourth power of that in capillary abundance. Pathological conditions with impaired capillaries exhibited deficient T-cell delivery when challenged by cancer cells, potentially explaining their susceptibility to cancer. This deficiency in immune cell recruitment can be mitigated by angiogenic drugs.

Conclusion: There is a simple and clear quantitative relationship between the change in capillary number or surface area and the incidence of tumorigenesis resulting from immune surveillance failure. Cancer risk can be predicted and managed by promoting the mobilization of immune cells on a systemic perspective.

Key Words: T-cell recruitment, immune surveillance, tumorigenesis, cancer risk

ID:126

Clock gene deficiency (Clock -/-) exacerbates post-ICH brain injury via oxidative stress and inflammatory pathways

Rabeea Siddique,Suliman khan,Mengzhou Xue*

Second affiliated hospital of Zhengzhou university

Objective: Circadian rhythm plays a crucial role in the severity of stroke, brain damage, pathogenesis, and recovery, however there is no study about its role and mechanism of action in Intracerebral Hemorrhage (ICH). The aim of this study is to investigate the effect of core circadian rhythm gene Clock (circadian locomotor output cycles kaput) deletion (Clock-/-) on secondary brain injury after ICH in mice. It is hypothesized that targeting circadian clock machinery might be helpful in enhancing therapeutic strategies for ICH.

Methods: Sleep monitoring using a piezoelectric sleep system, and wheel run activity were performed. The focal deficit neurological score and corner turn test was performed for neurobehavioral analysis. The small animal MRI scans, H&E staining, Immunofluorescent staining, immunohistochemistry staining and TUNEL assay were done where needed. Western blot was performed to evaluate BBB permeability, apoptotic proteins, inflammatory proteins, and oxidative stress-related proteins.

Results: Results: indicated that ICH decreased sleep bout number during daytime and increased the length of sleep bout during nighttime compared to the control group. ICH mice exhibited increase in period (longer free period) under light conditions (LL), unlike the control group, ICH mice failed to show dysrhythmia, suggesting that ICH may disrupt normal circadian rhythms. Further, Sham, wild type ICH, and Clock gene knockout (Clock-/-) ICH were compared. Overall, neurobehavioral scores, MRI scans, and H&E staining Results have shown that the Clock-/- ICH group presented severe neurobehavioral, pathophysiological, and neurodegenerative changes as compared WT ICH and sham group. The expression levels of MMP-9; vWF and MMP9 positive cells increased in the Clock-/- ICH group. The expression levels of ZO-1, Occludin, Claudin-5 and the number of ZO-1 positive cells decreased in the Clock -/- ICH group, whereas pro-apoptotic proteins (Bax, Cleaved Caspase-3), and the number of TUNEL-positive cells increased, while the expression levels of anti-apoptotic protein Bcl-2 and NeuN positive cells decreased. The western blot analysis of inflammatory proteins (NF-kβ, iNOS, TLR4, and IL-6), positive immune cells (Iba-1, MPO, GFAP) increased in Clock-/- ICH group. Lastly, the antioxidant proteins (GPX4) expression declined, while oxidative markers (HO-1, NF-kβ) and AIFM2 positive cells were increased in the Clock-/- ICH group compared to WT-ICH and sham group

Conclusion: The Clock gene deficiency (Clock -/-) aggravates the pathophysiology of ICH-induced brain injury, by increasing BBB leakage, neurological damage, neuroinflammation, oxidative stress damage, apoptosis, and necroptotic cell death.

Key Words: Cerebral hemorrhage, Secondary brain injury, Neuroinflammation, Molecular regulations.

ID:129

Clinical, MRI Characteristics and Treatment of GFAP Astrocytopathy: A two-center Chinese Cohort Study

Hao Zhang,Ti Wu*,Fu-Dong Shi
天津医科大学总医院

Objective: To report the clinical characteristics, imaging features, and treatment outcomes of a multicenter Chinese Glial fibrillary acidic protein astrocytopathy (GFAP-A) cohort.

Methods: We retrospectively included 42 adult patients diagnosed as GFAP-A from 2 centers between June 2019 and September 2024. Clinical features, semi-quantitative antibody test results, imaging characteristics, treatment approaches, and prognosis were collected.

Results: Among the 42 patients, 27 were male and the median age at disease onset was 47.5. The clinical phenotype contained myelitis (23.8%), encephalomyelitis (28.6%), encephalitis (19%), meningoencephalomyelitis (16.7%), meningitis/spinal meningitis (9.5%), peripheral neuropathy (2.4%). Eleven cases had comorbidities related to endocrine disorders and two cases presented accompanied autoimmune diseases. The median serum GFAP antibodies titer was 1:32 (range: 1:10-1:320), and the median CSF GFAP antibodies titer was 1:10 (range: 1:1-1:320). In the brain MRI, 21(50%) patients had white matter T2 hyperintense lesions, 11(26.2%) had brainstem lesions. For spinal cord lesions, 63% of those were longitudinally extensive T2 hyperintensities. In enhanced images, 5 (11.9%) of the patients showed enhancement of the cerebral meninges, 2 (4.8%) had enhancement of the ependyma, and 6 (14.3%) had enhancement of the spinal cord pia mater. During the disease attack period, 39 patients received intravenous methylprednisolone (IVMP) therapy, one of them received IVMP combination with Efgartigimod. 76.9% of the patients responded to the glucocorticoid treatment and 69% of the cohort presented with a monophasic course. The median mRS score and ADL score was 1 and 95 respectively at final follow-up. Spearman correlation analysis showed that OCB positive in cerebrospinal fluid (CSF) (CI=0.57, P = 0.002), GFAP-antibody in serum (CI=-0.38, P = 0.04) and its titer (CI=-0.53, P = 0.02) was positively correlated with 1-year relapse.

Conclusion: The clinical manifestations of GFAP-A are highly diverse and encompass encephalitis, myelitis, meningeal or spinal meningitis. The enhancement of the spinal pia and ependyma on MRI were confirmed. Most patients exhibit a favorable response to glucocorticoid therapy. Immunomodulatory treatments may contribute to reducing the likelihood of recurrence. The presence of oligoclonal bands in CSF, GFAP-antibody in serum and its titer could potentially serve as an indicator for predicting recurrence.

Key Words: Glial fibrillary acidic protein (GFAP), astrocytopathy, clinical characteristics, immunotherapy, recurrence

ID:130

4-Octyl itaconate inhibits inflammation via the NLRP3 pathway in neuromyelitis optica spectrum disorders

Ting Li,Jia-Wen Li,Ying-Hui Qin,Rui Liu,Li Yang,Chun-Sheng Yang*

天津医科大学总医院，天津市神经病学研究所

Objective: Neuromyelitis optica spectrum disorders (NMOSD) are rare inflammatory astrocytic diseases of the central nervous system (CNS). The roles of immune response gene-1 (IRG1) and the IRG1–itaconic acid–NLRP3 inflammatory pathway in the pathogenesis of NMOSD and the effects of 4-octyl itaconate (4-OI) on the NLRP3 inflammatory pathway in NMOSD are unclear. This study aimed to determine the role of IRG1 and the activation status of the NLRP3 inflammatory pathway in acute-onset NMOSD and to investigate the inhibitory effects of 4-OI on NLRP3 inflammasome activation via the IRG1–itaconic acid–NLRP3 pathway in monocytes and macrophages by using in vitro models.

Methods: Peripheral blood mononuclear cells (PBMCs) and serum were collected from patients with acute NMOSDs and healthy controls (HC), followed by monocyte typing and detection of the expression of NLRP3-related inflammatory factors. Subsequently, the effects of 4-OI on the IRG1–itaconic acid–NLRP3 pathway were investigated in peripheral monocytes from patients with NMOSD and in macrophages induced by human myeloid leukemia mononuclear cells (THP-1 cells) via in vitro experiments.

Results: Patients with acute NMOSD exhibited upregulated IRG1 expression. In particular, the upregulation of the expression of the NLRP3 inflammasome and proinflammatory factors was notable in monocytes in acute NMOSD patients. 4-OI inhibited the activation of the IRG1–itaconic acid–NLRP3 inflammatory pathway in the PBMCs of patients with NMOSD.

Conclusion: 4-OI could effectively inhibit NLRP3 signaling, leading to the inhibition of proinflammatory cytokine production in patients with NMOSD-derived PBMCs and in a human macrophage model. Thus, 4-OI and itaconate could have important therapeutic value for the treatment of NMOSD in the future.

Key Words: Neuromyelitis optica spectrum disorders; 4-OI; monocyte typing; IRG1–iconic acid–NLRP3 inflammatory pathway; macrophage

ID:131

Headache in myelin oligodendrocyte glycoprotein antibody-associated disease

Xixi Yang[1],Mengyao Zhang[1],Zhandong Qiu1,Qiao Xu[1,2],Jingsi Wang[1],Dawei Li[1],Fang Xu[1],Liang Liu[1],Huiqing Dong[1],Junwei Hao[1],Zheng Liu*[1]

1. 首都医科大学宣武医院

2. 重庆医科大学第一附属医院神经内科

Objective: Headache is reported more often in myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), compared to multiple sclerosis and neuromyelitis optica spectrum disorder. Our study is to describe the characteristics of headache in MOGAD.

Methods: We retrospectively reviewed patients diagnosed as MOGAD in Capital Medical University Xuanwu Hospital between January 2017 to June 2022, and followed them up until December 2023. Demographic information, clinical investigations, MRI tests and treatments were collected and compared between patients with and without headache. $P < 0.05$ was considered statistically significant.

Results: 96 MOGAD patients were included, including 57 (59.4%) females in total, 18/31 (58.1%) females in patients with headache and 39/65 (60%) without headache. The mean (standard deviation, SD) age of the cohort was 33.7 (13.98) years old and no difference in age was determined between the two groups. Compared with patients without headache, more patients with headache presented recurrent disease course ($p = 0.032$), had optic neuritis ($p = 0.014$), higher intracranial pressure ($p = 0.032$) and higher cerebral spinal fluid (CSF) white blood cell (WBC; $p = 0.330$). Statistically significant difference was found in CSF MOG-IgG between the two groups ($p = 0.046$) and more positive CSF MOG-IgG was identified in patients with headache. More cortical/juxtacortical ($p = 0.002$) and optic nerves (0.010) lesions were shown in patients with headache.

Conclusion: We described the headache in MOGAD and found out more relapse, more optic neuritis, higher intracranial pressure and CSF WBC count in patients with headache. The patient with headache could have positive CSF MOG-IgG more frequently and get more lesions in cortical/juxtacortical and optic nerves.

Key Words: Myelin oligodendrocyte glycoprotein antibody-associated disease, Headache

ID:132

Ferritin-ApoE prodrugs for targeted therapy of NMOSD in mice

Xin Zhao1,2,Jiang Shihe1,Guan Haonan1,3,Yang Tian1,Lan Tian1,Liang Qian4,Fan Kelong4,Jin Wei-Na*1,2

1. beijing tiantan hospital
2. First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology
3. The Third Affiliated Hospital of Zhengzhou University
4. CAS Engineering Laboratory for Nanozyme, Key Laboratory of Biomacromolecules (CAS), CAS Center for Excellence in Biomacromolecules

Objective: Neuromyelitis optica spectrum disorder (NMOSD) is an immune-mediated demyelinative disorder of the central nervous system affecting mainly the optical nerves and the spinal cord. Our previous research has illustrated the protective effects of ApoE peptide following intracranial administration in mice with NMOSD. In this study, we have developed a Ferritin-ApoE prodrug capable of effectively crossing the blood-brain barrier to investigate its therapeutic potential for treating NMOSD in mice.

Methods: The 8-week-old female C57BL/6J mice was used in this study and the acute mice model of NMOSD was established by transcranial co-injection of AQP4-Abs and human complement. The NMOSD mice were randomly divided into ferritin-ApoE, ferritin and PBS groups (n = 8/group), which received intravenous injections of ferritin-ApoE, ferritin and PBS (100 ug) on Day 0, separately. In the sham group, the mice did not receive any treatment. The seven-tesla MRI (7T-MRI) scanning was performed to score the pathological lesions of NMOSD mice in vivo. Immunostaining of MBP depicted the demyelination in NMOSD mice treated with treated/untreated groups. The immunofluorescence staining of brain tissue was performed on Day 4. Flowcytometry and immunostaining were performed to evaluate microglial population and inflammatory functions in NMOSD mice.

Results: In comparison to the sham group, both the PBS and ferritin groups exhibited a notable decrease in MBP and AQP4 levels in NMOSD mice models ($p < 0.0001$, for all). Conversely, the intravenous administration of Ferritin-ApoE effectively mitigated the reduction in MBP and AQP4 ($p < 0.001$). This suggests that injection of Ferritin-ApoE inhibited NMOSD lesion expansion and demyelination as compared to those of the PBS and ferritin groups. It is worth noting that the expression of GFAP around lesions was even higher in NMOSD mice treated with Ferritin-ApoE compared to the other two groups, prompting the potential recruitment of GFAP+ astrocytes for lesion repair. In addition, intravenous injection of Ferritin-ApoE reduced the number of ipsilateral microglia in NMOSD mice compared to mice received PBS or ferritin injection ($p < 0.001$). Flow cytometry detection of brain immune cells also indicated a significant reduction in total microglia counts (CD45intCD11b+) and CD86+ microglia in Ferritin-ApoE treated NMOSD mice, compared to PBS or ferritin controls ($p < 0.05$).

Conclusion: The findings indicate that the Ferritin-ApoE prodrug can successfully penetrate the blood-brain barrier and reduce brain damage in NMOSD mice by reducing microglial reactivity and neuroinflammation. This suggests the potential of Ferritin-ApoE for central nervous system-targeted therapy for NMOSD.

Key Words: neuromyelitis optica spectrum disorder, ferritin, ApoE, prodrug, therapy

ID:135

The BET PROTAC Inhibitor dBET6 Protects against Light-Induced Retinal Degeneration by Inhibiting Retinal Inflammation

Xingfei Zhu,Wei Liu,Xiangyu Ge,Haifeng Cui,Ziqing Chen,Lili Gong*
Zhongshan Ophthalmic Center, Sun Yat-Sen University

Objective: Chronic inflammation significantly contributes to photoreceptor cell death in blinding retinal diseases such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD). The bromodomain and extraterminal domain (BET) proteins are epigenetic readers that act as key proinflammatory factors. Here, we investigated the effects and action mechanism of dBET6, a proteolysis-targeting chimera (PROTAC) small molecule that selectively degrades BET proteins by the ubiquitin–proteasome system during light-induced retinal degeneration.

Methods: To induce the LIRD mouse model, BALB/c mice (5-8 weeks) were exposed to 15000 lux white light for 2 h. mice were intraperitoneally injected without (control group, n=15) or with 10 mg/kg of dBET6 (n=25-30) or vehicle (n=25-30) 1 h before LD and 24 h after LD, and retinal function and morphology were evaluated 48 h after LD. Hematoxylin and eosin(HE) staining and immunofluorescence(IF) access retinal morphology. Western blot assay determines the expression of proinflammatory cytokine in retinas. Optical Coherence Tomography(OCT) and Electroretinogram(ERG) evaluate retinal morphology and function *in vivo*.

Results: Intraperitoneal injection of dBET6 led to the rapid degradation of BET proteins in the retina without detectable toxicity. dBET6 improved retinal responsiveness and visual acuity after LD. dBET6 also repressed LD-induced retinal macrophages/microglia activation, Müller cell gliosis, photoreceptor cell death and retinal degeneration. Finally, dBET6 suppressed expression of proinflammatory factors, such as CD86, GFAP, IL1β in retina in response to LD.

Conclusion: In summary, our study shows that BET PROTAC dBET6 prevents light-induced retinal degeneration through inhibiting retinal inflammation. The Results suggest that the dBET6 may be a potential therapeutic drug for retinal degeneration.

Key Words: Retinal Degeneration; BET Protein; Neuroinflammation; PROTAC

ID:141

Light damage induces inflammatory factors in mouse retina and vitreous humor

Wei Liu,Lili Gong*
中山大学中山眼科中心

Objective: Increased inflammatory factor levels have been reported in the vitreous humor (VH) of diabetic retinopathy and neovascular age-related macular degeneration, ocular diseases generally associated with the formation of new retinal blood vessels and leakage. However, the levels of inflammatory mediators are less known in retinal degeneration without neovascularization. Human retinitis pigmentosa (RP) and animal models of light-induced retinal degeneration (LIRD) share several features, such as photoreceptor death and retinal inflammation. Here, we aimed to determine the levels of inflammatory factors in the VH of the LIRD mouse model.

Methods: LIRD was induced by exposing BALB/c mice to white light (15,000 lx, 2 h), and the mice were recovered for 2 days before analysis (n = 50 mice). We assessed retinal morphology using optical coherence tomography and hematoxylin and eosin staining; retinal cell viability was determined using terminal deoxynucleotidyl transferase dUTP nick-end labeling, and retinal responses were measured based on electroretinogram signals. Total retinal RNAs were extractedand subjected to RNA sequencing analysis. VH samples from control (n = 4) and LIRD mice (n = 9) were assayed in triplicate for a panel of four inflammatory mediators using the Simple Plex Cartridge on an Ella System.

Results: Retinal degeneration, photoreceptor death, infiltration of microglia/macrophages into the photoreceptor layer, and loss of a- and b-waves were obviously detected after LIRD. RNA sequencing revealed that light damage (LD) led to the significant upregulation of inflammatory factors in mouse retinas. In the VH, LD increased the total protein concentration. Dramatic induction of CCL2 (~3000 fold) and IL6 (~10 fold) was detected in VH in response to LD. Increased but not significant levels of TNFα and IL1β were also detected in light-exposed VH.

Conclusion: Given that the LIRD model mimics RP pathogenesis in some aspects, these Results suggest a causative link between retinal degeneration and VH inflammation in RP progression, and the increased CCL2 level in VH may Light damage induces inflammatory factors in mouse retina and vitreous humor reflect similar elevated CCL2 expression in the degenerative retina.

Key Words: Light damage ； Inflammatory factors; Vitreous humor ； Retinal degeneration

ID:146

Small-molecule targeting AMPA-mediated excitotoxicity has therapeutic effects in mouse models for multiple sclerosis

Dongxu Zhai1,Shuxin Yan1,Le Wang1,Ping Su1,Anlong Jiang1,Haorui Zhang1,Zhengping Jia3,Izhar Wallach2,Abraham Heifets2,Chih-Chung Tseng4,Albert H.C. Wong1,5,6,8,Iain R. Greig4,Fang Liu*1,5,6,7

1. Center for Addiction and Mental Health
2. Atomwise Inc., 221 Main Street, Suite 1350, San Francisco, CA 94105, USA.
3. Department of Neurosciences & Mental Health, The Hospital for Sick Children, 686 Bay St., Toronto M5G 0A4, Canada.
4. Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, Scotland, UK.
5. Institutes of Medical Science, University of Toronto, 1 King’s College Cir., Toronto M5S 1A8, Canada.
6. Department of Psychiatry, University of Toronto, 250 College St., Toronto M5T 1R8, Canada.
7. Department of Physiology, University of Toronto, 1 King’s College Cir., Toronto M5T 1R8, Canada.
8. Department of Pharmacology and Toxicology, University of Toronto, 1 King’s College Cir., Toronto M5S 1A8, Canada.

Objective: While most research and treatments for multiple sclerosis (MS) focus on autoimmune reactions causing demyelination, it is possible that neurodegeneration precedes the autoimmune response. Hence, glutamate receptor antagonists preventing excitotoxicity showed promise in MS animal models, though blocking glutamate signaling prevents critical neuronal functions.This study aimed to develop a small molecule compound to this end.

Methods: We used an artificial intelligence–enabled approach to predict small-molecule binding to the GluA2 AMPA subunit. We then tested and refined the hit *in vitro* to generate several leading compounds and tested in two of the rodent MS model-Experimental Autoimmune Encephalomyelitis (EAE) and cuprizone demyelinating model to verify its effect in vivo.

Results: To advance the development of a viable treatment for MS that provides neuroprotection by targeting glutamate excitotoxicity, we identified a number of drug-like small-molecule candidates that were predicted to bind to our discovered allosteric site using a convolutional neural network approach to screen a large chemical space. Using our in-house developed cell toxicity assay, we have validated the potency of these hits. In vivo, one of the lead candidate molecules-ZCAN262 improved neurological function in EAE mice and cuprizone-fed mice by restoring myelination, axon integrity, and oligodendrocytes, yet it has no effect on glutamate-mediated basal neurotransmission and recognition memory or spatial learning

Conclusion: The lead candidate has potent effects in restoring neurological function and myelination while reducing the immune response in experimental autoimmune encephalitis and cuprizone MS mouse models without affecting basal neurotransmission or learning and memory. These findings facilitate development of a treatment for MS with a different mechanism of action than current immune modulatory drugs and avoids important off-target effects of glutamate receptor antagonists. This class of MS therapeutics could be useful as an alternative or complementary treatment to existing therapies.

Key Words: drug screening, MS modeling, AMPA mediated excitotoxicity, molecular neuroscience

ID:147

The role and mechanism of GATA3 in regulating astrocyte differentiation and blood-brain barrier disruption in multiple sclerosis

Yiying Huang,Yipeng Zhao,Wei Qiu*

Third affiliated hospital of Sun Yat-sen University

Objective: Astrocytes are an important component of the blood-brain barrier (BBB) and participate in regulating its function. BBB disruption plays an important role in the pathology of multiple sclerosis (MS). This study aims to explore whether astrocytes are involved in BBB disruption in MS, whether GATA3 affects astrocyte differentiation, and further investigate the specific mechanism by which GATA3 promotes astrocyte differentiation in BBB breakdown.

Methods: Serum and cerebrospinal fluid samples were collected from MS patients to detect inflammatory astrocyte markers and BBB damage indicators; Experimental Autoimmune Encephalitis(EAE) model was constructed to detect the distribution of inflammatory astrocytes (A1 phenotype) in the spinal cord as well as constructing the phenotype of inflammatory astrocytes; Interleukin-4(IL-4) was used for stimulating inflammatory astrocytes to validates activation of the IL-4/STAT6/GATA3 pathway; knock-down and overexpression of GATA3 to verify that GATA3 regulates astrocyte differentiation; Chromatin immunoprecipitation sequencing of GATA3 binding genes was tested in astrocytes; BBB model in vitro and organotypic brain slice cultures were used for determining the effects of GATA3 in inflammatory astrocytes and BBB; EAE mice were injected with IL-4 and GATA3 overexpression plasmids intrathecally or edited by conditional gene knock-in technology, then evaluated the clinical score of EAE mice, and detect the destruction of BBB; Constructing IL-4 liposome microbubbles and targeting astrocytes for the treatment of EAE.

Results: There was an increase in inflammatory astrocytes in the spinal cord of EAE mice; Increased expression of IL-4ra, IL-13ra, and chemokines in inflammatory astrocytes; IL-4 stimulation can activate the IL4/STAT6/GATA3 pathway to promote the differentiation of astrocytes into A2 phenotype astrocytes; GATA3 can bind to the vascular endothelial growth factor alpha(vegfa) promoter region and intergenic region and regulates the phenotype of inflammatory astrocytes and BBB disruption; The disability score of EAE mice injected with IL-4 and GATA3 overexpression plasmids decreased, the levels of chemokines in the spinal cord decreased, the inflammatory astrocytes decreased, and the expression of tight junction proteins increased.

Conclusion: In MS, GATA3 regulates the differentiation of astrocytes into A2 phenotype and regulates the expression of vegfa, improving BBB permeability. IL-4 is expected to become a new treatment method.

Key Words: multiple sclerosis, experimental autoimmune encephalitis, blood-brain barrier, astrocyte, Interleukin-4, GATA3, vascular endothelial growth factor alpha

ID:148

Elevated Serum Complement Levels are Clinically Practical Biomarkers for Disease Activity in Myelin Oligodendrocyte Glycoprotein Antibody-Related Diseases

xiaonan zhong,Yiying Huang,Linling Wang,Xueqiang Hu,Zhengqi Lu,Wei Qiu*
中山大学附属第三医院

Objective: Complement activation plays an important role in the demyelinating pathology of myelin oligodendrocyte glycoprotein antibody-related disease (MOGAD). However, whether complement can be a biomarker for the disease activity of MOGAD remains unknown.

Methods: A total of 171 records of commonly used complement indicators from 95 MOGAD patients, and 185 records from 97 NMOSD cases were included retrospectively. Records of inflammatory markers including procalcitonin, C-reactive protein, interleukin-6, and erythrocyte sedimentation rate in serum, as well as total protein and white cell count in the cerebral fluid, were also collected.

Results: Comparing MOGAD and NMOSD, higher levels of C3 (acute phase, p=0.027; whole course, p=0.003), C4 (acute phase, p<0.001; whole course, p<0.001) and CH50 (acute phase, p=0.021) were observed in MOGAD patients. Within the MOGAD cohort, a large number of patients had elevated complement levels. Compared with MOGAD patients in the remission phase, patients in the acute phase showed increased levels of C4 (p=0.022), CH50 (p=0.021), and IgG (p=0.031). We also observed the dynamic changes in complement concentrations after clinical attacks in MOGAD, with complement concentrations often reaching a relatively high point during the acute phase and declining in the following remission phase. In MOGAD cases, levels of CH50 were positively related to IgG (r=0.317, p=0.006). Positive correlations were observed between complement and CRP (C3, r=0.316, p=0.006; C4, r=0.303, p=0.009; CH50, r=0.230, p=0.050), as well as between complement and ESR (C3, r=0.537, p=0.000; C4, r=0.280, p=0.043; CH50, r=0.478, p=0.000). C4 positively related to cerebral fluid white cell count (r=0.217, p=0.030) in MOGAD patients.

Conclusion: Commonly used complement indicators in clinical practice, can reflect the degree of inflammation in MOGAD and, therefore can serve as candidate prognostic biomarkers for MOGAD disease activity.

Key Words: MOGAD, NMOSD, complement, biomarker

ID:152

CAR T, CAR NK, and CAR-M Therapies for Ovarian Cancer

Liying Wang,Liang Wang,Pengming Sun*

福建省妇幼保健院

Objective: This study aimed to compare the advantages and disadvantages of CAR-T cells, CAR-NK cells, and CAR-macrophages therapies in the treatment of ovarian cancer and select the most suitable targeted therapy for patients, with the goal of enhancing treatment efficacy and reducing side effects.

Methods: The Methods involved conducting a comprehensive search for experimental studies and clinical treatments of ovarian cancer using CAR-T, CAR-NK, or CAR-M therapies in PubMed. The comparison encompassed various aspects such as the source of cells used, the incidence and severity of cytokine release syndrome and neurotoxicity, the ability of cells to infiltrate tumors, and the status of ongoing clinical trials in solid tumors, to evaluate the safety and efficacy of each approach.

Results: The Results indicated that targeted CAR-T therapy had the most extensive research base, with 22 ongoing clinical trials focused on solid tumors, specifically for ovarian cancer treatment. CAR-NK therapy was a close second, with 5 ongoing clinical trials. In contrast, CAR-M therapy had relatively less research, with only one ongoing clinical trial. Regarding cytokine release syndrome and neurotoxicity, CAR-T was found to be widespread and frequently severe, while CAR-NK showed less incidence and severity. For CAR-M, although there was a lack of clinical data, it was anticipated to have a similar profile to CAR-T.Compared to other cellular therapies, CAR-T utilizes autologous T cells or MHC-matched allogeneic cells; CAR-NK employs a broader range of sources including autologous, non-MHC-matched allogeneic cells, allogenic PBMC, UC, HSC, iPSC, and NK cell lines; CAR-M is predominantly autologous. Preclinical studies often utilize iPSCs and cell lines to explore potential treatments.

Conclusion: In summary, immunotherapy utilizing CAR technology for the treatment of OC is progressively advancing. CAR-related immunotherapy is continuously evolving in the field of OC treatment, with CAR-T cells, CAR-NK cells, and CAR-M each possessing their own respective strengths and weaknesses.

Key Words: Ovarian cancer,CAR T therapy, CAR NK therapy, CAR macrophage therapy

ID:154

Case Report: Miller Fisher Syndrome (MFS) Superimposed Acute Inflammatory Demyelinating Polyneuropathy (AIDP) with Bilateral Facial Palsy (BFP) Complicated with Rare Cerebral Salt Wasting Syndrome (CSWS): Treatment and Outcome

Djung Lilya Wati*,Luh Ari Indrawati
Mandaya Royal Hospital Puri, Fakultas Kedokteran Universitas Tarumanagara

Objective: MFS is one of the rare forms of a spectrum of Guillain-Barré syndrome (GBS). It is usually present as following symptoms: ataxia, ophthalmoplegia, and areflexia. Twenty percent of MFS patient showed facial palsy and hyponatremia was observed more in AIDP variant.

Methods: The patient gave consent for his clinical information to be presented as case report.

Results: 47 year-old Chinese Indonesian male presented with a worsening dizziness and diplopia followed by paresthesia and unable to sit up straight since 3 days before he was admitted. Neurological examination revealed total ophthalmoplegia, arreflexia, parethesia in upper and lower extremities, and ataxia. Brain imaging at the time of admission showed no significant findings. Conduction nerve studies on day 6 after onset showed demyelinating sensory and motor nerves supported to AIDP. He was diagnosed with MFS superimposed AIDP and underwent treatment with IVIG 2 g/kg for 5 days. On day 8 after onset, he showed lethargy and there was observed facial nerve palsy bilaterally despite he still undergoing IVIG. On laboratory examination: his natrium dropped to 110 mmol/L, his 24 hours urine natrium was high (328.32 mmol/24h), and low serum osmolality 242 mOsmol/kgH2O. There was no additional IVIG dose or steroid treatment and the patient was treated with 3% sodium chloride solution until his natrium back to normal level. He was discharge after thirty-three days in the hospital. He continued his physical therapy and accupuncture treatment. His neurology function improved to near normal after ninety-six days of onset.

Conclusion: Hyponatremia in MFS has been reported previously. Most of hyponatremia cases usually related to pseudohyponatremia after IVIG treatment, hyponatremias as the complication of GBS alone mostly were caused by syndrome of inappropriate anti diuretic hormone (SIADH) followed by CSWS. There is no specific guideline for hyponatremia in GBS. There was correlation of superimposed AIDP as predictor of hyponatremia in this case.

Key Words: Miller Fisher, Facial Palsy, Hyponatremia, CSWS