

Collaborative studies of U.S.–China neurologists on acute motor axonal neuropathy

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THE HISTORY AND FRIENDSHIP BETWEEN BEIJING CHILDREN'S HOSPITAL AND THE JOHNS HOPKINS HOSPITAL

The founder of modern pediatric medicine in China and the first president of Beijing Children's Hospital (BCH), academician of Chinese Academy of Sciences, Prof. Fu-Tang Chu (Prof. Futang Zhu's name was spelled as Fu-Tang Chu since early 1930s until 1964, later on as universal use of Chinese Phonetic Alphabet for people's name, his name has been spelled as Futang Zhu), developed a close relationship with his mentor, Prof. Charles F. McKhann, when he studied and worked in Boston Children's Hospital, the teaching hospital of Harvard Medical School in Boston in the early 1930s. He also became a good friend of Prof. Guy M. McKhann (son of Prof. Charles F. McKhann), the founder and the first director of neurology at the Johns Hopkins Hospital (JHH) years later.

THE PROPOSAL OF RESEARCH QUESTIONS

Prof. Fu-Tang Chu mentioned and discussed Guillain-Barré syndrome (GBS) several times in China during Prof.

Guy McKhann's visit to Beijing, which led to a perfect combination of academics and friendship between experts of China and the U.S., starting a new era of recognition and identification of acute axonal peripheral neuropathy and its diagnosis and treatment as well as other related studies. Prof. Chu told Prof. McKhann that there were children cases with clinical presentations very similar to those of GBS in northern China but most of those cases seemed to have different epidemiological characteristics, which were mainly: 1) the majority of the patients were preschool and school-age children and 2) a clear seasonal peak was present in summer from July to September, especially during the rainy season. On the contrary, GBS reported in Europe and the U.S. had no such clear age and seasonal differences. Therefore, the research questions were proposed: what is the reason for this difference? Is there a special type of GBS in northern China distinct from the classic GBS seen in Europe and the U.S.?

THE FORMATION OF A MULTIDISCIPLINARY RESEARCH TEAM

GBS-like cases in Chinese children discovered by Prof. Chu greatly interested Prof. McKhann and his colleagues in the U.S. To find out what the reason was for the

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differences between Chinese and American patients and what the pathogenesis and possible pathogen were, Prof. McKhann convened the top neurologists JW Griffin (Director of Neurology at JHH and President of the American Neurological Association), AK Asbury (Distinguished neurologist and neuropathologist at the University of Pennsylvania), DR Cornblath (Distinguished neurologist and electrophysiologist, President of International Peripheral Nerve Society, editor-in-chief of *Neurology*), T Ho (neurologist at JHH).

Chinese experts and doctors included Prof. Husheng Wu (Director of the Division of Neurology, BCH), Junlan Lv (neurologist of BCH, visiting scholar at JHH), Chunyan Li (Director of Department of Neurology in the Second Teaching Hospital of Hebei Medical University, visiting scholar at JHH), Qifen Ye, Wuchang Zhang and Jing Zhang (responsible for clinical electrophysiology). The research cooperation was guided by Prof. Zaifang Jiang (President of the Society of Pediatrics, Chinese Medical Association). The research team also involved Dr. Getu Zhaori (The Chief of the Virology Research Laboratory, Beijing Pediatric Research Institute, BCH).

SCIENTIFIC RESEARCH AND ACHIEVEMENTS

Prof. McKhann and the other American experts visited China once a year, for several years since early 1990. The experts worked with Chinese doctors very hard to collect clinical and epidemiological data of the patients. The Chinese neurologists led by Prof. Husheng Wu presented GBS-like cases to the American neurologists. The U.S. experts performed physical examinations, biopsy of the peripheral nerve, and guided the electrophysiological examination.

In 1991, Prof. McKhann published the article entitled "Clinical and electrophysiological aspects of the acute paralytic disease of children and young adults in northern China" in *Lancet*.¹ It reported a total of 36 children as well as young adult patients treated at BCH and the Second Affiliated Hospital of Hebei Medical University; 91% of these patients came from rural areas and 47% had a history of preceding infection within 4 weeks before onset. The number of admitted patients peaked in the summer, particularly in the rainy season. Weakness of lower limbs was the earliest symptom and progressed rapidly to involve the upper limbs and respiratory muscles; tendon reflexes gradually weakened or disappeared as the disease progressed. Maximum weakness occurred a mean of 6 days after onset of weakness; 61% of the children and young adult patients developed bulbar paralysis. Mechanical ventilation was required in 31% of the patients; 42% of patients had elevated protein with a normal cell count in the cerebrospinal fluid (CSF). Nerve conduction tests showed

that motor evoked potential amplitude decreased significantly in 22 cases while the sensory nerve action potential remained normal. An electromyogram indicated a denervation potential in the muscle. The epidemiological, clinical, and neurophysiological features described above suggest that this disorder was different from both classic GBS and poliomyelitis. From the neurophysiologic findings, experts raised the hypothesis that this disease was a reversible distal motor nerve or anterior horn cell lesion. Therefore, it was likely to be a previously unrecognized disease or syndrome with distinct major clinical, epidemiological, and laboratory examination features. The questions raised by Prof. Fu-Tang Chu decades ago were partially answered by the research team leading to an important academic breakthrough. But there remained many other questions in front of Chinese and American experts, for example, what is the pathogenic cause? What about the pathogenesis and pathological changes? Are there any therapeutic and preventive methods? To answer all these and even more questions, the collaborative research team continued the studies.

Prof. McKhann published another paper in *Ann Neurol*² two years later. The article referred that GBS was the most common cause of acute flaccid paralysis in China over the past 20 years. An analysis of 3200 patients illustrated that the majority of cases occurred in summer among children and adolescents, most of whom were from rural areas. Of the 90 patients with acute flaccid paralysis, 88 had clinical and CSF findings similar to demyelinating GBS; the clinical course was dominated by rapidly progressive ascending tetraparesis, often with respiratory failure but without fever, systemic disease, or sensory nerve involvement. In CSF the number of cells was normal while the protein level elevated in the second or third week after onset. Electrophysiological examination revealed normal latency and conduction velocity of the motor nerve as well as the decreased amplitude of compound muscle action potential. The sensory nerve action potentials and F-wave latency appeared normal. Most patients showed a good prognosis. These studies implied that this disease is a distinct syndrome, different from polio and demyelinating GBS. The GBS-like disease seen in northern China is distinct from the classical GBS and belongs to the axonal degenerative type.

The research team is also interested in the possible role of antibodies against ganglioside GD1a and GM1 in the pathogenesis of GBS or GBS-like cases. They reported in 1998 that positive anti-ganglioside GD1a IgG antibodies also appeared in classic GBS and other diseases, but there are differences between classic demyelinating GBS and those of Chinese cases in aspects of electrodiagnosis.³ The specificity and temporal relationship of anti-ganglioside GM1 IgG antibodies indicated that the anti-GM1 mechanism was associated with the pathogenesis of the disease. However, it was noteworthy that anti-GM1 IgG antibodies were only

found in a few patients with axonal neuropathy. Therefore, other antigen targets must have been involved in the pathogenesis. Anti-GM1 IgG antibody and *Campylobacter jejuni* infection were two factors appearing to be associated with acute motor axonal neuropathy (AMAN). Though it has been hypothesized that the anti-GM1 antibodies might cross-react with the *Campylobacter* antigens, some patients in China have certain titers of anti-GM1 IgG antibodies, while there was no evidence of *C. jejuni* infection.

A prospective study of 138 Chinese patients with GBS found that IgG anti-GD1a antibodies were closely associated with AMAN but not acute inflammatory demyelinating polyneuropathy (AIDP). The serological evidence of recent *C. jejuni* infection was detected in 81% of AMAN and 50% of AIDP patients. The results suggest that anti-GD1a antibody and *C. jejuni* infection may be involved in the pathogenesis of AMAN.⁴

Based on the autopsy results of Chinese cases, Griffin et al.⁵ proposed the concept of GBS spectrum updating GBS as a demyelinating disease. The early pathological changes in clinically diagnosed GBS cases were diverse because they were not restricted to the well-known AIDP type and the main pathological patterns varied in different regions of the world. GBS can therefore be classified into different disease profiles such as classical AIDP, AMAN, and acute motor-sensory axonal neuropathy (AMSAN).⁵ Studies of autopsy pathology demonstrated that pathological alterations in AMAN patients were almost limited to the motor nerve with macrophages invading axons, surrounding and destroying axons while myelin remains intact. The variation in the pathological outcome of AIDP versus axonal patterns might reflect differences in their pathogenesis. The periaxonal macrophages suggested that an important epitope might be located on the axonal membrane or in the periaxonal space. In AMAN cases, immunohistochemical findings of the autopsy samples showed the presence of IgG and complement activation product C3d bound to axolemma of motor fibers. Additionally in severe cases, IgG and C3d appeared in the periaxonal space between the node of Ranvier of myelinated nerve fibers, binding to the outer surface of motor axons. Hence, AMAN is a disease caused by antibody and complement-mediated involvement of motor fibers.⁶

Professors Mckhann and Asbury coauthored the article “Changing views of Guillain–Barré syndrome” in 1997.⁷ The research confirmed that GBS-like cases that emerged across adolescents during summer in northern China were different from classic GBS with satisfying prognoses, mainly motor nerve involvement while sensory nerve almost unaffected. It puts forward that the node of Ranvier is a site of immune invasion, and antibodies along with complement play a crucial role in this process. These stud-

ies provided important theoretical support for the subsequent treatment with high-dose immunoglobulin.

To further understand the pathological changes of GBS in children in northern China as well as its correlation with electrophysiology, Dr. Lv and her colleagues conducted a study on electrophysiology and sural nerve biopsy in children with GBS.⁸ According to electrophysiologic and pathologic features, GBS can be divided into the demyelinating type and axonal type. AMAN mainly involves motor nerve fibers with axonal damage; while AIDP involves both motor and sensory nerve fibers with demyelinating changes. Lv et al.⁸ explored the correlation between the sural nerve pathologic findings and electrophysiologic patterns in GBS patients. The nerve conduction study of GBS was highly consistent with pathologic changes of the sural nerve. In AMAN cases, the sural nerve was hardly pathologically involved whereas macrophage-mediated demyelination and lymphocyte infiltration of the sural nerve was common in cases of AIDP.

In order to investigate the etiology of AMAN, Prof. McKhann suggested applying for a research grant from Rockefeller Foundation. With the support from the Foundation, we formed a collaborative group with the Department of Epidemiology, Peking Union Medical College, Chinese Academy of Medical Sciences led by Prof. Zhenglai Wu to conduct a case-control study. In this study,⁹ 51 patients with GBS or AMAN and 51 matched controls were enrolled. Twenty patients had AIDP, which was regarded as the classic GBS, while 28 had AMAN, and three cases were unclassified. The analysis between the case group and the control group showed that several factors were associated with AIDP or AMAN, including vaccination for polio (OR = 7.27, $P < 0.01$) or hepatitis B (OR = 3.14, $P < 0.05$) before onset of illness, getting a cold (OR = 13.75, $P < 0.01$), going to river/lake site (OR = 12.20, $P < 0.01$), no hand washing before meals and after defecation (OR = 6.15, $P < 0.01$). Recent infection with *C. jejuni* was strongly associated with the development of AIDP or AMAN (OR = 9.5, $P < 0.001$). In addition to detection of the IgG antibody to *C. jejuni*, this study also determined the optical density (OD) of the IgG antibody, which can be regarded as semiquantitative values representing to a certain extent the titer of the antibody, and these values also had significant difference between the two groups, which further supports that the infection with *C. jejuni* may have etiological roles in the development of GBS or AMAN. We believe that *C. jejuni* might be one of our important targets for the prevention of GBS and AMAN if not the target of treatment, since by the time of onset of GBS or AMAN, this bacterium might have already been degraded.

We wish to thank Prof. McKhann and his colleagues for their suggestion for etiology-related study, and we also

sincerely thank Prof. Zhenglai Wu and his team for their nice work. We wish relevant studies on AMAN, GBS and other peripheral nerve diseases would be continued further.

THE NEW CHALLENGES IN FRONT OF US

Thanks to the long-standing friendship between experts of China and the U.S., the cross-border scientific research cooperation not only solved the problem of the high incidence and serious condition of GBS among teenagers in northern China in summer, which had puzzled Chinese pediatricians for many years but also found that in addition to classic AIDP, there are AMAN, AMSAN and other types of GBS. AMAN was the most common GBS in northern China with a high incidence in summer and mainly in adolescents. The electrophysiological features of AMAN patients were highly consistent with autopsy findings and peripheral neuropathological changes. Anti-GM1 and anti-GD1a antibodies were significantly elevated in the peripheral blood of some AMAN patients. Further studies illustrated that *C. jejuni* infection was the most common pathogenic agent in the summer, particularly in the rainy season. Hence, effective preventive measures may incorporate improving public health concepts, advocating the use of clean water along separating humans and livestock. The great achievements in GBS studies were published in the textbook of *Zhu Futang Practice of Pediatrics*.¹⁰

In recent years, China's economic take-off with the improvement of rural health environment has led to a significant decline of the incidence of GBS. Most patients tend to experience mild course and good prognosis. However, there are still some patients with AIDP and/or AMAN including a few critical patients without the seasonal peak. Research on the pathogenesis of GBS also guided the early application of high-dose immunoglobulin therapy, which has significantly reduced the mortality of GBS, achieving the goal of zero death for many years in BCH.

AMAN, being a well-recognized disease, still brings us new challenges. Sporadic cases of AMAN occurred after COVID-19 infection or vaccination were reported.¹¹ The factors related to the severity of the disease and how to avoid the serious sequelae need further study.

The collaborative studies by the neurologists and pediatricians at JHH and BCH formed a great paradigm for joint efforts to solve problems in the disease seen in different hemispheres and such collaboration brought benefits to patients and parents in different countries. We heartily appreciate the great contributions and friendship of the older generations of pediatricians and neurologists represented by professors Fu-Tang Chu and Guy McKhann and

sincerely hope that medical experts all over the world would make joint efforts to fight against diseases.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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