

Clinical electrophysiological characteristics and prognosis of acute motor axonal neuropathy in Uygur children of Xinjiang.

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Abstract

The aim of this study was to investigate the clinical electrophysiological features and prognosis of Acute Motor Axonal Neuropathy (AMAN) in Uygur children of Xinjiang province. Six patients, aged 2 to 12 years, were included in the study. Five of the six patients had a history of prodromal infection. Disease onset occurred between June and December, with myasthenia as the main onset sign (100%). The mean peak time of the disease was 5.8 d. The amplitude of motor nerve potential in all children decreased (21.1-70.3% of the normal lower limit), the degree of nerve injury at the distal end was greater than at the proximal end (P<0.05), and the degree of injury of the upper and lower extremity nerves showed no significant difference (P>0.05). The motor and sensory nerve conduction speeds were normal, and g-globulin was present. Myasthenia is the most common onset sign of AMAN in Uygur children, though multiple disease symptoms can reach their peak in early stages of the disease. Electromyography (EMG) is of great significance in the diagnosis and differential diagnosis of AMAN. Early Intravenous Immunoglobulin (IVIG) therapy is efficacious in promoting the recovery of clinical neurological function.

Keywords: Uygur, Acute motor axonal neuropathy, Clinical-electrophysiological feature, Prognosis, Children.

Accepted on October 3, 2017

Introduction

Guillain-Barre Syndrome (GBS) is an immune-mediated acute polyradiculoneuritis that is most frequently preceded by an unspecific infection. GBS is also known as Landry's paralysis. The incidence rate of GBS ranges from 0.6 to 4.0/100,000 of the population [1]. It manifests as evolving motor paralysis with or without sensory disturbance, with the most common pattern being ascending flaccid paralysis. Weakness typically evolves over hours to a few days and is frequently accompanied by tingling dysesthesias in the extremities. According to pediatric literature, children usually recover in a shorter time frame than adults, and have a mortality rate of 3-5%. Severe neurological disability leading to ventilatory insufficiency and autonomic failure are the main causes of death [2]. Acute Motor Axonal Neuropathy (AMAN) is a subtype of Guillain-Barre Syndrome (GBS) characterized by extensive axonal lesions in the motor cranial nerve fibers, anterior spinal root, and motor fibers [3]. GBS includes Acute Inflammatory Demyelinating Polyneuropathy (AIDP), Acute Motor Axonal Neuropathy (AMAN), Acute Motor-Sensory Axonal Neuropathy (AMSAN), Miller Fisher Syndrome (MFS), acute Immunoinflammatory neuropathy, Acute Sensory Neuropathy (ASN), and other neuropathy subtypes [4]. Different subtypes have relatively consistent clinical manifestations. Overall, the clinical course, severity, and

outcomes of GBS are highly variable. Neuroelectrophysiological (NEP) studies play an important role in diagnosing and typing GBS [5,6]. In addition to classical GBS performance, a prominent feature of AMAN is the nearly pure motor nerve involvement prompted by NEP examination, especially motor axonal injury [7,8]. The clinical manifestations of AMAN vary, and most patients' exhibit mild signs at onset. The disease progresses gradually, and can eventually develop into complete lack of independent walking ability or the need for mechanical ventilation [9]. Therefore, predicting trends in the early stages of the disease would be of significance in terms of effective intervention and treatment, as well as in reducing mortality. The incidence of AMAN in northern China is high [10], while the incidence of AMAN in Xinjiang Uygur children has not been reported in China or abroad. While there are a variety of ethnic minorities in Xinjiang, the Uygur are the majority. Studies involving Uygur children with AMAN have not been conducted. This may be related to the lack of acknowledgement of the disease by pediatricians. However, delayed treatment can result in permanent disability. Therefore, by studying these cases, we aimed to provide a basis on which the early identification and clinical treatment of the disease might be improved. This study analyzed and followed clinical and NEP data as well as investigated the prognosis and features of 6 Uygur children

with AMAN treated in our hospital, with the aim of providing information on the incidence of AMAN in Chinese children.

Materials and Methods

Clinical data

A total of 6 Uygur pedia-out or inpatients with AMAN treated in the Department of Pediatrics at the First Affiliated Hospital of Xinjiang Medical University between May 2012 and October 2014 were enrolled. All 6 patients, 4 males and 2 females, were from different regions of Xinjiang, and ranged in age from 2 to 12 y, with a mean age of 6.1 y. Five patients had a history of 2 to 4 w prodromal infection (all respiratory infection). Four patients experienced onset between August and December, and two patients experienced onset in June. This study was approved by the ethical committee of the First Affiliated Hospital of Xinjiang Medical University, agreed by the patients' parents, and obtained their informed consent.

The diagnostic criteria of AMAN

All six patients were in line with the diagnostic criteria of AMAN [11]: 1) acute onset, with acute phase progression in <4 w; symmetric retarded paralysis; weakening or disappearance of tendon reflex in the four extremities that may be associated with cranial nerve palsy and/or respiratory muscle paralysis without sensory impairment; possible exhibition of protein-cell separation in the cerebrospinal fluid; 2) poliomyelitis excluded by fecal polio virus test; 3) electrophysiological criteria: 1. absence of demyelination, or only one nerve exhibiting the characteristics of demyelination with its distal stimulation-induced muscle action potential amplitude (dCAMP)<10% of the Lower Limit of Normal Value (LIN); 2. dCAMP<80% LIN in two or more nerves; 3. normal action potential amplitude in the sensory nerves.

NEP examination

The Motor Conduction Velocity (MCV), Sensory Conduction Velocity (SCV), and Distal Motor Latency (DML) of the median nerve, ulnar nerve, common peroneal nerve, and tibial nerve in each patient were measured and recorded using the KEYPOINT Electromyography (EMG) potential evoking instrument. The amplitude of the Compound Muscle Action Potential (CMAP) of the above mentioned nerves and the F wave latency of the above motor nerves were also recorded. The operation was performed by a professional technician while the patient lay relaxed in a quiet and shielded room (room temperature 20-22°C, limb temperature 32-34°C).

NEP typing criteria of AMAN

The normal EMG values issued by the Johns Hopkins Hospital (USA) were set as the diagnostic criteria. Furthermore, the patients' ages and features from relevant literature [12], in which the nerve conduction parameters in children 3 years and older have been shown to be similar to adults, were taken into consideration. Values from patients 3 years or older were

compared with the normal values of healthy adults, and the nerve conduction velocity and CMAP in those 1-3 years old were set to 80% of normal adult values, while the DML value was set to 120% of normal adult values.

Criteria: 1. absence of demyelination, or only one nerve with features of demyelination and dCAMP<10% of LLN; 2. 2 or more nerves that exhibit dCAMP<80% of LLN; 3. normal action potential amplitude in the sensory nerves.

Treatment and follow-up

All patients were intravenously administrated large doses of immunoglobulin (IVIG), 400 mg/(kg•d), for five consecutive days. The follow-up methods included clinic visits (in the department of pediatrics in our hospital) and telephone follow-up. The follow-up time was 3-18 months.

Statistical analysis

SPSS version 16.0 was used for the statistical analysis. The measurement data were expressed as mean \pm standard deviation ($\bar{x} \pm s$), and the intergroup comparisons were conducted using t-tests, with $P < 0.05$ considered as a statistically significant difference.

Results

Clinical features

Myasthenia was the main onset sign in our patients (100%). Four patients (66.7%) exhibited four-limb involvement, and two patients (33.3%) exhibited bilateral lower-limb involvement. One patient (16.7%) exhibited visual disturbance; one patient (16.7%) exhibited drinking-induced bucking; two patients (33.3%) exhibited autonomic symptoms, manifesting as dysuria; four patients (66.7%) reached peak severity of the disease on the third to twelfth day following onset, while the other two patients (33.3%) reached peak severity within three days, with an average peak time of 5.8 d. The admission time ranged from 3 days to 4 months after onset. Two patients (33.3%) exhibited protein-cell separation in their CSF 2 w following onset, but two other patients (33.3%) had no such phenomenon in the second week. One patient (16.7%) was admitted 4 months after onset and another patient (16.7%) was admitted 2 months after onset, but no phenomena were found in the CSF. The cephalic and spinal cord MRI of the six patients (100%) showed no abnormalities (Table 1).

Nerve conduction

All six patients showed changes in motor nerve conduction in the examination, among which the potential amplitude was significantly reduced by 21.1-70.3% of LIN, with a mean of $42.7 \pm 17.0\%$ of LIN. MCV was normal. Detection of motor nerve potential amplitude revealed that the distal potential amplitude was reduced by $30.8 \pm 14.3\%$ of LIN, while the proximal potential amplitude was reduced by $60.2 \pm 16.9\%$ of LIN. The difference between them was statistically significant ($P < 0.05$), indicating that the distal nerves were severely injured

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($t=3.226$, $P<0.05$). The distal potential amplitude of the lower limbs was reduced by $32.0 \pm 15.3\%$ of LIN, while that of the upper limbs was reduced by $37.7 \pm 16.4\%$, with no statistically significant difference between them ($t=0.67$, $P>0.05$). The proximal potential amplitude of the lower limbs was reduced by $58.1 \pm 16.8\%$ of LIN, and that of the upper limbs was

reduced by $54.0 \pm 13.3\%$, with no statistically significant difference between them ($t=0.458$, $P>0.05$). The above results revealed that there were no significant differences in nerve injury between the upper and lower limbs. The potential amplitude and conduction velocity in the sensory nerves were normal (Table 2).

Table 1. Clinical features of the six Uyghur AMAN children.

Case (no)	Age (y)	Gender	Onset sign	Associated sign	Peak time of the course (days)	Protein-cell separation in CSF (2 w after onset)	Admission time (w)	Cephalic and spinal cord MRI
1	7	M	Myasthenia in lower limbs	Visual disturbance	3	N/A	0.5	No abnormality
2	5	M	Myasthenia in four limbs	Drinking-induced bucking	2	N/A	0.5	No abnormality
3	2	F	Myasthenia in lower limbs	Dysuria	2	yes	1	No abnormality
4	6	M	Myasthenia in four limbs	N/A	12	yes	4	No abnormality
5	4	F	Myasthenia in four limbs	N/A	9	N/A	8	No abnormality
6	13	M	Myasthenia in four limbs	Dysuria	7	N/A	16	No abnormality

Table 2. NEP results of the six AMAN children ($n=6$).

Nerves detected (the median nerve, ulnar nerve, common peroneal nerve, and tibial nerve)	Reduction degree of CMAP (% of LIN)	t	P
Distal end of four limbs	30.8 ± 14.3	3.226	0.009
Proximal end of four limbs	60.2 ± 16.9		
Distal end of lower limbs	32.0 ± 15.3	0.67	0.518
Distal end of upper limbs	37.7 ± 16.4		
Proximal end of lower limbs	58.1 ± 16.8	0.458	0.66
Proximal end of upper limbs	54.0 ± 13.3		

EMG

All children exhibited motor unit time widening, increased amplitude, slowed conduction velocity, and spontaneous potential.

Treatment effect

Following immunoglobulin treatment, 3 patients (50%) exhibited significantly improved signs, two patients (33.3%) exhibited mild improvement, and one patient (16.7%) did not show significant improvement. Three patients (50%) underwent IVIG treatment within 1 w of onset, and their signs improved significantly. One patient (16.7%) underwent IVIG treatment within 4 w of onset, and the signs improved slightly. Two patients underwent IVIG treatment within 8-16 w of onset. In these patients, one patient (16.7%) showed slight

improvement while the other (16.7%) showed no obvious improvement.

Follow-up

The 6-month and 1 y follow-up visits revealed that two patients achieved complete remission of their signs together with a recovery in muscle strength. The muscle strength in three patients increased by 1-2 levels, and independent walking was achieved. One patient exhibited an increase in muscle strength less than 1 level. Among the five patients who could walk independently, two patients (40%) completely recovered within 1 month after disease onset due to inpatient treatment (admitted for 3 d after onset), two patients (40%) recovered within 6 months after onset, and one patient (20%) recovered 1 year after onset.

Discussion

The proportions of AMAN in GBS patients vary widely in different countries and regions [13-16], with lower rates in Europe and North America (3% to 17%) and higher rates in East and South America (23% to 78%). Northern China and Japan have high incidence rates that also exhibit marked seasonal patterns. AMAN can occur at any age, is more common in males, and has an average age of onset of 4.5 y [15,16]. In this study, the average onset age of the six Uyghur pedia-patients was 6.1 y, similar to other reports. These 6 cases exhibited a significant seasonal pattern, with onset occurring between June and December. In this study, 5 patients were from rural areas, suggesting that this disease may be related to the living conditions of their residences. Among AMAN

patients, *Campylobacter jejuni* infection is the most common precursor event. Five patients in this study exhibited this prodromal event, and all had upper respiratory tract infections. No cases of diarrhea were found in this study, but further investigation on whether Uyghur AMAN patients have a special pathogenetic cause of the disease or if there was a certain omission of their disease histories. The one patient without the prodromal event (3 y old) had experienced disease onset 4 months prior to being admitted to our hospital, so the possibility of a precursor event cannot be completely ruled out. Because the existing cases are still few in number, the epidemiological data on the prevalence of AMAN in Xinjiang Uyghur children still requires further study.

AMAN is clinically similar to Acute Inflammatory Demyelinating Polyneuropathy (AIDP), but there are many differences in their clinical manifestations as well as in their NEP, neuropathological, and immunological pathogenesis. Furthermore, compared with AIDP, the signs of motion paralysis in AMAN progress faster and can reach their peak earlier [17], while AMAN patients may exhibit normal or increased tendon reflexes [18]. The patients in this study exhibited myasthenia as the main clinical manifestation; 5 patients lost their tendon reflexes, and one patient remained with normal tendon reflexes. Some children exhibited protein-cell separation in the CSF examination, but the NEP examination showed no demyelination, which was in line with the NEP changes of AMAN and did not support the diagnosis of AIDP. Meanwhile, the NEP monitoring showed similar degrees of upper and lower extremity nerve damage, and the distal extremity nerve damage was more serious, similar to a previous report [19]. NEP can provide an objective basis for the diagnosis and differentiation of AMAN that cannot be done by other tests [20]. Immunological and pathologic studies have identified that AMAN is caused by the cross reactions of homologous antigens in the gangliosides of lipopolysaccharides and motor nerve axons on the surface of bacteria [21,22], with typical pathological changes presenting as myelin loss-free axonal degeneration, while AIDP mainly presents as inflammatory myelination degeneration in peripheral nerves. In summary, the disease conditions in AMAN patients are more severe than those in AIDP patients, and include earlier muscle atrophy and worse recovery. In this study, 5 patients experienced a restored ability to walk independently, 4 within 6 months of disease onset, and one within 1 year of disease onset.

Studies have shown that receiving IVIG in early stages (within 2 w) of disease onset may independently predict of IVIG's therapeutic efficacy [23]. In this study, the 3 patients with significant improvement of clinical signs received IVIG treatment less than 1 week after onset, consistent with the literature [23]. The two patients with muscle strength \leq level 1 were first admitted 2 and 4 months after onset. Three months after IVIG treatment, NEP examination showed continuous CAMP amplitude reduction in one case and certain improvement in the other case. Therefore, AMAN patients should be diagnosed and treated with IVIG as early as possible, and although some patients may have a longer disease course,

IVIG treatment should be given so as to be aid in improving the prognosis.

Conflicts of Interest

The authors declare no conflict of interest.

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