Case Report

Intravenous Immunoglobulin Responsive in Two Distinct Patterns of Steroid Resistance Chronic Dysimmune Neuropathies: Case Report

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Chronic dysimmune neuropathies are heterogeneous immune-mediated disorders affecting peripheral nervous system. The main stay of treatment is regulation of the immune system by immunosuppressive or immunomodulatory drug. The authors described two patients with rare form of chronic dysimmune neuropathies that were multifocal acquire demyelinating sensory and motor neuropathy (MADSAM) and chronic ataxic neuropathy ophthalmoplegia IgM paraprotein cold agglutinins disialosyl antibodies (CANOMAD). Their symptoms were worsening after high dose steroid but dramatically responded to the Thai Red Cross intravenous immunoglobulin (IVIg). This data suggested effectiveness and safety of the Thai Red Cross IVIg in patients with chronic dysimmune neuropathies.

Keywords: Chronic inflammatory demyelinating polyneuropathy (CIDP), Multifocal acquire demyelinating sensory and motor neuropathy (MADSAM), Chronic ataxic neuropathy ophthalmoplegia IgM paraprotein cold agglutinins disialosyl antibodies (CANOMAD), Intravenous immunoglobulin (IVIg)

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Chronic dysimmune neuropathies are heterogeneous immune-mediated disorders affecting peripheral nervous systems that have diverse clinical presentation[1]. The classification depends on the type of nerve fiber (motor, sensory, or small fiber), the pattern of involvement (symmetrical, asymmetrical, or multifocal), the electrophysiological, the presence of monoclonal M protein, or if it is associated with malignancy. Chronic inflammatory demyelinating neuropathy is one of the prototypes in chronic dysimmune neuropathies. The symptoms are of typical progress or relapse of sensorimotor disorder with proximal and distal involvement[2]. There is a variant of Chronic inflammatory demyelinating polyneuropathy (CIDP) called multifocal acquire demyelinating sensory and motor neuropathy (MADSAM)[3]. The symptoms are slowly progressive demyelinating neuropathy with asymmetrical multifocal presentation that affect upper limbs more than lower limbs. There is a special clinical characteristic of patients with chronic sensory ataxic neuropathy with IgM paraproteinemia reacting with the disialylated ganglioside such as GD1b or GQ1b. Patients usually present with gait ataxia with or without ophthalmoplegia accompanied by relatively preserved motor function in the limbs. The acronym chronic ataxic neuropathy ophthalmoplegia IgM paraprotein cold agglutinins disialosyl antibodies (CANOMAD) was used to describe these clinical phenotype[4].

Treatment of chronic dysimmune neuropathies depend on the nature of the disease. However, in case of idiopathic cause, the main stay of treatment is regulation of the immune system. The mode of treatment includes high dose steroid, intravenous immunoglobulin (IVIg), and plasmapheresis. The authors described two patients with distinct clinical phenotype of chronic dysimmune neuropathies with worsening clinical after high dose steroid but had good response to the IVIg.

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Case Report

Case 1

A 52-year-old man presented with unsteadiness of gait and ophthalmoparesis. The symptoms developed in June 2013. He had an episode of fever and chill without a significant systemic infection. Three days later, he developed numbness from feet up to both thighs and left eye ptosis with binocular diplopia. Within few days, he developed ataxia and imbalance posture without significance of loss of muscle power. This symptom reached a plateau in one week and the deficit remained stable. He had no significant past medical history except the motorcycle accident 20 years ago with some residue deficit in right arm and right foot. There was no family history of neuropathy or other systemic diseases. On admission, he had anisocoria (right 2.5 mm, left 3.5 mm), and light reflexes were absent on left side. Ocular movement was impaired in upward and downward direction of left eye. The other cranial nerves were intact. Muscle power in the limbs was normal. All deep tendon reflexes and Babinski's sign were absent. Touch, cold, and pinprick sensations were slightly impaired in his feet up to above knees and distal part of his hand, but not in his face and trunk. There was profound loss of position and vibration senses in lower limbs, but intact in upper limb. A finger to nose test showed mild dysmetria, but severely impaired in heel to knee. Romberg's sign was positive. He could not stand nor walk alone due to severe ataxia. Autonomic functions were intact. Routine laboratory tests were normal. Serum immunofixation did not show monoclonal gammopathy. There was no cerebrospinal fluid (CSF) pleocytosis and CSF protein content was 188 mg/dl with normal level of CSF glucose. Motor nerve conduction studies showed proximal conduction block in bilateral ulna and left median nerves with minimal effect on distal motor latency. Absences compound muscle action potential (CMAP) amplitude were demonstrated in right median and peroneal nerves. F wave latencies were prolonged in left median, right ulna, and bilateral tibial nerves. Sensory nerve conduction studies showed absence sensory nerve-action potential (SNAP) amplitude of left sural nerve. Absence H reflex was observed in bilateral tibial nerves. Magnetic resonance imaging (MRI) brain showed multiple cranial nerve hypertrophies, including bilateral CN3, CN6, CN7 as well as extradural portion of CN V2 and CN V3 with mild gadolinium enhancement without evidence of spinal nerve hypertrophies. Antiglycolipid antibodies were investigated by EUROLINE Anti-Ganglioside Profiles (Euroimmun, Lübeck, Germany). The results showed IgM antibody activities against multiple anti-ganglioside antibody including GM1, GD1a, and GQ1b but not IgG. Sural nerve biopsy demonstrated reduction of myelinated axons with endoneural fibrosis consistent with demyelinating process. During that period, the authors gave the possible diagnosis of CANOMAD. The patient was treated with 1 gram per day of intravenous methylprednisolone (IVMP). After the third dose of IVMP was introduced, the patient's symptoms worsened. He developed upper limb ataxia, higher degree of diplopia, and peri-oral numbness. He could not use his hands due to severe proprioception and vibration in upper extremities. The steroid was discontinued and IVIg (IVIg 0.4 g/kg/day) was started for five days. Improvement begun after one week of IVIg treatment, and he regained the ability to walk with a cane, completely resolved the diplopia, but he still had some minor left eye ptosis. After one month, he could walk without support. Physical examination showed wide base gait with motor grade V by medical research council (MRC), and left eye ptosis without ophthalmoparesis. The decreased pinprick sensation was restricted from the ankle to the soles of the feet. The proprioception was normal but he still had some vibratory sensation in both feet. His deep tendon reflexes were still absent. In temporary improvement, his symptoms gradually worsened again after three months of IVIg. His symptoms gradually progressed while continuation of azathioprine (2 mg/kg/day). He was lost to follow-up for four years. Presently, he developed severe unsteadiness that required bilateral assistance. On examination, he had severe lower limbs ataxia (impaired heel to knee and positive for Romberg's test). The sensory examination in lower extremities showed vibratory sensation loss from distal feet to knees and proprioceptive loss up to the ankle joints. He also had mild degree of lower limbs weakness (MRC grade 4). He was started with IVIg (Thai Red Cross IVIg 0.4 g/kg/day) for five days. Improvement begun within a few days after administration. The numbness decreased, limited only to the sole area. Two weeks after treatment, he was able to walk few steps without support. Limb ataxia was improved. His vibratory and proprioception sensation were normal at the ankle but still have some residual deficit at the distal feet.

Case 2

A 53-year-old woman presented with tingling and paresthesia on the left palm for two months. Within a few days, she developed weakness on her left hand.

One month before admission, she developed first, second and third finger paresthesia in the right palm, then the weakness developed in her right hand. She could not perform her job (as an architect) and daily life activities. She also had left leg numbness. There was no family history of neuropathy or other systemic diseases. On admission, there was evidence of muscle weakness MRC grade III in left wrist flexion, finger flexion, and intrinsic hand muscles and grade IV in left wrist extension and finger extension. The right hand demonstrated grade IV of finger flexion, finger extension, and intrinsic hand muscles. Sensory examination demonstrated abnormal decrease pinprick sensation in the left ulna nerve, the right median nerve, and the left superficial peroneal distribution. Without motor complaint, the weakness of the left ankle dorsiflexion and eversion were also be noted in this patient. Nerve conduction study showed motor conduction block in the right median, the left ulna, and the left peroneal nerves. SNAP was absent in the right median nerves. Antiglycolipid antibodies were negative in both IgG and IgM. There were unremarkable CSF protein and cells. Other laboratory tests including Anti-SSA, SSB, C-ANCA, and P-ANCA were negative. The possible diagnosis in the present patient was MADSAM. Therefore, high dose oral prednisolone 1 mg per kg per day were given. Two weeks after treatment, her symptoms were worsening with MRC grade 3 in the right finger flexor and in the intrinsic hand muscles. Due to severe weakness under high dose steroid, IVIg (Thai Red Cross) was given 0.4 g per kg per day for five days. The motor symptom had marked improvement after the IVIg administration. Only minimal deficit (MRC grade IV) was demonstrated in the left intrinsic hand muscles. However, five weeks after IVIg administration, she complained of the new episode of fingers paresthesia at the fourth and fifth finger in her right palm, then the weakness developed in her right hand that required the second course of IVIg.

Discussion

The authors described two patients with rare form of chronic dysimmune neuropathies that did not respond to steroid but had an excellent response to the Thai Red Cross IVIg treatment. In case 1, the patient was diagnosed with CANOMAD, which is the sensory ataxic chronic dysimmune neuropathies associated with paraprotein with IgM anti-disialosyl antibody. The term CANOMAD was first discussed by Willison et al in 1996[5]. Although, large series of clinical and laboratory features of CANOMAD had been published in 2001[4], the standard treatment of CANOMAD has not yet been established. Corticosteroid treatment had been reported but only few showed improvement[6,7]. IVIg had been used in many studies and showed benefit in up to 70% of the patients[7,8]. The benefit of IVIg was reported in case studies[9,10]. In the present patient, the steroid not only had no benefit but also worsened the neurological symptoms. The dramatic response to IVIg in the present patient supported the use of IVIg in treatment of patient with CANOMAD. In case 2, the patient was diagnosed with MADSAM, which is considered to be a part of CIDP variant[11]. This disease was first described by Lewis et al in 1982[12]. The patient typically presented with motor and sensory deficits that started in the upper extremities. Electrophysiological study shows a pattern of demyelination (conduction blocks, temporal dispersion, and slow conduction velocity). However, when comparing to classic CIDP, patients with MADSAM are usually more refractory to treatment[13] and a lower percentage respond to corticosteroid[14]. The response rate of IVIg is about 48% to 55%, whereas corticosteroid is 33%. Some patients get worse under corticosteroid treatment[14,15]. Similar to the authors' patient, they still had progressive weakness under corticosteroid therapy and required IVIg for the rescue treatment.

In conclusion, the authors described patients with two distinct clinical phenotypes of chronic dysimmune neuropathy. The disease continued worsening under corticosteroid therapy but had an excellent response under IVIg treatment. Therefore, IVIg should be considered in patients with idiopathic chronic dysimmune neuropathies.

What is already known on this topic?

MADSAM and CANOMAD are rare forms of chronic dysimmune neuropathies. The mode of treatment includes high dose steroid, IVIg, and plasmapheresis.

What this study adds?

IVIg therapy should be considered in patients diagnosed with CANOMAD and MADSAM who did not respond or worsened after steroid therapy.

This data provides the information about the effectiveness and safety of the Thai Red Cross IVIg.

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Conflicts of interest

The authors declare no conflict of interest.

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