윌슨병 환자에서 발생한 D-페니실라민 유발성 중증근무력증: 증례 보고

현성은, 김인수, 김신후, 성민용, 이유경

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Electrodiagnostic Studies of D-Penicillamine Associated Myasthenia Gravis in a Pediatric Patient with Wilson's Disease: A Case Report

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A 15-year-old girl with Wilson's disease complained of progressive proximal muscle weakness and difficulty with mastication aggravated by prolonged chewing with a diurnal variation for 3 weeks. Repetitive nerve stimulation using supramaximal stimuli revealed post-synaptic disorder and the needle electromyographic study showed the myopathic motor unit action potentials without any abnormal spontaneous activity in all sampled upper and lower limb muscles and the masseter, consistent with the suspicion of penicillamine-induced myasthenia gravis (PMG). The patient showed clinical improvement after discontinuation of D-penicillamine. Because of its favorable prognosis and curable treatment option, when proximal weakness with diurnal variation occurs after long-term administration of D-penicillamine, PMG should be suspected. In the electromyography laboratory, PMG should be distinguished from myositis and other neuromuscular diseases by performing the repetitive nerve stimulation test of proximal muscle recording. The discontinuation of penicillamine and administration of anticholinesterase are promptly considered to lead to better outcomes in those populations.

Key Words: penicillamine, myasthenia gravis, neuromuscular junction diseases

Introduction

D-penicillamine is a pyridoxine antagonist and the

first choice of treatment for Wilson's disease because it is a potent copper chelating agent to protect patients against copper accumulating toxicity in multiple organs.¹ Owing to its immunoregulatory effects, however, penicillamine has been reported to cause several immune-mediated disorders, for example, myasthenia gravis, polymyositis, systemic lupus erythematosus, pemphigus, and sometimes combined of these.²⁻⁴ Penicillamine-induced myasthenia gravis (PMG) has

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mainly been reported in rheumatology patients but rather less common in Wilson's disease.³ In this report, we present an adolescent PMG patient with abnormal electroneuromyographic evidence who does not have any pre-existing autoimmune diseases but only Wilson's disease.

Case Report

A 15-year-old girl visited our hospital complaining of progressive proximal muscle weakness and difficulty with mastication aggravated by prolonged chewing since December 2017. She visited the outpatient clinic 3 weeks after developing muscle weakness. A manual muscle test yielded grade 3 at the proximal and grade 4 at the distal upper and lower extremities, with diurnal variations aggravated by fatigue. Although the patient had been a talented athlete and the best runner in her class before developing muscle weakness, she experienced difficulty when climbing stairs and transitioning from sitting to standing that was only alleviated after a 3-minute rest. Her weakness spread from lower extremities to upper extremities and bulbar muscles as well and resulted in difficulty of brushing hair, writing, and chewing food. However, the cranial nerve examination did not reveal any abnormalities including ptosis, facial palsy, or limitation of extra-ocular movement. The deep tendon reflexes were intact at first but decreased with subsequent examinations of 5~6 times. There was neither evidence of spasticity nor upper motor neuron sign along with cerebellum function test.

The patient had been taking penicillamine for 15 months before developing her neurological symptoms. She was taking this medication after diagnosed with Wilson's disease in September 2015. Together with hepatomegaly, ascites, and liver enzyme elevation as well as copper accumulation evidence in her brain and cornea with a pathognomic Kayser-Fleisher ring, she got her final diagnosis of Wilson's disease based on gene sequencing analysis demonstrating pathogenic mutations in *ATP7B* in both alleles. At first, she had tried trientine but switched to penicillamine again because her serum and urine copper level were unadjusted with uncontrolled ascites. Since October 2015, she has taken the same dose of penicillamine (150 mg twice a day) every day without any reported toxicity for two years.

When the patient experienced generalized but proximal-dominant weakness, she was first suspected to have penicillamine-induced myositis and recommended to quit her penicillamine. Then, she was referred to the department of pediatric rehabilitation for electrodiagnostic studies. At her visit to the electromyography laboratory, 3 days after the discontinuation of penicillamine, her symptom was already being improved than before. Because of her fast recovery, diurnal variation, and normal creatine kinase level (61 IU/L), myasthenia gravis was newly considered to differentiate; hence, the repetitive nerve stimulation test was also added to the routine electrodiagnostic studies.

Standard motor and sensory nerve conduction studies of both upper and lower extremity were normal.

Table 1. Findings of Needle Electromyography

	Spontaneous activity				MUAP			Interference	Recruitment
	IA	Fib	PSW	Fasc	Amp	Dur	Phase	Pattern	Pattern
Rt.Deltoid	-	-	-	-	Small	Short	Polys	Full	Normal
Rt.FDI	-	-	-	-	Small	Short	Polys	Full	Normal
Rt.VM	-	-	-	-	Small	Short	Polys	Full	Normal
Rt.TA	-	-	-	-	Small	Short	Polys	Full	Normal
Rt.Iliopsoas	-	-	-	-	Small	Short	Polys	Full	Normal
Rt.Masseter	-	-	-	-	Normal	Short	Polys	Full	Mild early

IA: insertional activity, Fib: fibrillation, PSW: positive sharp wave, Fasc: fasciculation, MUAP: motor unit action potential, Amp: amplitude, Dur: duration, Rt: right, FDI: first dorsal interossei, VM: vastus medialis, TA: tibialis anterior

Needle electromyography revealed voluntary motor unit action potentials (MUAPs) of small amplitude, short duration, and increased polyphasicity in all sampled upper and lower limb muscles and early recruitment pattern in her right masseter (Table 1). These myopathic MUAPs can appear in neuromuscular junction

disorders as well, nonetheless, there were no denervation potentials indicating any membrane instabilities to demonstrate active ongoing myositis correlated with the patient's progressive weakness.

A repetitive stimulation test using supramaximal stimuli for 3 seconds of low-frequency stimulation (LFS,

Fig. 1. The repetitive nerve stimulation test from the right ulnar motor at abductor digiti minimi muscle. (A) The baseline LFS (low-frequency stimulation of 3 Hz for 3 seconds) revealed 13.0% decrement in CMAP area but not in CMAP amplitude. (B) The LFS immediately after the HFS (high-frequency stimulation of 50 Hz for 3 seconds) revealed 29.2% decrement in CMAP area and 20.6% in CMAP amplitude between the first and fourth response. The CMAP amplitudes slightly increased again from the fifth stimulus to the end after the maximal decrement at the fourth stimulus, giving the final result to be in U-shapes. (C) At 2 minutes after the HFS, the maximal decrement of 39.3% in CMAP area, and (D) at 3 minutes after the HFS, the maximal decrement of 28.5% in CMAP amplitude were noted. (E) At 5 minutes and (F) at 10 minutes after the HFS, the gradual recovery of CMAPs to the resting level as baseline LFS was recorded (y-axis: 5 mV/division, x-axis: 50 msec/division).

3 Hz) before and immediately after 3 seconds of high-frequency stimulation (HFS, 50 Hz) was conducted. The HFS was given instead of the maximal voluntary exercise for consistency. Then, subsequent series of LFS at 1, 2, 3, 5, and 10 minutes after HFS followed. Both right ulnar motor at abductor digiti minimi (ADM) (Fig.

1) and right spinal accessory motor at trapezius (TPZ) (Fig. 2) were examined. Any decrement or increment in both compound motor action potential (CMAP) amplitude and area were recorded, because CMAP area of the negative peak was reported to better represent the total number of activated motor units and show higher

Fig. 2. The repetitive nerve stimulation test from the right spinal accessory motor at trapezius muscle. (A) The baseline LFS (low-frequency stimulation of 3 Hz for 3 seconds) showed 47.5% decrement in CMAP area and 39.4% in CMAP amplitude. (B) The LFS immediately after the HFS (high-frequency stimulation of 50 Hz for 3 seconds) revealed 47.5% decrement in CMAP area and 40.2% in CMAP amplitude between the first and fourth response with U-shapes. (C) At 2 minutes after the HFS, the maximal decrement of 55.0% in CMAP area and 47.9% in CMAP amplitude were noted. (D) At 3 minutes, (E) at 5 minutes, and (F) at 10 minutes after the HFS, the gradual recovery of CMAPs to the resting level as baseline LFS were recorded. The “early dip phenomenon”, the largest sequential inter-potential decrement between the first and second potential, is explicit in TPZ recording (y-axis: 5 mV/division, x-axis: 50 msec/division).

sensitivity for a diagnosis of neuromuscular junction disorder than CMAP amplitude decrements alone.

The initial LFS at the ADM revealed a significant decrease of > 10% in CMAP area (13.0%) but not CMAP amplitude (4.4%). For this reason, we decided to evaluate the proximal TPZ muscle because it is recommended to sample more number of muscles, especially clinically affected proximal muscles to eliminate the possibility of false negative results in repetitive nerve stimulation tests. We detected no signs of increased CMAP amplitude or area using HFS at the ADM or TPZ. LFS performed immediately after HFS revealed significant decreases in responses of > 10% at the 4th stimulus: 20.6% in CMAP amplitude and 29.2% in CMAP area at the ADM, and 40.2% in CMAP amplitude and 45.7% in CMAP area at the TPZ. Such decreases after HFS, known as “post-exercise exhaustion (PEE)”, are most prominent at approximately 2~4 minutes after HFS. This is a specific characteristic of myasthenia gravis. The highest decrements are 28.5% in CMAP amplitude at 3 minutes and 39.3% in CMAP area at 2 minutes after HFS for ADM (Fig. 1). For TPZ, decrements of 47.9% in CMAP amplitude and 55.0% in CMAP area at 2 minutes after HFS were maximally noted (Fig. 2). Thereafter, the decrements recovered again to 20.1% in CMAP amplitude, 33.0% in CMAP area at ADM, and 37.5% in CMAP amplitude, 51.6% in CMAP area at TPZ from the final LFS at 10 minutes after the HFS. Moreover, at each LFS after the HFS for both sampled muscles, CMAP amplitudes slightly increased again from the fifth stimulus to the end after the maximal decrement at the fourth stimulus, giving the final result to be in U-shapes. The early dip phenomenon is more noticeable in TPZ than in ADM (Fig. 2).

Therefore, the patient was finally diagnosed with post-synaptic neuromuscular junction disorder in that 1) normal CMAP with decrements > 10% from the initial LFS at TPZ, 2) post-exercise exhaustion which was maximum at 2~4 minutes after HFS, 3) early dip phenomenon with U-shapes in TPZ by acetylcholine depletion and following mobilization-related facilita-

tion from secondary quanta of acetylcholine vesicle, 4) reproducibility of decremental response at each LFS, and 5) absence of incremental response at HFS. Then, PMG was suspected clinically due to her rapid remission after the cessation of penicillamine.

Discussion

The clinical, serologic, and electroneuromyographic features of PMG are indistinguishable from idiopathic autoimmune MG.⁵ Therefore, PMG can be diagnosed by typical clinical signs of neuromuscular junction disorders including diurnal variations, elevated anti-acetylcholine receptor (AChR) antibody titer which is correlated with severity of symptoms, and its short temporal course and, most importantly, recovery of symptoms after discontinuation of penicillamine.⁶ PMG can be differentiated from penicillamine-induced myositis (either polymyositis or dermatomyositis) in that there is an effect of anticholinesterase and no obvious creatine kinase enzyme elevation. The duration of penicillamine administration before the onset of myasthenia gravis was varied from 2 days to 5 years with a mean of 8 months, and there was no correlation between duration of penicillamine administration and occurrence of myasthenia gravis from a previous report.⁴ The daily dosage of penicillamine also various from 250 to 1500 mg and there was no evident association between severity of symptoms and the cumulative dosage either.⁷ Our patient is also diagnosed with PMG because of its causal and temporal relationship between penicillamine administration and myasthenia, and the repetitive nerve stimulation result which indicates post-synaptic neuromuscular junction disorders.

In the literature review summarizing previously published case reports of PMG,⁷ only 9 out of 23 PMG patients revealed a decrement on repetitive stimulation of which the reason is not determined. One of the possible reasons is that repetitive stimulation in distal intrinsic hand muscles may be normal while decremental responses can be demonstrated only in proximal

muscles, so our case included TPZ recording as well as ADM. Moreover, serum anti-AchR antibodies have been lower and less frequently elevated than in patients with idiopathic MG.^{2,7,8} Such differences could reflect milder or more local symptoms in PMG compared with idiopathic MG, and clinicians should be cautious not to overlook trivial symptoms of patients taking penicillamine. Our patient also did not reveal any definite symptoms of myasthenia such as ptosis or diplopia but the only mild proximal weakness of grade 3 and difficulty with mastication. If PMG is suspected, therefore, penicillamine must be discontinued immediately and serum anti-AchR antibodies evaluation and anticholinesterase or steroid treatment should be followed even when there was not enough electrodiagnostic evidence of neuromuscular junction disorders.

Though pathophysiology of PMG is not yet clear, penicillamine may initiate drug-induced autoimmune dysregulation.⁹ PMG is more common in rheumatoid disease patients than in Wilson's disease and none has been reported in cystinuria.⁷ Anti-AchR antibody titers and reduced availability of AchRs, covalent bond between penicillamine and AchR resulting in antigen alteration, autoantibody formation, and abnormal T cells were all reported as supporting evidence for penicillamine effect on immunity.^{5,6,9,10} Therefore, a further study to delineate pathophysiology of PMG and how to block this autoimmune dysregulation will help to use penicillamine more safely without such neuromuscular complications.

In conclusion, both myasthenia gravis and myositis are possible in any penicillamine-taking patients with weakness, regardless of the duration or cumulative dosage of medication. Furthermore, repetitive nerve stimulation test of proximal muscle recording is always recommended despite lack of typical symptoms of

myasthenia, because ptosis or diplopia can be absent unlike idiopathic autoimmune MG. It is paramount to remember in mind that PMG must be always carefully differentiated, since it is easily treatable by the immediate discontinuation of penicillamine and administration of anticholinesterase, only if correctly diagnosed.

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