Multisystem involvement in Chinese patients with neuromyopathic phenotype of mitochondrial trifunctional protein deficiency

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Mitochondrial trifunctional protein (MTP) is a multienzyme complex, which catalyzes the last three steps of mitochondrial β-oxidation of the long-chain fatty acids. Structurally, MTP consists of four α-subunits and four β-subunits, which are encoded by *HADHA* gene (OMIM 600890) and *HADHB* gene (OMIM 143450), respectively. Mutations in *HADHA* or *HADHB* lead to varying degrees of decline in MTP activity, that in turn results in three types of clinical manifestations: a severe phenotype with neonatal onset, a hepatic phenotype with infantile onset, and a neuromyopathic phenotype with later onset.[1] The neuromyopathic type is the mildest one, characterized by myopathy, sensorimotor neuropathy, and recurrent rhabdomyolysis.[1,2] To the best of our knowledge, only 33 cases have been reported worldwide to date,[1,2] of which there were only two cases (including Patient 3 of this study) in China.[3] Here, we described three early-onset Chinese cases that not only showed neuromyopathy and rhabdomyolysis but also involved the central nervous system (CNS), which are uncommon in this phenotype.

Patient 1 and Patient 2 were sisters, born from non-consanguineous healthy parents. Patient 1 was a 13-year-old girl. Her early motor development milestones were slightly delayed. She was able to walk independently at the age of 21 months but always unwilling to walk. From the age of five, she presented with gait abnormalities and muscle weakness, which progressed gradually. When she was 10-year-old, she was referred to our clinic. Her past medical history included mild mental retardation and cataract. Although she had complained of blurred vision from the age of 5 years, she was diagnosed with cataract at 8 years of age and underwent bilateral intraocular lens implantation. Physical examination showed distal muscle weakness, tendon areflexia, and strephenopodia. Laboratory tests revealed a significantly elevated creatine kinase (CK) level (>8000 IU/L, reference range: 45–170 IU/L) and a moderately increased transaminase level. The parathyroid hormone (PTH) and serum electrolyte levels were normal. Routine blood acylcarnitines testing suggested a mild decrease in the free-carnitine level and a slight increase in the level of long-chain 3-hydroxy acylcarnitine species. The urine organic acid analysis was normal. A brain computed tomography scan revealed calcifications in the bilateral basal ganglia and subcortical white matter of the frontal and parietal lobes [Figure 1A]. According to the muscle weakness and tendon areflexia, motor unit diseases were suspected. The significant elevation of the CK level suggested the involvement of muscle. However, further electromyogram (EMG) showed high-amplitude and long-duration motor unit potentials, and nerve conduction velocity test indicated a reduced amplitude in the compound motor action potential, supporting a neurogenic injury. A muscle biopsy taken from the left biceps brachii muscle, found fiber type grouping and type 1 fiber pre-dominance, also implying peripheral neuropathy. Oil red O staining showed a mild increase in the number of fatty droplets, while no ragged red fibers or glycogen aggregates were observed [Figure 1B]. In terms of etiology, a genetic disease was suspected based on the chronic progressive course of the disease. Whole exome sequencing identified a homozygous known mutation c.1175C>T (p.A392V) in the *HADHB* gene [Supplementary Figure 1, http://links.lww.com/CM9/A220], which is reportedly pathogenic. Both her parents were carriers. The patient was finally diagnosed with the neuromyopathic phenotype of MTP deficiency and treated with a low dose of L-carnitine and a special diet that limits the intake of long-chain fatty acids and supplements with medium-chain fatty acids. During the follow-up, she presented with soy urine after a long walk at the age of 11 years, which was

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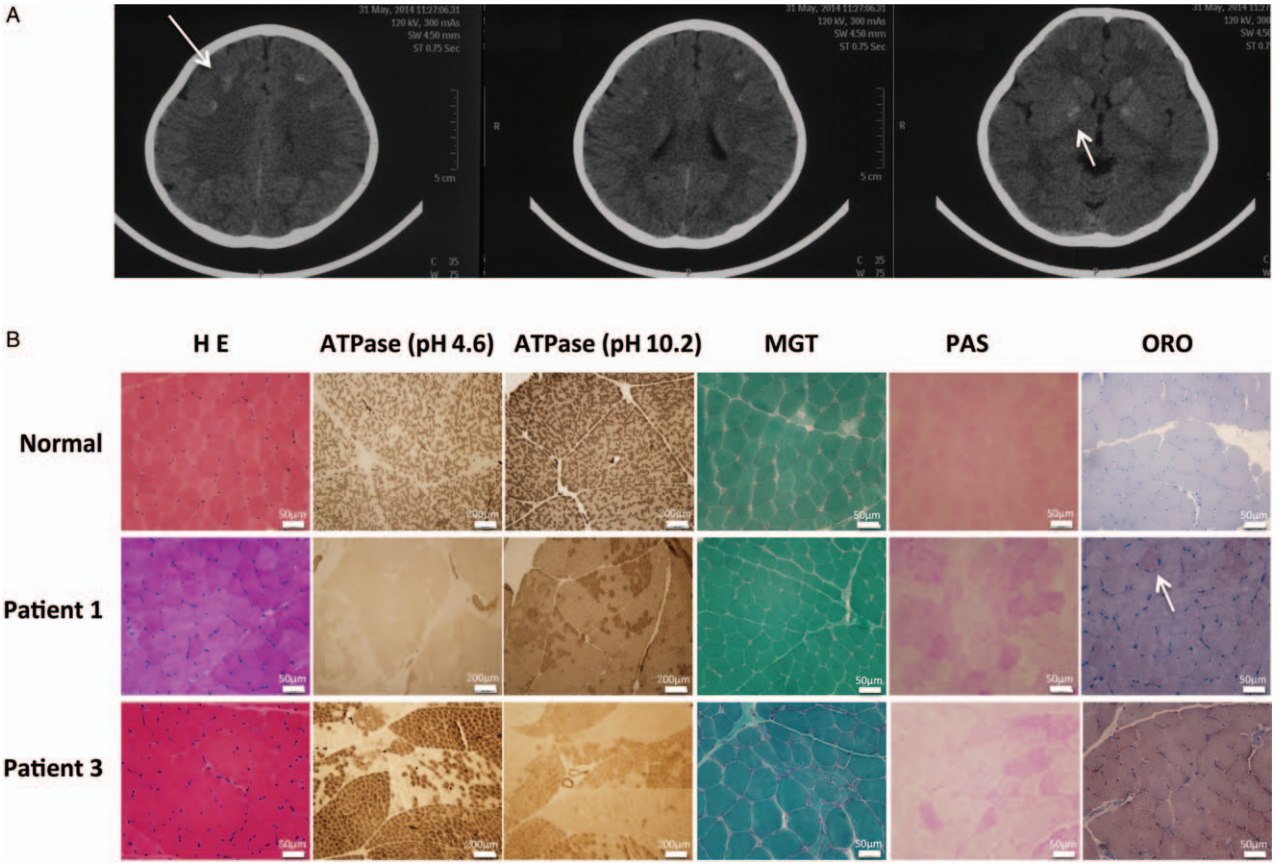

Figure 1: (A) The brain computed tomography scan of Patient 1 shows calcifications in the bilateral basal ganglia (arrow) and subcortical white matter (arrow). (B) Muscle pathology specimens of Patient 1 and Patient 3. Hematoxylin and eosin (HE) staining shows mild variation in muscle fiber size. Adenosine triphosphate diphosphohydrolase (ATPase) pH 4.6 and pH 10.2 staining shows fiber type grouping and type 1 fiber pre-dominance. Oil red O (ORO) staining indicates a mild increase in the number of fatty droplets (arrow). No ragged red fibers (RRF) or glycogen aggregates are detected in modified Gomori trichrome (MGT) and periodic acid Schiff reaction (PAS) staining.

considered rhabdomyolysis. But she did not experience rhabdomyolysis again.

Patient 2, the younger sister of Patient 1, had mild motor development delay and exercise intolerance since early childhood. When she was 4-year-old, she came to our hospital for the first time and showed very slight muscle weakness. The CK level was normal. Because she had symptoms similar to her sister, we performed Sanger sequencing of *HADHB* for her, which confirmed that she had the same c.1175C>T mutations as her sister [Supplementary Figure 1, http://links.lww.com/CM9/A220]. As her condition was relatively mild, her parents did not strictly follow our treatment recommendations. At the age of 5, she developed rhabdomyolysis and lethargy during a flu-induced high fever. On the way to the superior hospital, she suffered a cardiac arrest. Despite being successfully resuscitated, she fell into a coma and died 3 days later.

Patient 3 had previously been reported[3] with a homozygous missense mutation of c.739C>T (p.R247C) in *HADHB* [Supplementary Figure 1, http://links.lww.com/CM9/A220], and here we updated her recent conditions. As previously described, she developed the following symptoms in order from the age of three: progressive muscle weakness, infection-induced lethargy, exercise-induced muscle pain, and intermittent hyperCKemia. The results of the blood acylcarnitines analysis, EMG, and muscle biopsy were similar to Patient 1. At the age of eight, she was genetically diagnosed with the MTP deficiency in our hospital. At follow-up, she presented with myalgia and soy-colored urine after fever at the age of 11, which was diagnosed as rhabdomyolysis based on markedly elevated CK and myoglobinuria. After that, she developed rhabdomyolysis 1 to 3 times a year. Two months ago, she developed coma and respiratory failure during fever and needed non-invasive ventilation. She has gradually recovered recently and can withdraw from the ventilator. Her intelligence remains unaffected, but she has lost the ability to walk.

MTP, a multienzyme complex in the inner membrane of the mitochondria, catalyzes the last three steps of β-oxidation of the long-chain fatty acids.[1] When a patient with MTP deficiency encounters stress, such as fever or exercise, he or she was unable to utilize fatty acids to meet the additional energy requirements, resulting in organ dysfunction, especially in organs with high energy requirements.[1] As to the mildest, the neuromyopathic phenotype is characterized by the involvement of muscles and peripheral nerves.[2]

In this study, all three cases showed progressive muscle weakness and recurrent rhabdomyolysis. It should be noted from our cases that rhabdomyolysis often occurs late, as previously reported, but it can also occur earlier with poor prognosis. In addition to the above classic

manifestations, the cases in this study were complicated with CNS and eye manifestations. Patients 2 and 3 both experienced infection-induced lethargy, which has never been reported in the neuromyopathic phenotype but common in the neonatal phenotype.[1] As in other phenotype,[1] the lethargy may also be related to insufficient brain energy supply or the injury of the brain caused by abnormal metabolic substrates.

Despite the lack of lethargy, Patient 1 showed intracranial calcifications and cataracts, two rare complications of MTP deficiency. Hypoparathyroidism has been reported in three patients with MTP deficiency, which may explain calcifications and cataracts. But the levels of serum calcium, phosphorus, and PTH were all normal, so there was currently no evidence to support hypoparathyroidism. However, two Japanese siblings,[4] who harbored the same A392V mutation as patients 1–2, were reported to present with infantile-onset hypoparathyroidism and peripheral neuropathy. And their parathyroid function gradually approached normal range with age. Moreover, the adjacent *N389D* mutation was also reported to be associated with hypoparathyroidism, while the *F398L* mutation[5] was related to intracranial calcification, but not accompanied by hypoparathyroidism. So we speculate that mutations in this region of *HADHB* may lead to MTP deficiency with symptomatic or insidious hypoparathyroidism.

Besides, despite sharing the same gene, Patient 2 has a more severe clinical condition than Patient 1. By analyzing their clinical data, we consider that the poor prognosis of Patient 2 may be due to the severe infection and non-compliance with treatment.

In conclusion, here we describe multisystem involvement in three Chinese patients with neuromyopathic phenotype of MTP deficiency. In addition to the involvement of nerves and muscle, this phenotype also affects the CNS and possible parathyroid glands.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

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