A rare young case of Charcot-Marie-Tooth with stroke-like presentation and transient leukodystrophy

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Abstract: A 21-year-old male was diagnosed with leukodystrophy because of an acute-onset right-sided hemiparesis, dysarthria and a mild hyperintense T1 and T2-weighted in the white matter of brain MRI, without abnormal DSA study in the brain, even no vascular risk factors and any neuropathy were found. But two years later, the male suffered from progressive weakness in extremities, it was hard to explain the presentation by leukodystrophy. Finally, this case was corrected diagnosis of Charcot-Marie-Tooth (CMT) disease by the peripheral neurophysiologic test, the sural nerve biopsy, and gene detection.

Keywords: Leukodystrophy, charcot marie tooth, electrophysiology, gene detection

Case report

A previously healthy 21-year-old male was admitted to the hospital because of an acute episode of transient right hemiparesis and dysarthria. In the past 7 days, he experienced 3 consecutive episodes of transient right hemiparesis or right upper limb paralysis, accompanying by inarticulate speech. Each episode lasted for 1 to 2 hours, and then recovered fully. After the first episode, he was treated for cerebral ischemia, with little response. And 4 days after the last attack, an MRI of the brain demonstrated a mild hyperintense T1 and T2-weighted in the white matter of bilateral centrum ovale, genu and splenium region of corpus callosum (Figure 1A). On neurological examination, reduced limb tendon reflex and mild weakness with 4/5 proximal strength in distal muscle of limbs were found. In addition, we also found a mild high arches. The sensory examination was unremarkable. The peripheral neurophysiologic test showed slightly lower MCV in bilateral forearms, and neural latency was mild long in bilateral ulnar nerve and musculocutaneous nerve. Laboratory tests including thyroid function, cardiac enzymes, UCG, blood lactic acid, and the cerebrospinal fluid examination, were all normal. Given his age and white matter changes, leukodystrophy was strongly considered. Leukodystrophy is a group of disorders characterized by degeneration of the white matter in the brain, and peripheral nerve may also be involved. Alternative potential diagnoses included TIA, vasculitis, or mitochondrial encephalomyopathy (ME). However, a DSA study did not detect any abnormalities in the brain. The patient’s parents denied any neuropathy, and no vascular risk factors were found.

Two years later, the male was admitted again because of progressive weakness in extremities. This time, brain MRI did not show any abnormalities (Figure 1B). Therefore, it is hard to explain the presentation by leukodystrophy. Upon further questioning, he said that the limbs’ strength was weaker than his contemporary since he was 12 years old. As this condition did not influence his daily life, his parents did not care about it. On physical inspection, we found the both lower legs were much thinner than they were two years before. Meanwhile, muscle atrophy and disappeared tendon reflex were found in limbs. The investigation was refocused due to these findings. The electrophysiological detection showed a decreased conduction velocity and prolonged latency in bilateral median nerve. Muscle biopsy (gastrocnemius) revealed a typical nervine myatrophy, and
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Figure 1. Brain MRI displayed (A) a mild hyperintense T1 & T2 weighted in the white matter of bilateral centrum ovale, genu and splenium region of corpus callosum, (B) but no abnormalities were shown 2 years later.

Figure 2. Muscle biopsy (gastrocnemius) revealed a typical nerve myatrophy, and severe demyelination was confirmed by sural nerve biopsy.
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severe demyelination was confirmed by sural nerve biopsy (Figure 2). To rule out the possibility of inherited diseases, physical examinations were also performed on his parents. Encouragingly, the high arches and abnormal neural atrophy were found in his mother.

We prefer the diagnosis of CMTX1 (X-linked Charcot-Marie-Tooth disease, type 1), the most common form of CMTX which is caused by mutations in the connexin 32 gene (or GJB1), which codes for the connexin 32 protein, a gap junction protein widely expressed in Schwann cells as well as oligodendrocytes [1, 2]. It has been supposed that the involvement of central nervous system in CMTX1 is likely related to the expression of Cx32 in oligodendrocytes in the CNS and Schwann cells in the peripheral nervous system [3, 4]. Accordingly, PCR analysis of connexin 32 gene was conducted. Unexpectedly, we did not find any mutation in this gene. In addition to CMTX1, there are also some previous reports, although not too much, that CMT1A can also present central symptoms [5-7], and duplication of PMP22 gene was considered to be involved in it. Therefore, PMP22 gene was sequenced to detect potential changes in it. Unfortunately, our result indicated that PMP22 gene was normal. Although there was no any proof of gene detection, according to the male’s age, clinical symptom and sign, electrophysiology and sural nerve biopsy, the diagnosis of CMT was appropriate, furthermore, other possible pathogenic gene locus need to be found.

Discussion

CMT is the most common inherited neuropathy characterized by distal limb weakness and atrophy, sensory loss, and decreased or absent tendon reflexes. Despite the fact that the main symptoms of CMT involve the peripheral nervous system, CNS involvement either in the form of clinical symptoms or magnetic resonance imaging (MRI) white matter lesions has been occasionally reported, mainly for the X-linked type of CMT [8, 9], and a minority of cases for CMT1A have also been reported [10]. For this male, transient neurological dysfunction and white matter changes that are atypical for leukodystrophies, plus the electrophysiologic evidence of myelin dysfunction and axonal damage all support the diagnosis of CMT. Interestingly, we failed to find any changes in connexin 32 gene and PMP22 gene, which are responsible for CMTX1 and CMT1A respectively. Hence, we hypothesized that, in addition to common types of CMT-CMTX1 and CMT1A, similar CNS presentation may also occurred in other uncommon or unknown CMTs. Therefore, further studies are needed to determine. Above all, for such cases, if there is no family history of detailed inquiry, long-term follow-up, may appear missed and delayed diagnosis, it’s a warning for our clinic scientists.

Disclosure of conflict of interest

None.

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