Clinical Reasoning: A young man with reversible paralysis, cerebral white matter lesions, and peripheral neuropathy

Le Zhong, MD*
Kai Yan, BS*
Chentao Liu, MD
Jinjie Xue, MS
Lingqian Wu, MD, PhD
Fei Yin, MD

Correspondence & reprint
requests to Dr. Wu:
wulingqian@sklmg.edu.cn
or Dr. Yin:
yf2323@hotmail.com

SECTION 1

A 17-year-old boy experienced 3 consecutive episodes of transient tetraplegia or monoparesis over the course of 5 days, after a week of low-grade fever. He was alert but had dysarthria and diplopia during the attacks. The paresis persisted for 5 to 7 hours and resolved completely.

Three years prior, he had presented with a 1-day episode of transient right hemiparesis and dysarthria, and recovered completely without any treatment. At that time, cerebral MRI showed bilateral symmetric confluent hyperintense lesions in the parieto-occipital region and splenium and genu of the corpus callosum on T2-weighted images (figure). Three months later, these MRI abnormalities were markedly reduced (figure).

for these symptoms. The patient's mother denied any neuropathy.

On examination, no abnormalities were found in his upper and lower limbs. The results of motor examination, including strength, tone, posture, involuntary movements, and reflexes, were normal. The sensory examination was unremarkable. Cerebral MRI showed white matter lesions in approximately the same distribution as on the MRI performed 3 years prior, but increased in severity (figure). These lesions spared the subcortical U-fibers and did not enhance.

EMG performed 1 week after the onset showed prolonged distal motor latencies (median 10.6, ulnar 8.7 [ms, normal value <3.2 ms], tibial 20.6, peroneal 19.2 [ms, normal value <3.0 ms]) and marked uniform and symmetric slowing of conduction velocities (median 40.4, ulnar 36.8 [m/s, normal value >40 m/s], tibial 25.1, peroneal 30.5 [m/s, normal value >45 m/s]), with reduced amplitude of the distal compound muscle action potentials (median 4.0, ulnar 4.0 [mV, normal value >3 mV], tibial 0.72, peroneal 0.19 [mV, normal value >5.0 mV]) and sensory nerve action potentials (median 6.3 μ V [normal value >15 μ V], ulnar 6.2 μ V [normal value >15 μ V], sural no response). The sensory potential of the right sural nerve was not detected. These abnormalities suggested both myelin dysfunction and axonal damage. Laboratory tests, including electrolytes, lactate, and CSF, were all normal. Aortocranial angiography and EEG were normal.

Figure Brain MRI

Episode 1: transverse T2-weighted brain MRI shows confluent hyperintense lesions in the temporal-occipital region and splenium and genu of the corpus callosum (A). (B) Hypointensity in the same regions, evidence of reduced diffusion. Episode 2: (C) recurrent T2 signal abnormality in similar regions to episode 1.

Family history is significant for a maternal grandfather with progressive claudication since his 30s. He is 65 years old now, has amyotrophy in the lower limbs, but still can walk. He never received a diagnosis

Questions for consideration:

1. What is the differential diagnosis?
2. Virtually all categories of pathology may cause white matter lesions. Does the imaging appearance limit the differential diagnosis?

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*These authors contributed equally to this work.

From the Department of Pediatrics, Xiangya Hospital (L.Z., C.L., F.Y.), and State Key Laboratory of Medical Genetics (K.Y., J.X., L.W.), Central South University, Changsha, China.

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SECTION 2

The clinical features of this patient included cerebral white matter lesions, recurrent paralysis, and peripheral neuropathy. As the patient had confluent cerebral white matter lesions, acute disseminated encephalomyelitis (ADEM) and adrenoleukodystrophy were considered. ADEM is a demyelinating disease that is thought to be of autoimmune origin. It usually occurs after a recent infectious prodrome.¹ Cerebral white matter and periphery nerves may both be involved in ADEM.² However, the lesions in cerebral white matter are usually asymmetric with spotty enhancement. The clinical picture is one of abrupt onset with a monophasic course. Relapse or recurrent phase may occur 3 months after the first attack,³ but cannot occur within several days, as seen in this patient.

Symmetric lesions in cerebral white matter are usually caused by drugs, toxins, or inherited disease. Adrenoleukodystrophy is an inherited metabolic disorder caused by a defect in the metabolism of myelin proteolipids. The peripheral nervous system can be involved along with the CNS. The MRI abnormalities are characterized by symmetric massive involvement of the white matter in the parieto-occipital and temporo-occipital lobes. The splenium of the corpus callosum can be involved at an early stage, but the genu is usually spared. Sites of active demyelination along the advancing edges may be associated with blood–brain barrier disruption and enhance with contrast. The course of adrenoleukodystrophy is progressive. Complete recovery has not been reported.

Reversible paralysis may be seen in patients with periodic paralysis, alternating hemiplegia, Todd paralysis, moyamoya disease, mitochondrial encephalo-

pathy with lactic acidosis and strokelike spells, and familial hemiplegic migraine. However, clinical and examination findings in this patient were incompatible with the diagnosis of these diseases.

Some demyelinating peripheral neuropathies can induce cerebral demyelination, such as Guillain-Barré syndrome or hereditary motor sensory neuropathy. Guillain-Barré syndrome can also simultaneously or sequentially be accompanied by cerebral demyelination.⁴ Paralysis usually lasts over 4 weeks and EMG abnormalities appear 10 days after the attack. This patient's paralysis only lasted several hours, and EMG abnormalities presented only 8 days after the attacks, findings which were inconsistent with the diagnosis of Guillain-Barré syndrome.

Charcot-Marie-Tooth disease (CMT) denotes a group of hereditary motor sensory neuropathy that differ relatively little by phenotype. On the basis of electrophysiologic properties and histopathology, CMT has been divided into primary peripheral demyelinating (type 1) and primary peripheral axonal (type 2) neuropathies. X-linked Charcot-Marie-Tooth disease (CMTX) has both demyelinating and axonal features.⁵ As an X-linked disorder, males are more severely affected than females.

Among the group of CMT diseases, CMTX1 can usually involve the CNS.⁶ Although CNS symptoms are subclinical in most patients, some case reports have described patients with CMTX1 who presented with recurrent paralysis and reversible cerebral white matter lesions.^{7–10}

Questions for consideration:

1. What is the most likely diagnosis?
2. What test can be ordered to confirm the diagnosis?

GO TO SECTION 3

SECTION 3

A diagnosis of CMTX1 was suspected for the following 3 reasons. First, the electrophysiologic features were consistent with those of CMTX1. Second, recurrent paralysis and reversible cerebral white matter lesions have been reported in patients with CMTX1. Finally, the patient's maternal grandfather's claudication and amyotrophy in the lower limbs can be symptoms consistent with CMT. An affected male and spared female in this family may suggest an X-linked disease.

CMTX1 is caused by mutations in *GJB1*, the gene encoding connexin32, which forms gap junctions in noncompact myelin. In the setting of metabolic stress such as fever or infection, it is likely that reduced or disrupted functioning gaps between oligodendrocytes and astrocytes leads to a temporary inability of these cells to regulate intracellular fluid exchange, resulting in transient paralysis and cerebral white matter lesions. In this patient, analysis of the connexin 32 gene was performed and revealed a missense mutation (Asn 54 Ser). This mutation had not been reported previously. Genetic analysis performed on the mother and maternal grandfather showed the same mutation. Two months after the last episode, the cerebral MRI showed markedly reduced abnormalities in the white matter. The EMG abnormalities remain mostly unchanged.

DISCUSSION The most notable clinical characteristics of this patient were recurrent paralysis and cerebral white matter lesions, which were atypical features of CMTX1, and might be confused with ADEM.^{7,8} Typical manifestations of CMTX1, such as claudication or weakness in the lower limbs, were not exhibited in this patient. As the patient's maternal grandfather was an undiagnosed patient and his mother had no symptoms, the only clue to the diagnosis was the EMG abnormalities. This case suggests that when the diagnosis is questionable, careful clinical characteristic analysis and literature review may help us find the necessary clues to the correct diagnosis.

AUTHOR CONTRIBUTIONS

All authors participated in developing the study concept and analysis/interpretation of data. Dr. Zhong drafted/revised the manuscript. Dr. Yin and Dr. Wu supervised the study.

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