Clinical Reasoning: A 50-Year-Old Man With Progressive Limb Weakness and Slurred Speech

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Abstract

A 50-year-old man presented with a 9-month history of progressive left arm weakness and dysarthria. Family history showed that his parents are cousins, and one of his siblings died of motor neuron disease. Brain MRI showed T2-weighted white matter hyperintensities along the course of pyramidal tracts. Neurologic examination and EMG revealed upper and lower motor neuron signs involving the bulbar, cervical, thoracic, and lumbosacral segments, which meets the criteria of a definite amyotrophic lateral sclerosis (ALS), according to the revised EI Escorial criteria. Whole-exome genetic sequencing found 2 novel *LYST* missense variations, confirming the diagnosis of Chediak-Higashi syndrome (CHS), a rare autosomal recessive hematologic disorder. Our case indicates that CHS can present as ALS phenotype, and the *LYST* might be a novel causative gene for ALS.

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Video

Section 1

A 50-year-old man with progressive left arm weakness was referred for evaluation. He had been well until 9 months previously when he first noticed that the left hand was not as flexible as usual. Gradually he had difficulty lifting heavy things. Seven months ago, his speech also became slurred. No other symptoms were reported. Six months ago, he was referred to us. His medical history was unremarkable. Toxin exposure and substance abuse were denied. His parents are cousins. Neither of them has similar symptoms. One of his siblings was clinically diagnosed with motor neuron disease and died at the age of 37 years.

On neurologic examination, he was alert, oriented, and slightly dysarthric. The Mini-Mental State Examination score was 27. Cranial nerve tests revealed central facial palsy, lingual palsy, and tongue fasciculations (Video 1). The left arm strength was rated 4/5 both proximally and distally, with increased muscle tone and brisk deep tendon reflexes. The strength of other limbs was rated 5/5. Hoffman and Babinski signs were present bilaterally. Sensation, coordination, and gait were normal. General examinations for skin, heart, lung, and abdomen were unremarkable.

Questions for Consideration:

1. Where would you localize the lesion?
2. What would be your initial laboratory workup?

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Section 2

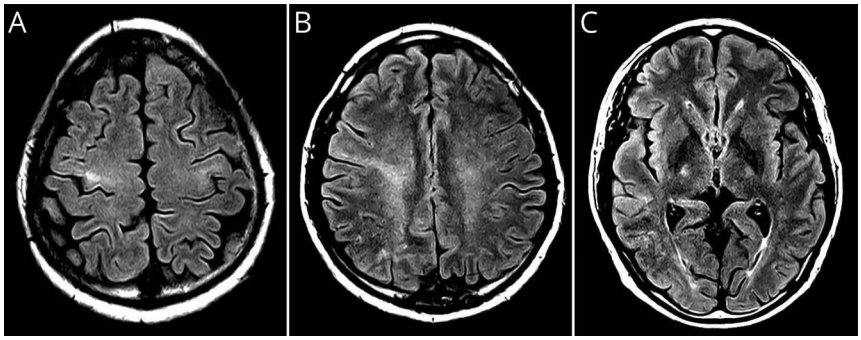
Central facial palsy, lingual palsy, left arm weakness with increased muscle tone and hyperreflexia, and the presence of pathologic reflexes suggest upper motor neuron (UMN) damage involving the bulbar, cervical, and lumbosacral segments. The tongue fasciculations indicate lower motor neuron (LMN) damage in the bulbar segment. Given the presence of both upper and lower motor neuron signs, motor neuron disease and its mimics are suspected. The differential diagnosis is extensive, including amyotrophic lateral sclerosis (ALS), ALS frontotemporal dementia (ALS-FTD), infection, metabolic abnormality, paraneoplastic syndromes, and hereditary disorders. Therefore, initial laboratory workup should include routine screenings for these etiologies, as well as nerve conduction studies/electromyography (NCS/EMG) and cerebrospinal MRI.

The following investigations were unremarkable or negative: complete blood count, urine and stool analysis, liver and renal function, cardiac enzymes, electrolytes, blood glucose, lipids, coagulation, thyroid function, homocysteine, vitamins, serum tumor markers, paraneoplastic antibodies (anti-Hu, Yo, Ri, Ma2/Ta, CV2/CRMP5, and amphiphysin), infectious panel (tuberculosis, hepatitis, HIV, Lyme, and syphilis), urine and serum protein electrophoresis, very-long-chain fatty acids (VLCFA), and electrocardiogram. Brain MRI showed symmetric T2-hyperintense signals along the course of pyramidal tracts (Figure 1). Cervical spinal MRI and chest-abdomen-pelvis CT were normal, as was the initial NCS/EMG result performed 3 months after onset.

Question for Consideration:

1. What differential diagnosis would you consider at this stage?

Figure 1 Brain MRI



(A–C) FLAIR images showing symmetric hyperintense signals along the course of pyramidal tracts.

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Section 3

According to the revised EI Escorial criteria, this patient has upper motor neuron and lower motor neuron signs in 1 region and UMN signs in 3 regions, suggesting a possible ALS.[1] The MRI findings also support this diagnosis. However, it is uncommon that the NCS/EMG test did not show any signs of neurogenic impairment. Alternative diagnosis needs to be considered. The absence of cognitive decline excludes ALS-FTD. Infectious causes such as Lyme disease, HIV, and syphilitic amyotrophy and metabolic disorders such as vitamin B-12 deficiency and hyperthyroidism were also ruled out by the negative blood tests and history. The normal serum tumor markers, negative paraneoplastic antibodies, absence of M protein, and normal chest-abdomen-pelvis CT argue against a paraneoplastic syndrome. Given the positive family history, a hereditary neurodegenerative disorder is the most likely diagnosis at this stage. Several possibilities are discussed below.

Adrenomyeloneuropathy (AMN) is a variant of adrenoleukodystrophy. It is caused by variations in the *ABCD1* gene and has an X-linked recessive mode of inheritance. Typical onset age is in the late twenties. AMN can present as mixed UMN and LMN signs by causing myelopathy and peripheral neuropathy, with or without adrenal insufficiency. Less frequently, brain MRI can show cerebral demyelination. In patients with milder phenotypes, VLCFA levels can be normal.[2,3] However, the onset age and absence of myelopathy and peripheral neuropathy in this patient make AMN less likely. Moreover, lingual palsy is very uncommon for AMN.

Spinocerebellar ataxia 3 (SCA3) is caused by the CAG repeat expansion variations in the *ATXN3* gene. It can cause spasticity and tongue fasciculations in patients with early-onset age. However, most SCA3 is autosomal dominantly inherited. Had SCA3 been the diagnosis, at least one of the parents should be symptomatic.[4] Besides, there is no ataxia in this patient.

Adult hexosaminidase deficiency is caused by variations in the *HEXA* gene and inherited in an autosomal recessive pattern. It is easily mistaken for ALS in the early stages because neurologic symptoms such as spasticity, progressive muscle weakness, and dysarthria are often the initial manifestations. However, adult hexosaminidase deficiency is more commonly seen in Ashkenazi Jewish, Celtic, and French-Canadian populations. NCS/EMG can detect signs of chronic anterior horn cell neuropathy.[5] This patient is of Asian descent and has normal NCS/EMG results.

Another autosomal recessive disorder that can cause UMN signs, LMN signs, and diffuse T2-weighted white matter hyperintensities is adult polyglucosan body disease (APBD). It is caused by variations in the *GBE1* gene. Mutant GBE, a glycogen-branching enzyme, leads to the accumulation of misfolded glycogens, that is, the polyglucosan bodies, in various tissues including muscles, peripheral nervous system, and CNS. The observation of periodic acid-Schiff-positive polyglucosan bodies on skin or peripheral nerve biopsy is pathognomonic.[6] However, the most common initial sign of APBD is urinary incontinence, which is not reported in this patient.

Question for Consideration:

1. What would you do next to clarify the diagnosis?

GO TO SECTION 4

Section 4

Although the possibility of diseases discussed above was relatively low, they still cannot be excluded. Genetic testing is warranted. Whole-exome genetic sequencing revealed compound heterozygous missense variations (Exon 3: p.Val24Ala; Exon 21: p.Arg1986Gln) in the patient's *LYST* gene, which have not been reported previously. His parents are mutation carriers (Figure 2). The diagnosis of Chediak-Higashi syndrome (CHS) was established. We further examined his peripheral blood smear. No giant cytoplasmic granules were observed in leukocytes. During the 6-month follow-up, he developed bucking when drinking water. The left limb weakness and dysarthria were not improved. Palmomental reflexes appeared bilaterally. Repeat needle EMG performed 9 months after onset indicated acute and chronic neurogenic impairment involving the bulbar, cervical, thoracic, and lumbosacral segments (eTable 1). Nerve conduction studies were normal. The EMG results and physical signs together suggest a definite ALS.[1]

Discussion

CHS is a rare autosomal recessive disorder caused by variations in the *LYST* gene. LYST is a lysosomal trafficking regulator. Variant LYST causes lysosomal dysfunction, leading to aberrant organellar protein trafficking and incompetent immunocytes. Genotypes of CHS are highly diverse. Loss-of-function and missense variations correlate with typical and atypical CHS, respectively.[7] The typical form is characterized by immunodeficiency, oculocutaneous albinism, coagulation defects, a high risk of developing hemophagocytic lymphohistiocytosis (HLH), and the presence of giant cytoplasmic granules in leukocytes. Patients usually die in the first decade without allogeneic hematopoietic cell transplantation (HCT).

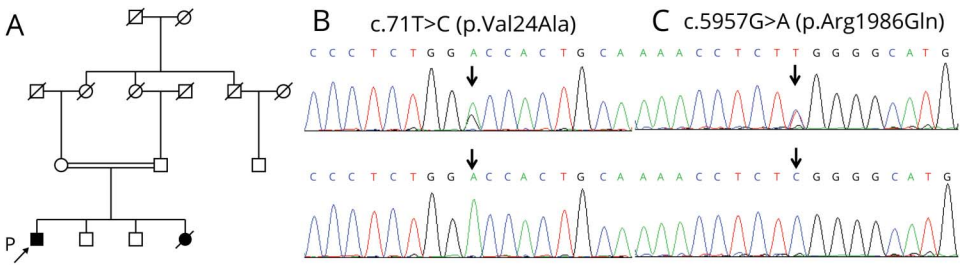
By contrast, patients with atypical CHS survive into adulthood and manifest as progressive neurodegeneration, including parkinsonism, ataxia, peripheral neuropathy, and cognitive decline. EEG may detect epileptiform discharges. Brain MRI may show cerebral atrophy. Symptomatic treatments are the mainstay option. Although patients with atypical CHS escape the life-threatening complications in childhood, they are still at the risk of developing HLH by suddenly entering an accelerated phase. The outcome will be fatal without timely HCT. However, early diagnosis of atypical CHS is challenging because of the absence of hematologic presentations.[8,9] Family history provides critical diagnostic clues.

Our case described an atypical CHS patient with an ALS phenotype. To the best of our knowledge, this was first reported in CHS. To confirm the diagnosis, gene analysis found 2 novel *LYST* missense variations. As aforementioned, *LYST* regulates lysosome functions. The autophagy-endosome-lysosomal system plays a critical role in ALS pathogenesis. Several genes involved in the endolysosomal pathway, including *CHMP2B*, *VCP*, and *ALS2*, have proved to be associated with a risk of ALS.[10-12] Moreover, using the cDNA array and RT-PCR method, Daniel Offen et al.[13] reported that the *LYST* mRNA level is markedly increased in the postmortem spinal cord specimens of 4 sporadic patients with ALS compared with controls. These findings together with our case indicate that the *LYST* gene may be associated with ALS.

Notably, the giant cytoplasmic granules in leukocytes, formed by dysregulated lysosomes and vesicles, are thought to be a pathognomonic feature for CHS. However, they are not present in our patient's blood smear, although Wendy J. Introne et al. observed these granules in leukocytes of patients with atypical CHS.[9] Given the absence of giant cytoplasmic granules and the lack of strong experimental data on the pathophysiologic role of LYST in human motor neurons, the co-occurrence of ALS phenotype and LYST in our patient may be coincidental. To clarify whether there is a true causative relationship between them, *LYST* sequencing should be considered in patients with ALS and more functional studies are needed. These data will be beneficial not only for understanding the pathophysiology of congenital immunodeficiency but also for ALS.

In summary, we reported a rare CHS case presenting as ALS. Our findings expanded the clinical phenotypes of CHS and implicated that *LYST* might be a novel causative gene for ALS.

Figure 2 Pedigree and Sequencing Results



(A) His parents are variations carriers. A sibling died of motor neuron disease. (B-C) Sequence chromatogram showing the 2 novel compound heterozygous variations (Exon 3: p.Val24Ala; Exon 21: p.Arg1986Gln) in the patient's *LYST* gene.

Ethics Approval

Written consent form was obtained from the patient. This study was approved by the Medical Ethics Committee of Central South University.

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