

Clinical Reasoning: A 14-Year-Old Girl With Reversible Peripheral Neuropathy and Encephalopathy

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Abstract

A 14-year-old girl presented with acute ascending, symmetric numbness, and flaccid paralysis 3 weeks after a suspected gastrointestinal infection. She had experienced anorexia since this gastrointestinal episode. EMG showed a sensorimotor axonal polyneuropathy. Routine CSF analysis and serum-specific antibodies (antiganglioside and node of Ranvier-associated antibodies) were all negative. Laboratory investigations for possible etiologies revealed only mild metabolic perturbations. During her hospitalization, she developed mild cognitive deficits. Brain MRI showed bilateral symmetric basal ganglia lesions with hyperintensity on T2 fluid-attenuated inversion recovery, diffusion-weighted imaging hyperintensity, and corresponding apparent diffusion coefficient hypointensity, but without contrast enhancement. A more thorough and detailed history indicated exercise intolerance, and specific examinations subsequently revealed an underlying etiology. This case presentation discusses specific etiology of an acute-onset diffuse and symmetric neuropathy after an acquired injury in a teenager, emphasizing the need of a broad differential diagnosis in this condition.

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Section 1

A 14-year-old girl was admitted to our neurology department because of a 10-day history of limb weakness and numbness. Initially, she presented with acute-onset symmetric weakness and numbness in the distal upper and lower extremities within several hours. The symptoms progressed to the proximal limbs and peaked within 1 week. Six days before admission, she also developed bulbar symptoms, characterized by hoarseness, dysphagia, and choking cough while drinking water. Three weeks before onset, the girl complained of abdominal pain, severe vomiting, and diarrhea after eating left-over food placed at room temperature overnight. Digestive symptoms improved after combination therapy with levofloxacin, metoclopramide, and montmorillonite, but anorexia

remained. She denied an exposure history to other medications, heavy metals, pesticides, toxicants, and radiation.

At the time of her neurologic examination, she was alert and oriented with intact attention and memory. Gag reflexes were bilaterally diminished. She exhibited reduced superficial and proprioceptive sensations in a stocking-glove pattern, 1/5 muscle strength in her distal extremities, and 2/5 muscle strength in her proximal extremities. Deep tendon reflexes were absent, and Babinski signs were not elicited.

Questions for Consideration:

1. What is the differential diagnosis?
2. What investigations should be ordered to narrow the differential diagnosis?

GO TO SECTION 2

Section 2

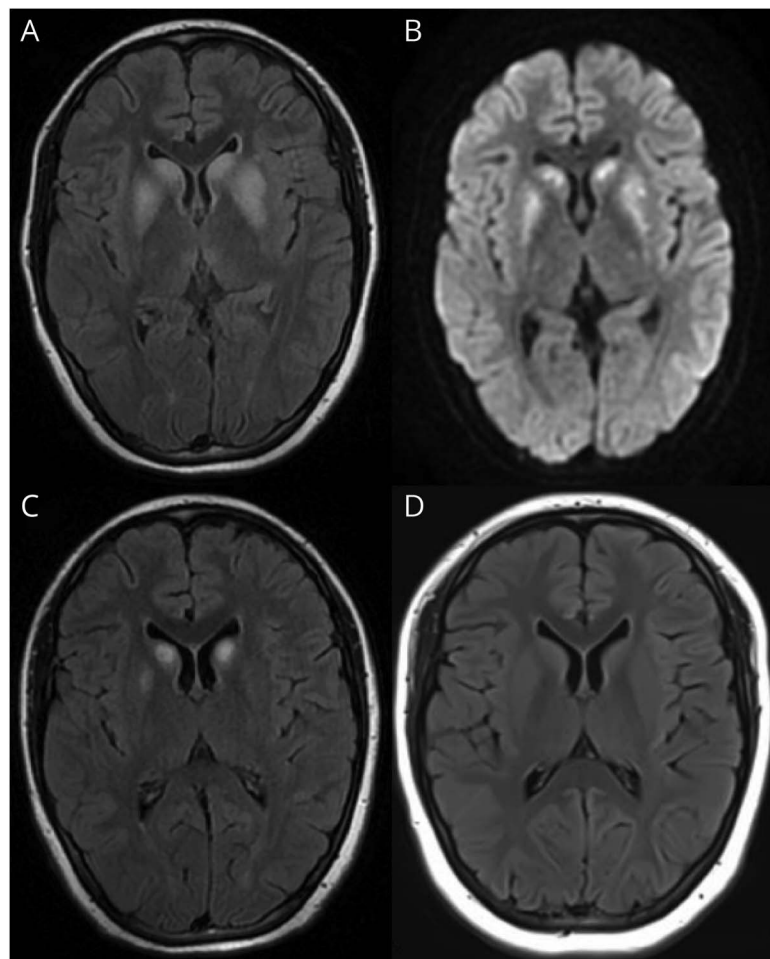
Symmetric sensory disturbance in the distal limbs (stocking-glove hypesthesia) and lower motor neuron paralysis (flaccid quadriparesis and bulbar palsy) are typical manifestations of polyneuropathy localized to the peripheral nervous system. Given the clinical course of acute onset and rapid progression, the etiology was considered to be acquired. Differential diagnoses included infectious or autoimmune-mediated inflammatory diseases (Guillain-Barré syndrome [GBS] would be a primary consideration based on suspected prodromal infection by *Campylobacter jejuni*), metabolic disturbances (such as vitamin B12 deficiency peripheral neuropathy due to inadequate intake), intoxication (limited by the lack of corresponding exposure history), and paraneoplastic syndromes (less likely possibility as she was a previously healthy adolescent).

Routine screenings for these etiologies revealed hyperhomocysteinemia (27.4 $\mu\text{mol/L}$, reference range of 5–15 $\mu\text{mol/L}$), hyperlactatemia (2.7 mmol/L, reference range of 0.5–1.7 mmol/L), and hypokalemia (3.2 mmol/L, reference range of 3.5–5.5 mmol/L). Results from other

examinations, including routine blood tests, serum biochemistry, inflammatory indicators, thyroid function, antinuclear antibody spectrum, antinuclear cytoplasmic antibodies, anticyclic citrullinated peptide antibody, rheumatoid factor, vitamin detection, trace element test, ceruloplasmin, heavy metal analysis, tumor markers, ECG, pulmonary CT, and abdominal ultrasound, were in the normal ranges. EMG evaluations indicated widespread denervation, consistent with axonal sensory and motor neuropathy (eTable 1, links.lww.com/WNL/C758). Lumbar puncture was performed on the third day of hospitalization (at 2 weeks from onset). CSF analysis showed a pressure of 4.4 mm Hg (reference range of 5.1–13.2 mm Hg); $0 \times 10^6/\text{L}$ and $2 \times 10^6/\text{L}$ white and red blood cell counts, respectively; 0.25 g/L (reference range of 0.15–0.45 g/L) protein; 3.87 mmol/L (reference range of 2.5–4.5 mmol/L) glucose; and normal immunoglobulin levels. In addition, antiganglioside and node of Ranvier-associated serum antibody tests were negative.

During her hospitalization, we observed mildly impaired short-term memory and slightly prolonged reaction times in the patient compared with that noted at admission.

Figure 1 Brain MRI Images



(A, B) Brain images on T2-FLAIR and DWI at onset. Brain images on T2-FLAIR after (C) 1 month and (D) 1 year of riboflavin treatment. DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery.

Subsequent cognitive assessment revealed mild impairments in attention, calculations, and memory domains, and evaluations in language and executive function domains were not available because of dysarthria and limb weakness. Cognitive impairment suggested cerebral dysfunction; therefore, cerebral MRI was performed. Symmetric lesions in the bilateral basal ganglia were noted with hyperintensity on T2 fluid-attenuated inversion recovery, diffusion-weighted imaging

(DWI) hyperintensity, corresponding apparent diffusion coefficient hypointensity, and no contrast enhancement (Figure 1, A and B).

Questions for Consideration:

1. How does your differential diagnosis change at this point?
2. What medical history should be specifically focused on according to the present considerations?

GO TO SECTION 3

Section 3

Acute ascending flaccid paralysis, cognitive impairment, and corresponding EMG and MRI findings suggested broad and symmetrical neurologic involvement, including CNS and peripheral nervous system involvement. The temporal relation of these 2 symptoms led us to favor the same etiology. Poisoning and paraneoplastic syndrome were excluded based on negative exposure history and screening tests. GBS combined with CNS demyelination might represent a relatively plausible inflammatory cause for extensive neuropathy despite its rare occurrence.¹ However, the patient lacked CSF albumin-cytologic dissociation and antiganglioside or anti-Ranvier's node antibodies, specific characteristics strongly supporting the diagnosis of GBS.² In addition, basal ganglia demyelination is uncommon and rarely exclusively presents as bilateral symmetric lesions.³ This acute-onset presentation is more indicative of toxic, metabolic, hypoxic-ischemic, vascular, or infectious encephalopathy.^{3,4}

At this time, we felt that metabolic dysfunction was the most likely etiology. Similar to the findings in our patient, it can

cause symmetric central and peripheral lesions because axons and the basal ganglia are both highly sensitive to these changes.^{5,6} In addition, the trigger of inadequate nutritional intake leading to derangements in serum metabolites suggested the presence of a metabolic disorder in the patient. Nevertheless, the altered levels of metabolites detected seemed inconsistent with the clinical severity of neuropathy. For an adolescent, significant alternations of an underlying metabolic factor may be implicated when other factors showed no or insignificant changes under the same circumstances. The alterations in this factor together with unexplained hyperlactatemia suggested a congenital defect.

To further prove this notion, we again evaluated the family history and medical history in more detail. The patient grew and developed relatively normally, reporting only easy fatigability and poor motor performance that revealed potential signs of exercise intolerance.

Question for Consideration:

1. What would you do next in terms of diagnosis and treatment?

GO TO SECTION 4

Section 4

The finding of exercise intolerance supported the possibility of an inherited metabolic disease. Accordingly, muscle biopsy and genetic testing were performed. The muscle biopsy indicated increased mitochondria in some subsarcolemmal regions (Figure 2). The pathologic changes together with exercise intolerance most likely pointed to a mitochondrial disorder, although the pathologic levels of typical ragged red and blue fibers were not observed. Whole-exome sequencing revealed that the patient carried compound heterozygous variants in trans in the *ACAD9* gene, c.943C>T (p.L315F) and c.1297C>T (p.R433W), which were confirmed to be respectively inherited from the healthy parents through Sanger sequencing, but the mitochondrial genome did not harbor any abnormalities. These missense variants not previously reported were predicted as damaging by multiple protein function prediction software and classified as variants of undetermined significance according to the American College of Medical Genetics and Genomics guidelines.⁷ Subsequent functional tests revealed significantly decreased complex I activity in the patient by comparing the changes in OD 450 nm and mOD/min observed in the muscles of the patient and healthy control over time, which supported the pathogenicity of these variations (eFigure 1, [links.lww.com/WNL/C757](https://www.lww.com/WNL/C757)).

Normal cardiac ultrasound excluded myocardial involvement. Riboflavin (20 mg/kg/d) was recommended for treatment.⁸ After a 1-month course, her muscle strength returned to approximately 3/5, and she was able to walk independently. MRI reexamination showed smaller lesions, consistent with improved memory (Figure 1C). After 1 year of follow-up, her symptoms, including extremity numbness and weakness, impaired cognitive function, and intracranial lesions, almost completely resolved (Figure 1D), whereas exercise endurance worsened more than that noted preonset.

Discussion

ACAD9 deficiency is a rare autosomal recessive mitochondrial disorder that affects the assembly of respiratory chain complex I.⁹ In most reports, riboflavin, the precursor of flavin adenine dinucleotide (FAD), can improve symptoms and thus benefit patients.¹⁰ Regarding a potential mechanism, riboflavin supplementation may facilitate complex I assembly by increasing the mitochondrial FAD concentration and improving *ACAD9* stability.^{8,10}

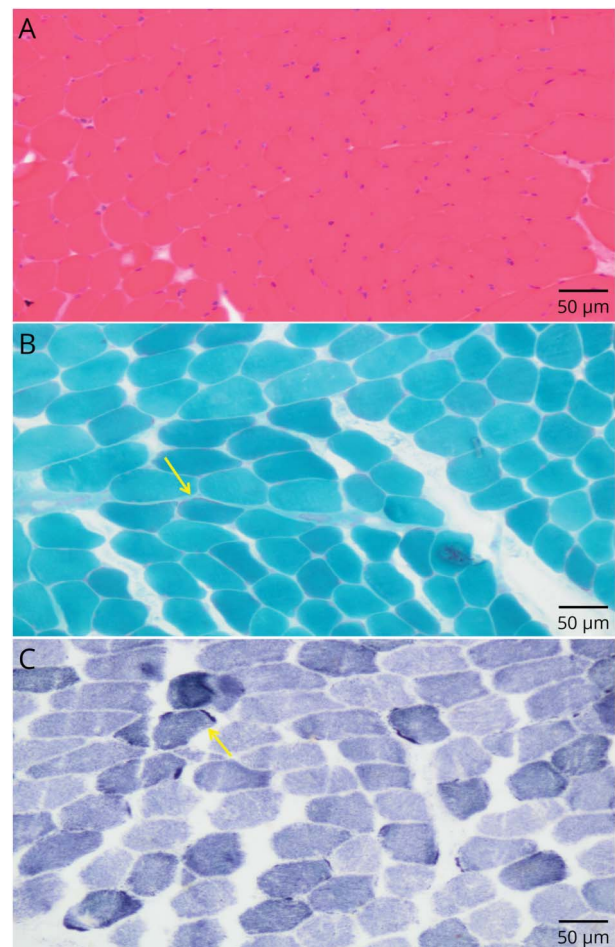
Typically, the most common clinical phenotypes of *ACAD9* deficiency are cardiomyopathy, muscular weakness, and exercise intolerance. Earlier onset correlates with more severe symptoms and lower survival, especially in the first year of life.⁸ Cardiomyopathy dominates disease burden and causes of death in most patients, but a few exceptions with no cardiac involvement were observed.¹¹

Neurologic findings are relatively uncommon and generally mild. In mitochondrial diseases, peripheral neuropathy is

not typically observed as the initial or main symptom but rather a concomitant mild or subclinical condition.¹² Chronic sensorimotor axonal polyneuropathy is the dominant type because of rich mitochondrial content and high energy demand in long axons.¹³ Neuroimaging changes are diverse, encompassing basal ganglia alterations, such as Leigh-like syndrome, leukoencephalopathy, global brain atrophy, isolated cerebellar atrophy, and lactate peak on MRS. The severe neurologic phenotype is often combined with Leigh-like abnormalities on brain MRI in complex I deficiency, and restricted diffusion on DWI indicates drastically impaired mitochondrial function and poor survival outcome for patients in the acute phase.^{14,15}

Fortunately, our patient exhibited mild symptoms. She manifested only exercise intolerance without cardiomyopathy; therefore, she grew and developed relatively normally. However, an opportunity to establish earlier diagnosis was missed because of unappreciated subtle symptoms. In the absence of early directed intervention, this patient currently

Figure 2 Muscle Biopsy Results



(A) Hematoxylin and eosin staining showed unequally sized myofibers. Increased mitochondria in some subsarcolemmal regions were observed based on (B) modified Gomori trichrome staining and (C) succinate dehydrogenase staining (magnification 200 \times).

suffered a severe neuropathy after a mild metabolic perturbation. Regrettably, she failed to return to her preonset condition of exercise endurance despite treatment with riboflavin.

This case illustrates an uncommon presentation of ACAD9 deficiency that provoked an acute-onset and rapidly progressive clinical course with profound but reversible peripheral neuropathy and encephalopathy. Notably, inherited metabolic diseases can have an acute exacerbation and occasionally even new symptoms in the context of environmental factors, such as infection or dietary change. Timely supplementation with essential nutrients may improve or even reverse injury. Moreover, this case suggests the importance of early recognition and management in inherited metabolic diseases. Although a secondary metabolic perturbation may be tolerated by ordinary people, it may cause severe injury to patients with congenital metabolic defects.

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Appendix (continued)

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Bo Xiao, MD	Department of Neurology, and National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan, China	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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