



Clinical Reasoning: A 12-year-old boy with ascending weakness

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SECTION 1

A 12-year-old boy presented with 3 weeks of calf pain, tripping, and progressive inability to walk. The onset was preceded by a sore throat 4 weeks prior, but no recent immunizations and no sick contacts. He began having problems “catching his toes” for 2 weeks. He had no visual complaints and no bowel or bladder incontinence. He had no recent travel and there were no heavy metal or solvent exposures. He had no prior medical history and he was on no prescription medications. Developmentally, he was on track and had just successfully completed fifth grade. However, he was reported to be behaviorally oppositional, especially regarding his diet which was restricted to beef jerky, yogurt from a squeeze tube, and fruit drinks. Family history included diabetic peripheral neuropathy in his mother, idiopathic peripheral neuropathy in his maternal grandfather, and left lower extremity neuropathy from trauma in his father. There was no known family history of recurrent pressure palsies or cardiac problems.

His vital signs were normal with the exception of a body mass index of 11.1 kg/m². His general examination showed periorbital edema and was otherwise normal including cardiac and skin examinations. Mental status examination revealed an apathetic affect with normal alertness and mentation. Cranial nerves were normal. Motor examination revealed normal strength in the upper extremities and proximal lower extremities with mild weakness on knee flexion and extension but absent ankle dorsiflexion and eversion. There was tenderness to palpation of both calves. Deep tendon reflexes were absent at the patellae and Achilles. Response to plantar stimulus was flexion bilaterally. Sensation was normal in the upper extremities but decreased to light touch, temperature, and pinprick on the dorsum of both feet to the level of the ankles. Coordination testing was normal. He was able to stand independently but was wide-based and he ambulated with a high-steppage gait bilaterally.

Question for consideration:

1. What is the differential diagnosis for ascending weakness in a child?

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SECTION 2

Progressive, symmetric, ascending weakness in children has a broad differential that typically includes neoplastic (spinal compression), autoimmune, such as acute inflammatory demyelinating polyradiculoneuropathy (AIDP), infectious, spinal cord lesions, toxic exposure such as heavy metal poisoning, and nutritional deficiencies. Spinal compression syndromes can present with symmetric or asymmetric lower extremity weakness and sensory loss. Diminished deep tendon reflexes, urinary retention, and poor rectal tone are typical.¹ AIDP classically presents with symmetric ascending weakness and should always be suspected in this setting. Absence of reflexes and sensory changes are common. Infectious etiologies such as HIV, enterovirus, and West Nile virus can cause subacute progressive weakness. Enterovirus and West Nile viral infections can cause acute flaccid paralysis similar to poliomyelitis. However, enteroviral radiculomyelitis tends to be unilateral and painful.² Flaccid paralysis from West Nile virus is also more commonly asymmetric and is often associated with encephalitis or meningitis.² Transverse myelitis and other myelopathies can cause progressive ascending weakness, but can often be differentiated from

neuropathy by physical examination and a history of back pain.³ The usual presenting feature of transverse myelitis is sudden onset of combined motor and sensory disturbance in the trunk and legs. Sphincter dysfunction is common and there is often a sensory level to pain and temperature that indicates the level of the lesion. Deep tendon reflexes below the lesion may be initially depressed and then become hyperactive. Motor symptoms are seldom the sole complaint of toxic or metabolic neuropathies. The list of potentially offending medications is long and the most common medications that could produce neuropathy include chemotherapeutics (vincristine), cardiovascular drugs (amiodarone), immunosuppressives (colchicine), and antimicrobials (nitrofurantoin).³ Heavy metal toxicity is rare and the neuropathy is usually associated with gastrointestinal, hematologic, and CNS dysfunction.³ Nutritional deficiencies can cause myelopathy and neuropathy, but are less common in developed countries with routinely fortified foods. Sensory abnormalities, without a sensory level, are common in vitamin deficiency neuropathies.³

Question for consideration:

1. What tests would you order?

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SECTION 3

The patient underwent spinal MRI with and without gadolinium. There was no spinal nerve root enhancement or other explanation of his clinical presentation. A lumbar puncture was acellular with normal protein and glucose and was negative for West Nile virus immunoglobulin G and immunoglobulin M antibodies.

Two days later, he became lethargic and was noted to have a bounding heart rate and a new S3 heart sound on auscultation. He was subsequently transferred to the pediatric intensive care unit where an urgent transthoracic echocardiogram demonstrated normal systolic function but a small pericardial effusion. Brain natriuretic peptide was markedly elevated at 2,189 pg/mL (0–100), troponin I was elevated at 0.18 ng/mL (0.00–0.04), and he was started on milrinone infusion. He remained hemodynamically stable and did not require intubation.

Electrodiagnostic testing revealed distal predominant sensorimotor axonal peripheral neuropathy. On nerve conduction, bilateral superficial peroneal sensory nerve responses were absent, the left peroneal motor response was absent, and the right was markedly reduced in amplitude to 0.7 mV (normal >3 mV). F-wave responses were absent in the bilateral peroneal motor nerves but normal in the upper extremities. Needle EMG revealed evidence of acute denervation as well as reinnervation. There was evidence of both acute and chronic denervation including diffuse fibrillations as well as morphologically large and complex rapid firing motor units in the right tibialis anterior, vastus lateralis, and gastrocnemius.

Questions for consideration:

1. Does this information change the differential diagnosis?
2. What further investigations would you order?

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SECTION 4

The differential diagnosis for ascending motor neuropathy and heart failure in the pediatric population is limited and consists of AIDP and vitamin deficiency. Acute heart failure in the setting of AIDP has been reported.^{4,5} The mechanism is neurogenically stunned myocardium as is seen with Takotsubo cardiomyopathy from sympathetic overactivation in the setting of inflammatory disease.⁴ Another known cause of peripheral neuropathy and heart failure is nutritional deficiency of vitamin B1. Classic terminology has categorized the clinical manifestations of thiamine deficiency into dry beriberi, characterized by sensorimotor neuropathy of the lower extremities, and wet beriberi, characterized by edema and heart failure.⁶ Acute presentation of wet beriberi results in rapid cardiac deterioration whereas the chronic form results in high-output heart failure and hypertension.⁷ Dry beriberi is chronic and results in symmetric, ascending paralysis with calf pain and absent deep tendon reflexes.⁷ It is not currently evident why certain people exhibit different forms of thiamine deficiency. Our patient developed both neurologic and cardiac problems associated with thiamine deficiency. Most cases of pediatric thiamine deficiency have been reported as Wernicke encephalopathy.⁸ The reason thiamine deficiency can present so heterogeneously is unknown and it is unclear why most cases of pediatric thiamine deficiency present as an encephalopathy.⁹

In this patient, serum vitamin B1 was <2 mol/mL (8–30) (table). With the history of severely restricted diet and low thiamine, a diagnosis of thiamine deficiency was made. He was started on 100 mg IV thiamine once followed by IV treatment of 25 mg daily. The electrodiagnostic findings supported his diagnosis via a distal-predominant axonal polyneuropathy affecting both motor and sensory nerves.

Table Serologic study results

Laboratory tests	Results
Folate, vitamin B ₁₂ , MMA	Normal
Vitamins A, B ₆ , E	Normal
CBC	Hgb 11.6 g/dL (13–16)
Copper, zinc	Normal
CPK, TSH	Normal
TTG, RBP	Negative
ESR, CRP, ferritin	Normal

Abbreviations: CBC = complete blood count; CPK = creatinine phosphokinase; CRP = C-reactive protein; ESR = estimated sedimentation rate; Hgb = hemoglobin; MMA = methylmalonic acid; RBP = retinol binding protein; TSH = thyroid-stimulating hormone; TTG = tissue transglutaminase.

Whole blood thiamine is a good laboratory indicator of body stores of thiamine whereas plasma thiamine concentration is more indicative of recent thiamine intake and can be transiently decreased as part of an acute inflammatory response, especially in critically ill patients.⁶ Similar to plasma thiamine, red blood cell transketolase activity is sensitive to thiamine replacement and will normalize within a few hours after thiamine treatment.⁸

The persistent restricted eating pattern was likely behaviorally mediated, as he had no medical (gastroesophageal reflux), anatomical (cleft palate, microgastria), or developmental disabilities to explain the problem with food refusal. The behavior seemed to have begun during the toddler years, but rather than resolve as expected, it developed into a chronic restricted pattern.

Questions for consideration:

1. Is there a genetic predisposition toward developing beriberi from thiamine deficiency?
2. How would you manage this patient?

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SECTION 5

Some literature suggests a genetic sensitivity toward a lower threshold of developing clinical manifestations in the setting of low thiamine.⁹ Whether a patient will develop either neurologic or cardiac manifestations may be due to an underlying genetic predisposition.⁸

Children with comorbidities including neuropsychiatric disorders such as depression and eating disorders are at risk of poor diet leading to potential vitamin deficiency. In thiamine deficiency, initial replacement with 100 mg IV thiamine followed by daily administration of 25–50 mg is necessary to avoid further progression of neuropathy or cardiomyopathy.⁷ Repeat serum and whole blood thiamine are useful to monitor recent thiamine intake and overall thiamine body stores, respectively.⁸ Physical rehabilitation is necessary in severe cases of neuropathy or cardiac involvement. Management of children with continued food refusal requires psychological and behavioral management as well as caregiver training.¹⁰ Due to poor oral intake, a nasal feeding tube is often required for nutrition.¹⁰ Follow-up electrodiagnostic testing may be valuable for assessment of peripheral nerve improvement.

The patient was lost to neurologic follow-up.

AUTHOR CONTRIBUTIONS

Dr. French is the principal author in the drafting and medical writing of the manuscript. Dr. Candee was involved in preparing the manuscript and in editing/interpreting. Dr. Stahl was involved in this patient case and involved in the review of psychiatric literature for contribution of the manuscript. Dr. Giles was involved in this patient case and contributed to the psychiatric management of this patient case. Dr. Glasgow contributed to editing the manuscript and was involved in the care of the patient. Dr. Morita oversaw the patient case as well as the overall editing of the manuscript.

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DISCLOSURE

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