Clinical Reasoning: A 6-Year-Old Boy With Muscle Twitching

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Section 1

A 6-year-old biracial (Black and White) boy presented with worsening muscle twitching and stiffness. He had normal birth and development. His family noticed muscle twitching involving his thighs when he was 3 years old. Over the next 3 years, twitching spread to involve shoulders, chest, lower back, arms, and lower legs. The patient would feel muscle twitching underneath his skin and at times, these could be visible. His symptoms were worse with cold exposure. Recently, he started experiencing difficulties with fine motor activities such as writing, holding pencils, tying shoelaces, and buttoning. The patient denied myalgia, weakness, rhabdomyolysis, and paresthesias. Medical history includes well-controlled asthma, allergic rhinitis, right hydrocelectomy, and a small bowel intussusception. Family history was unremarkable. Neurologic examination revealed increased appendicular muscle tone, fasciculations involving upper and lower extremities, anterior chest, and paraspinal muscles, mild difficulty releasing hand grip, nasal dysarthria, and bilateral tight heel cords. Sensory examination, reflexes, and gait including heel and toe walking were normal.

Question for Consideration:

1. What is the differential diagnosis?

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Section 2

Fasciculations are quick, visible, spontaneous, and intermittent contractions of muscle fibers that correspond with muscle twitching. Fasciculations can be benign or pathologic. Spontaneous fasciculations occur in up to 70% of healthy people.[1] Benign fasciculation syndrome commonly involves lower limbs without neurologic disease.[2] Worsening consistent and widespread fasciculations interfering with functioning in our patient argue against this.

Pathologic fasciculations are common in peripheral nervous system disorders, more frequently with lower motor neuron and peripheral nerve problems, but can also be seen in muscle diseases.

Motor Neuron Diseases

Amyotrophic lateral sclerosis is exceedingly rare in children. Other motor neuron disorders such as late-onset spinal muscular atrophy, benign monomelic amyotrophy, postpolio syndrome, and Kennedy disease typically involve progressive muscle weakness, atrophy, contractures, and dysphagia in addition to fasciculations.

Peripheral Nerve Disorders

Fasciculations can be rarely seen in inherited neuropathies such as Charcot-Marie-Tooth (CMT) disease and acquired immune-mediated neuropathies such as chronic inflammatory demyelinating polyneuropathy. Typical presentation includes progressive muscle weakness, atrophy, decreased/absent reflexes, pes cavus, and sensory abnormalities. Lack of the aforementioned features makes these disorders unlikely in our patient.

Peripheral Nerve Hyperexcitability

Peripheral nerve hyperexcitability (PNH) syndromes arise from spontaneous discharges of the motor nerve fibers leading to increased muscle activity. Predominant features include muscle twitching, stiffness, and cramps. Cramp fasciculation syndrome is a benign entity characterized by myalgia, cramps, fasciculations, or myokymia with an otherwise normal examination.[3] Isaacs syndrome or acquired neuromyotonia is an immune-mediated disorder characterized by muscle twitching, progressive muscle stiffness, hyperhidrosis, delayed muscle relaxation, fasciculations, or myokymia.[3,4] Morvan syndrome has similar symptoms concomitantly with CNS features like headaches, encephalopathy, and hallucinations.[3,4] The pathophysiology of these immune-mediated syndromes involves voltage-gated potassium channels playing a major role in neuronal excitability.[3,4] Although the clinical presentation of our patient resembles that of the aforementioned syndromes, he lacks features suggesting an autoimmune process. Genetic etiology for PNH is increasingly recognized.

Muscle Diseases

Nondystrophic myotonic disorders can present with muscle stiffness due to myotonia, delayed hand grip release, pain, weakness, and fatigue. They are caused by skeletal muscle ion channels dysfunction and altered muscle membrane excitability. Myotonia congenita is most common, caused by *CLCN1* mutations, and inherited in autosomal dominant and recessive fashion. Muscle stiffness is most pronounced during rapid voluntary movements following a period of rest but improves with repeated activity. Paramyotonia congenita and the sodium channel myotonias are autosomal dominant conditions caused by skeletal muscle *SCN4A* point mutations. Paramyotonia congenita is characterized by myotonia worsened by cold and episodic weakness. Sodium channel myotonias do not have episodic weakness but may exhibit cold-sensitive or potassium-aggravated myotonia. Some patients with nondystrophic myotonias develop myopathy.[5] Brody myopathy due to biallelic mutations in *ATP2A1* is another rarer cause of myotonia with muscle cramping and stiffening after exercise, especially in cold temperatures. Rippling muscle disease due to *CAV3* mutation could be mistaken for myotonia. Schwartz-Jampel syndrome due to biallelic *HSPG2* mutations involves facial features and chondrodysplasia in addition to myotonia. Fasciculations are not typical for the aforementioned disorders. Electrophysiologic and genetic studies aid in precise diagnosis.

Other Causes

Endocrine abnormalities such as hyperthyroidism, especially syndrome of inappropriate secretion of thyrotropin, hypophosphatemia, and hyperparathyroidism, can cause muscle twitching, weakness, and wasting.[2,6] Hypomagnesaemia can cause muscle cramping and contractions and is usually accompanied by hypocalcemia and hypokalemia.[7] Vitamin D deficiency can also cause muscle spasms and pain, especially when it progresses to rickets.[8] Drugs including penicillamine, oxaliplatin, neostigmine, corticosteroids, succinylcholine, isoniazid and flunarizine, heavy metals (gold, mercury, platinum, lithium, manganese), and toxins (herbicides, insecticides, toluene, alcohol, timber rattlesnake envenomation) are associated with muscle twitching and fasciculations.[2,3] Caffeine is a common agent to cause muscle twitching. Our patient's family did not disclose relevant history, making this category unlikely.

Question for Consideration:

1. What investigations should be considered?

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Section 3

Initial investigations in our patient revealed unremarkable complete blood count, basic metabolic panel, and liver function tests. Thyroid-stimulating hormone, thyroxine, parathyroid hormone, magnesium, and vitamin D levels were normal. Antinuclear, anti-SSA, and anti-SSB antibodies were negative. Serum creatinine kinase level was elevated (340 units/L; range 4–87). Given the broad differential diagnoses and unremarkable initial workup, further evaluation, electrodiagnosis, or broader genetic testing was considered. It was decided to proceed with the genetic testing. The patient underwent next-generation sequencing and deletion/duplication analysis of a panel of genes associated with neuromuscular diseases. The results revealed a pathogenic variant, c.316C>T (p.Gln106*), and a variant of uncertain significance (VUS), c.188T>A (p.Ile63Asn) in the *HINT1* gene associated with autosomal recessive neuromyotonia and axonal neuropathy (NMAN). Heterozygous VUS were also noted in *ALG2*, *ITGA7*, and *MEGF10*, associated with autosomal recessive disorders, likely noncontributory to the patient's phenotype.

Question for Consideration:

1. What are the next steps?

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Section 4

VUS are commonly identified in next-generation sequencing multigene panel testing. It can be challenging for physicians to analyze the pertinence of VUS to the patient's phenotype. Parental testing may aid with this. Testing of our patient's asymptomatic parents revealed that the 2 variants in *HINT1* were on opposite chromosomes (pathogenic variant inherited from father and VUS from mother). The VUS (c.188T>A) sequence change replaces isoleucine with asparagine at codon 63 of *HINT1*. The isoleucine residue is moderately conserved and there is a large physicochemical difference between isoleucine and asparagine. This variant is not present in population databases. Several in silico analyses (SIFT, PolyPhen-2, Align-GVGD, MutationTaster) suggest that this variant is likely to be disruptive. Based on the clinical and genetic features, we strongly speculated autosomal recessive NMAN associated with *HINT1* in our patient. He then underwent electrophysiologic evaluation. Nerve conduction studies showed findings consistent with axonal motor neuropathy. EMG showed fibrillation potentials, fasciculations, and neuromyotonia. These findings established the diagnosis of NMAN. The patient remained stable at his recent follow-up. He is managed supportively with physical therapy and shoe inserts.

Discussion

NMAN due to recessive mutations in *HINT1* was initially described as axonal CMT with neuromyotonia.[9,10] *HINT1* encoding histidine triad nucleotide binding protein 1 is ubiquitously expressed and acts in complex transcriptional and signaling pathways; its function in the peripheral nerves is not understood.[9] Initial clinical presentation of NMAN includes distal lower extremity weakness, muscle stiffness, twitching, fasciculations, and muscle cramps. Most patients describe difficulties in releasing grip after strong voluntary contraction beginning in childhood. Typical phenotype is axonal, motor > sensory, polyneuropathy with action neuromyotonia and electrical neuromyotonia or myokymia. This is a slowly progressive disorder with onset in the first decade and no loss of ambulation until the sixth decade. Neuromyotonia is seen in 70%–80% of patients and is characterized by spontaneous muscle activity at rest, impaired muscle relaxation, and contractures of hands and feet. It is a result of spontaneous peripheral nerve discharges often augmented by voluntary muscle contraction. NMAN is an underdiagnosed entity because neuromyotonia, a diagnostic hallmark, can be difficult to recognize. Skeletal deformities such as pes cavus, pes equinovarus, pes cavovarus, scoliosis, and flexion contractures of fingers are described. Mild to moderate creatine kinase elevation has been reported. Electrodiagnosis reveals axonal polyneuropathy with decreased compound muscle action potential and sensory nerve action potential amplitudes and normal conduction velocities. EMG demonstrates neuromyotonic discharges (150–200 Hz high-frequency, decrementing, repetitive discharges from one motor unit) occurring spontaneously or by muscle activation. Management is symptomatic and supportive. Physical therapy, ankle-foot orthoses, show inserts, and orthopedic corrections for limb deformities are valuable. Medications targeting the symptoms of neuromyotonia and PNH including voltage-gated sodium channel blocking antiepileptics such as phenytoin and carbamazepine can be beneficial.[9]

Awareness of NMAN is critical for proper recognition and management. The c.188T>A variant can be added to the repertoire of *HINT1* mutations causing NMAN. This report emphasizes the challenges of selecting and analyzing results of next-generation sequencing panel testing and highlights the importance of electrophysiologic examination for establishing a precise diagnosis.

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Appendix Authors

Name	Location	Contribution
Hannah Smashey Lewis, MD	University of Arkansas for Medical Sciences, Little Rock	Data collection, drafting and revising manuscript
Balaji Subramanian Srinivasa Sekaran, MBBS	University of Louisville, KY	Drafting and revising manuscript
Vikki Stefans, MD	University of Arkansas for Medical Sciences, Little Rock	Cared for the patient, revising manuscript
Aravindhan Veerapandiyan, MD	University of Arkansas for Medical Sciences, Little Rock	Cared for the patient, study concept, revising manuscript

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