A 48-Year-Old Man With Syncope and Diffuse Muscle Twitches

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A 48-year-old Haitian man with a history of hypertension presented to our hospital following an episode of loss of consciousness. The episode occurred while the patient was standing at a sink, and was preceded by several hours of non-exertional chest discomfort and a brief period of dizziness. He regained consciousness on the floor and felt diffusely weak. There were no lateralized symptoms, post-ictal confusion, incontinence, or tongue contusions. When he returned to a standing position, he saw prominent “beating, pulsating” movements of his periorbital and perioral muscles in the mirror, and also noted some blurred vision. There was additional muscle twitching involving the hands, legs, chin and neck, which the patient described as “a heart beating under the skin”. There was no associated pain, weakness, or numbness.

The patient revealed that he had experienced intermittent but frequent abnormal beating of the periorbital muscles for approximately two months prior to presentation. He initially thought it was secondary to anxiety. One month after the onset of these symptoms, he developed similar sensations in his fingers and legs bilaterally, and then in the perioral muscles. In addition to these symptoms he had diarrhea as well as an unintentional 25 pound weight loss over three months, due to anorexia. He had not had fevers. He reported hyperlacrimation which he felt was the result of frequently rubbing his eyes. He denied dysphagia, paresthesias, muscle cramps, headaches, or difficulty with balance. He had had a few episodes of near syncope in the two months prior to presentation, which were not associated with falls.

Past medical history included essential hypertension which had been diagnosed five years prior to presentation, as well as vitiligo of the bilateral hands and lips which had been noticeable for six months prior to presentation. He denied neonatal or childhood infections and achieved normal developmental milestones. There was no personal or family history of seizures or other neurological disease. Medications included nifedipine, hydrochlorothiazide, and lisinopril, and there had been no recent medication changes.

On initial evaluation, the patient was afebrile, with supine blood pressure 90/50 and heart rate 65, and standing blood pressure 74/50 and heart rate 82. General examination

revealed a thin but well developed man in no acute distress. Cardiac rhythm was regular without murmurs. Depigmented patches of skin were noted on the lips and dorsal surfaces of the fingers and hands. The lungs were clear and there was no costovertebral angle tenderness. The abdomen was not tender and no abdominal masses were palpated. There was no extremity edema.

Neurological exam revealed normal cognition, language, and memory. There was mild ptosis of the right upper eyelid with no additional ptosis following sustained upward gaze. There was no dysarthria or inability to clear oral secretions, and speech was not nasal in quality or effortful. Muscle bulk, tone, and power were normal. Posture was normal with no rigidity. Continuous arrhythmic undulating myokymic muscle spasms were seen in the bilateral periorbital and perioral muscles, as well as within individual muscle fibers of the right forearm, bilateral hands, and interosseous muscles of the right fifth toe. These abnormal muscle contractions were not painful or bothersome to the patient. Deep tendon reflexes were symmetric and diffusely diminished, and no pathological reflexes were seen. Sensation was normal to all modalities and there was no dysmetria.

Discussion, Part I

Discussant: Jenelle A. Jindal

This patient presented with a first syncopal episode in the setting of recent additional symptoms including unintentional

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weight loss, chronic diarrhea, intermittent blurred vision, vitiliginous skin changes, involuntary muscle twitching, and orthostatic hypotension. The initial concern was whether the presenting event was syncope or seizure. Historical clues including post-ictal confusion and focal neurological findings would be more suggestive of seizure as the underlying etiology. Lightheadedness prior to the event would be more suggestive of syncope. Convulsive limb movements and bladder and/or bowel incontinence may occur in either seizure or convulsive syncope. Though this patient's event was unwitnessed, the preceding lightheadedness, lack of post-ictal neurological deficits, and presence of orthostatic hypotension, were together less suggestive of seizure.

The finding of orthostasis producing syncope is seen in both primary neurological and medical conditions. Neurodegenerative diseases such as Parkinson disease and Multiple System Atrophy (formerly the Shy-Drager syndrome) are often associated with prominent dysautonomia which can lead to orthostatic hypotension. Disequilibrium secondary to sensory neuropathy can be seen in the settings of diabetes, amyloidosis, lupus, as well as other connective tissue diseases. Orthostatic hypotension can result from medication side effects (antihypertensives, diuretics), endocrine disease (adrenocortical insufficiency, pheochromocytoma), hypovolemia, and electrolyte disturbances. Hypotension can also be seen in reflex syncope including vasovagal syncope, neurocardiogenic syncope, and in association with urination and defecation. Lastly, orthostatic hypotension and syncope can result from cardiac dysrhythmias.

With regard to this patient, he had no evidence of dementia or neuropathy. He revealed that he had taken an antihypertensive medication thirty minutes prior to the syncopal episode, and in the setting of chronic diarrhea, he most likely experienced syncope due to orthostatic hypotension caused by hypovolemia and medications.

The muscle twitching is notable as well. Given the diffuse involvement of many muscle groups, the lack of synchronicity of twitches, and the small bundles of muscle fibers involved, a peripheral neurological process was felt to be more likely than a central cause of the symptoms. Specifically, disorders of the lower motor neuron, peripheral nerve, neuromuscular junction, and muscle were further evaluated. Though the patient reported blurred vision and was found to have asymmetrical ptosis, there was no fatigability with sustained or repeated muscle contractions. The patient's weight loss was concerning for an underlying systemic illness, such as infection, an immunocompromised state, or an occult malignancy. Initial serum laboratory studies are shown in Table 1.

Discussion, Part II

Discussant: Jenelle A. Jindal

The initial serum studies revealed hypokalemia and anemia. The hypokalemia was felt to be secondary to chronic diarrhea,

Table 1. Initial Serum Studies

Laboratory test	Value	Reference range
Na (mmol/L)	138	136-145
K (mmol/L)	2.8	3.4-5.0
TSH (mIU/L)	1.18	0.5-5.7
Hemoglobin (g/dL)	11.6	13.5-18.0
Hematocrit (%)	33.7	40-54
Platelets (K/uL)	219	150-450
WBC (K/uL)	3.81	4-10
MCV (μm^3)	87.8	80-95
Iron ($\mu\text{g/dL}$)	107	37-158
TIBC ($\mu\text{g/dL}$)	241	220-460
UIBC ($\mu\text{g/dL}$)	134	112-346
Vitamin B12 (pg/mL)	214	250-900
INR	1.4	0.9-1.1

Abbreviations: Na, sodium; K, potassium, TSH, thyroid stimulating hormone; TIBC, total iron binding capacity; UIBC unsaturated iron binding capacity; INR, international normalized ratio.

and subsequently improved with hydration to 3.4 mmol/l. The anemia and hypcobalaminemia was suggestive of pernicious anemia which in this case may have resulted from diarrhea-associated malabsorption. However, the presence of pernicious anemia, vitiligo, and cachexia raised suspicion for an underlying autoimmune process. The additional finding of persistent diffuse myokymia suggested a possible paraneoplastic autoimmune process.

There are a finite number of disorders which involve persistent hyperexcitability of muscle. These can be subdivided on the basis of the underlying etiology: centrally mediated hyperexcitability, hyperexcitability of the peripheral nerves, and primary muscle hyperexcitability.

Central causes for motor hyperexcitability include stiff person syndrome, in which there is prominent axial rigidity and hyperlordosis. The excess muscular activity in this condition disappears during sleep and following peripheral nerve blockade. Antibodies against glutamic acid decarboxylase (GAD) are positive in the majority of cases. Gamma-aminobutyric acid (GABA)-ergic medications including diazepam are helpful in treating symptoms in this disorder. Congenital neonatal rigidity, another central cause for motor hyperexcitability, typically develops during infancy and clinically presents with generalized muscle stiffness.

Muscle hyperexcitability may be due to a primary muscular disorder as well. Diseases in this category include rippling muscle disease, an autosomal dominant disorder in which muscles appear to contract in a rippling fashion after being stretched, and Schwartz-Jampel syndrome, an autosomal recessive disorder with stiffness and dysmorphic features.

Peripheral nerve hyperexcitability can be further subclassified into the following syndromes: benign fasciculation syndrome, cramp-fasciculation syndrome, myokymia, Morvan's syndrome, and Isaac's syndrome. Benign fasciculations may occur in healthy people, and involve twitching of a muscle or part of a muscle, and can last for days, or uncommonly,

Table 2. Additional Serum Studies

Laboratory test	Value	Reference range
Anti-intrinsic factor antibody	Positive	Negative
Acetylcholine receptor antibody (nmol/L)	14.1	0.0-0.2
Voltage-gated potassium channel antibody (pmol/L)	189	<450 negative, 450-650 borderline
HIV antibody	Negative	n/a
ANA titer	0	0
RF (IU/mL)	<11	0.0-15
ESR (mm/hr)	2	0-12
Serum immunofixation	No monoclonal gammopathy	n/a

Abbreviations: HIV, human immunodeficiency virus; ANA, anti-nuclear antibody; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; n/a, not applicable.

years. The neurological exam in these patients shows normal reflexes and sensation, and normal nerve conduction studies. Cramp-fasciculation syndrome is associated with cramps and fasciculations as well as muscle stiffness. Fasciculation potentials are seen on needle electromyogram (EMG) and slow repetitive nerve stimulation results in after-discharges of motor unit action potentials. Peripheral nerve stimulation causes persistent motor unit action potentials. Myokymia refers to muscle activity which appears rippling in nature, and can be either localized or diffuse. It can be seen in the setting of Guillain-Barre syndrome and post-radiation therapy where its presence is thought to result from peripheral nerve demyelination. EMG shows spontaneous bursts of motor unit action potentials and repetitive firing of a single motor unit. Morvan's syndrome is an autoimmune process which produces peripheral nerve hyperexcitability combined with autonomic nervous system features (sweating, lacrimation, constipation, cardiac arrhythmias), as well as central nervous system symptoms including hallucinations, insomnia, and disorientation. There is no standardized treatment beyond case reports of modest improvement with intravenous immunoglobulin (IVIg) and plasma exchange (PE).

Isaac's syndrome, or neuromyotonia, can be inherited or acquired. Clinically it presents as continuous spontaneous muscular activity, often with muscle twitching at rest, without the behavioral changes seen in Morvan's syndrome.¹ An autoimmune etiology has been suggested since neuromyotonia has been associated with diseases such as myasthenia gravis, Addison's disease, vitiligo, Hashimoto's thyroiditis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, celiac disease, amyloidosis, and pernicious anemia.²⁻⁴ It has also been associated with a variety of cancers including small-cell lung cancer, lymphoma, and thymoma.⁵ Direct evidence of an autoimmune etiology has been demonstrated by a reduction in neuromyotonic discharges following plasmapheresis. Neuromyotonia itself can also be seen without an underlying autoimmune process, as in motor neuron disease, voltage-gated potassium channel gene mutations,⁶ and in the setting of toxin exposures such as insecticides, toluene, ethanol, and rattlesnake venom.

EMG is used to diagnose neuromyotonia. Testing reveals irregular spontaneous high-frequency single or partial motor

unit discharges. Serum assay for anti-voltage-gated potassium channel antibodies is positive in approximately 40% of patients with acquired neuromyotonia.^{3,7} If a thymoma is identified, the probability of finding positive voltage-gated potassium channel antibodies increases to approximately 80%.⁷ Treatment of an underlying malignancy alone can in some cases reduce muscle hyperactivity. In other cases, symptomatic management with anticonvulsive medications such as phenytoin, carbamazepine, or gabapentin, and additionally with the skeletal muscle calcium channel blocker dantrolene, can help reduce muscular hyperactivity. In patients who have persistent uncontrolled muscular hyperactivity despite anticonvulsants, a trial of immunosuppression can be considered. A combination of PE or IVIg, plus oral steroids with or without azathioprine, may be used.⁸ This treatment may not fully eliminate symptoms but is likely to significantly reduce muscle hyperexcitability within days to weeks.

Diagnostic Results

Given the patient's diffuse spontaneous myokymia without cramping, lack of underlying central nervous system signs, and a high suspicion for an underlying systemic disease, we focused our investigations on peripheral nerve hyperexcitability, in particular, Isaac's syndrome (Table 2).

An EMG was performed which revealed increased insertional activity in all muscles tested. Specifically, fasciculation potentials were noted in the right biceps, vastus lateralis, and tibialis anterior muscles. The left orbicularis oris muscle showed continuous motor unit activity and a normal recruitment pattern. Nerve conduction studies were normal except for reduced motor conduction velocity across the right elbow, consistent with a mild ulnar neuropathy. Repetitive stimulation testing was not performed. A routine electroencephalogram (EEG), performed during the waking, drowsy, and sleeping states, was unremarkable with no epileptiform discharges.

A positron emission tomography-computed tomography (PET-CT) of the body was obtained to evaluate for occult malignancy. This study revealed a well-circumscribed lobular mildly FDG-avid anterior mediastinal mass with punctate

Figure 1. Imaging of anterior mediastinal mass. A, Axial noncontrast CT of the chest showing an anterior mediastinal soft-tissue density mass (arrows) containing several internal punctate hyperdense calcifications. B, FDG-PET overlay on the CT shows a focus of mildly elevated FDG-avidity within the center of the lesion (arrow).

internal calcifications, measuring 2 (craniocaudal) $\times$ 3 (antero-posterior) $\times$ 4 (transverse) centimeters. The radiographic appearance of this lesion was felt to be most consistent with thymoma (Figure 1).

Resection of the anterior mediastinal mass was subsequently performed. Pathological evaluation was consistent with a diagnosis of type B2 thymoma (Figure 2).

Within days following thymectomy, the patient's myokymia completely resolved. Serum acetylcholine receptor antibody levels decreased following surgery to 9.58 (nmol/l). Given the spontaneous symptom resolution after surgery with no other specific treatment, the neuromyotonia was felt to be paraneoplastic in origin, i.e. related to the thymoma. In this case voltage-gated potassium channel antibodies were not found to be elevated. We suspect that in addition to neuromyotonia there was likely subclinical myasthenia gravis, given the presence of elevated serum acetylcholine receptor antibodies.

Figure 2. Pathological evaluation of the resected anterior mediastinal mass. A, Grossly, a well demarcated, irregularly shaped, firm lesion, with heterogeneous tan and brown areas, with intermixed off-white foci of calcification was seen. B, At scanning magnification, a lobulated mass with haphazard arrangement, loss of classical thymic architecture, and absence of a corticomedullary distinction within lobules was seen. C, At 40X magnification, the lobules were noted to be separated by thick fibrous bands. D, At 200X magnification, the lobules were noted to be composed of a mix of small lymphocytes and epithelioid cells with large nuclei, high nuclear-cytoplasmic ratio, and prominent nucleoli. These findings are diagnostic of a type B2 thymoma.

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