Residents' Clinic

32-Year-Old Man With Episodic Weakness

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A 32-year-old Vietnamese man presented to the emergency department after sudden onset of weakness. He was in excellent health earlier in the evening when he consumed a large meal, cake, and 2 beers at his son's birthday party. Several hours later, while descending a flight of stairs, he collapsed and was unable to move his arms or legs. His legs ached mildly, but he had no paresthesias or dysesthesias. He reported that 2 similar episodes had occurred during the previous month, noting that they usually began in the middle of the night and resolved by morning. Bulbar muscles were not affected.

The patient had been in a low-velocity motor vehicle collision 2 months previously when his vehicle was struck from behind. The patient had no notable injury; thus, radiography was not performed. The patient had no family history of episodic weakness. He consumed 1 to 2 alcoholic beverages per week and had never used tobacco or illicit drugs. His medications included occasional ibuprofen and acetaminophen. A review of systems showed the patient's weight had decreased 3 kg during the preceding 3 months and that he had experienced occasional chest palpitations.

The patient's bilateral arm and leg paralysis suggested a catastrophic neurologic event. However, a sudden, episodic tetraparesis with complete recovery between events might suggest a psychogenic disorder. The patient appeared to believe his symptoms were real, and there was no indication of external incentives or a desire to assume the sick role.

1. Which one of the following psychogenic disorders best explains this patient's symptom complex?

a. *Conversion disorder*
b. *Somatization disorder*
c. *Factitious disorder*
d. *Malingering*
e. *Munchausen syndrome by proxy*

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See end of article for correct answers to questions.

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Somatoform disorders are psychiatric conditions that have the appearance of a general medical condition in which patients believe their symptoms are real. A conversion disorder is one type of somatoform disorder in which voluntary motor or sensory function is lost in a patient who believes his or her symptoms are real. This psychogenic disorder best fits our patient's symptom complex. Another somatoform disorder, somatization disorder, is characterized by numerous somatic symptoms involving multiple organ systems and is driven by psychological needs.

Factitious disorder and malingering involve deliberate feigning of symptoms. Patients with factitious disorder create symptoms to assume the sick role. Malingerers are motivated by external incentives, such as economic gain or avoidance of legal responsibility. Munchausen syndrome by proxy is a factitious disorder in which a parent makes his or her child ill, or any individual makes a person under his or her care ill, to obtain treatment.

Several clues suggest that our patient's symptoms do not indicate a psychogenic disorder. Disorders of medically unexplained somatic symptoms, such as conversion disorder, typically involve impairment of psychological and social functioning. Often, patients with these disorders also have mood disorders, dissociative symptoms, and interpersonal difficulties.[1] Our patient had no history of depression, anxiety, or other psychiatric comorbidity. Moreover, he seemed appropriately concerned about his spells of weakness. Therefore, alternative diagnoses were entertained.

Physical examination revealed a healthy-appearing muscular man in no distress while sitting in a wheelchair. His blood pressure level was 110/80 mm Hg, his heart rate was 84 beats/min and regular, and he was afebrile. Cardiovascular, pulmonary, and abdominal examination findings were normal. Cognition was normal, and cranial nerves II through XII were intact. Muscle bulk and tone were normal with mild, nonfatigable weakness throughout the upper extremities and moderate weakness throughout the lower extremities. The patient's effort was steady, without sudden "giving way." Power was uniform in the proximal and distal limbs and similarly involved both flexor and extensor muscles. Reflexes were symmetrical and mildly brisk throughout, with no Babinski and Hoffmann signs. All sensory modalities were intact, including pinprick, temperature, vibration, and proprioception. Alternating motion

rates were normal. The patient was unable to walk because of weakness.

2. Which one of the following best describes where this patient's disorder could be anatomically localized, given the timing and distribution of the deficits?

a. *Bilateral precentral gyrus (frontal motor cortex)*
b. *Medullary pyramids*
c. *Lateral corticospinal tracts (spinal cord)*
d. *Peripheral nerves*
e. *Muscle*

Sudden onset of neurologic symptoms suggests a vascular event. A bilateral lesion of the frontal motor cortex would be a catastrophic ischemic event involving the vascular distributions of both cerebral hemispheres. In this patient, this diagnosis is extremely unlikely because of the intermittent symptoms and normal mentation.

A bilateral pyramidal lesion could cause bilateral weakness. However, a lesion large enough to affect the pyramids bilaterally likely would involve other nearby brainstem structures such as the corticobulbar tract, causing facial weakness; the hypoglossal nerve, causing tongue weakness; or the medial lemniscus, causing diminished proprioception and vibration perception. Given the dorsolateral location of the corticospinal tracts in the spinal cord, involvement of adjacent structures such as the dorsal columns (proprioception and vibration) and spinothalamic tract (pinprick and temperature) would be expected. Brisk and symmetrical reflexes suggest both intact afferent sensory nerves and efferent motor nerves, making the diagnosis less likely to be of primary peripheral nerve pathology. Therefore, the patient's diffuse, symmetrical weakness best fits with a process affecting muscle.

While in the emergency department, the patient underwent a psychiatric evaluation, which indicated no emotional or psychological trauma suggestive of a conversion reaction; further investigation for organic illness was recommended.

3. Which one of the following disorders is the most likely cause of this patient's episodic weakness?

a. *Chordoma of the clivus*
b. *Myasthenia gravis*
c. *Hypokalemic periodic paralysis*
d. *McArdle disease*
e. *Polymyositis*

Chordomas are slow-growing bone neoplasms that can occur at the skull base, including the clivus (anterior to the medulla and pons). A tumor in this location could compress the pyramids of the medial medulla. However, neoplasms typically produce a progressive deficit, not seen in our patient.

Myasthenia gravis causes weakness that worsens with exertion. Often, weakness begins in ocular muscles causing diplopia or ptosis but may manifest simply as periodic limb weakness. Reflexes are often normal. The diagnosis is suggested by fatigability, for example progressive ptosis on sustained upgaze. Characteristically, strength improves with rest. Our patient had no fatigability or improvement with rest.

Hypokalemic periodic paralysis is episodic paralysis associated with low serum potassium concentrations. Weakness commences proximally and rapidly becomes generalized. The time course and distribution of deficits best fit our patient's symptoms.

McArdle disease is an abnormality of the glycolytic pathway in muscle, causing exercise intolerance, muscle pain, and myoglobinuria. None of these symptoms were seen in our patient.

Polymyositis causes weakness, often associated with pain. Polymyositis can be painless; however, episodic symptoms would be highly unusual.

Laboratory test results, determined during our patient's attack, revealed the following (reference ranges shown parenthetically): potassium, 3.0 mEq/L (3.6-4.8 mEq/L); sodium, 146 mEq/L (135-145 mEq/L); creatinine, 0.9 mg/dL (0.9-1.4 mg/dL); serum urea nitrogen, 16 mg/dL (8-24 mg/dL); chloride, 109 mEq/L (100-108 mEq/L); bicarbonate, 23 mEq/L (22-29 mEq/L); and creatine kinase, 1123 U/L (52-336 U/L). Breath alcohol concentration was 0.097%. The patient's weakness improved within several hours without intervention. He returned home and was followed up at the neurologic clinic as an outpatient; a few days later he was symptom free.

4. Which one of the following studies is the most likely to be abnormal at the time of this patient's follow-up appointment?

a. *Serum potassium concentration*
b. *Electrocardiography*
c. *Nerve conduction/electromyography*
d. *Serum lactate level after exercise*
e. *Thyrotropin level*

Hypokalemic periodic paralysis usually involves transient changes in serum potassium concentration while total body stores remain at normal levels. Because our patient had weakness with minimal hypokalemia, the low serum potassium concentration reflects an underlying transcellular disorder rather than a true potassium depletion. Serum potassium concentrations should be normal between paralytic attacks. Electrocardiographic changes can be seen with flattened T waves and prominent U waves during attacks of hypokalemic periodic paralysis. However, an electrocardiogram obtained at this point would likely be

normal. Nerve conduction studies and electromyography can show decreased insertional activity and diminished numbers of motor unit potentials fired during episodes of periodic paralysis.[2] However, between paralytic attacks, nerve conduction study results and electromyographic findings should be normal, reflecting normal neuromuscular function. Failure of serum lactate levels to increase after exercise is suggestive of McArdle disease or of other defects in the conversion of glycogen or glucose to lactate.

The most common acquired form of hypokalemic periodic paralysis is thyrotoxic hypokalemic periodic paralysis in which episodes of hypokalemic paralysis occur in the setting of thyrotoxicosis. Thyrotoxic hypokalemic periodic paralysis is more common in Asian males than in other racial populations and would explain our patient's chest palpitations, weight loss, and brisk reflexes. Laboratory test results revealed a thyrotropin level less than 0.01 mIU/L (0.3-5.0 mIU/L) and a free thyroxine level of 3.1 ng/dL (0.8-1.8 ng/dL), confirming the diagnosis.

Before these laboratory results were addressed, the patient had experienced another paralytic attack, awaking at 3 AM unable to move. He returned to the emergency department, where his physical examination results were similar to those of his prior visit. His serum potassium concentration was 1.8 mEq/L.

5. Which <u>one</u> of the following therapeutic measures is <u>contraindicated</u> in this patient?

a. *Oral potassium chloride*
b. *Intravenous glucose in a 5% normal saline solution with potassium chloride*
c. *Propranolol*
d. *Triamterene*
e. *Spironolactone*

Potassium replacement has become standard therapy during attacks of thyrotoxic hypokalemic periodic paralysis; however, its efficacy is debatable. Glucose or saline is contraindicated in this situation. Serum potassium concentration can decrease precipitously, despite the potassium content of the solution. Therefore, oral potassium chloride is preferred. If the patient is too weak to swallow and emergency administration of intravenous potassium is indicated, intravenous potassium chloride in 5% mannitol should be used.[3] These effects of glucose are intuitive because the combination of insulin and glucose is used commonly to treat hyperkalemia.

Several small studies suggest that the β-blocker propranolol relieves paralytic episodes.[4,5] Moreover, propranolol has been shown to prevent the induction of paralysis with insulin and glucose.[4] Potassium-sparing diuretics, such as spironolactone and triamterene, prevent potassium loss but had disappointing results in our patient. Acetazolamide, effective in reducing attack severity and frequency in familial hypokalemic periodic paralysis, has no role in thyrotoxic hypokalemic periodic paralysis. Of these choices, propranolol and potassium may be used to treat attacks. However, any solution with dextrose or saline, even as a vehicle for potassium administration, is contraindicated.

The patient was referred to the endocrinology clinic where a 24-hour study using radioactive iodine I 131 revealed only 15% uptake by the thyroid. Although this uptake percentage was believed to be inappropriately high in the presence of suppressed thyrotropin, it was not optimal for ^{131}I treatment. Therefore, the patient underwent surgical thyroidectomy. Pathologic findings revealed chronic lymphocytic thyroiditis. The patient's paralytic episodes resolved subsequently.

DISCUSSION

Hypokalemic paralysis is a heterogeneous group of disorders characterized by diffuse weakness and hypokalemia. Secondary hypokalemic paralysis results from profound potassium depletion of any cause, including renal losses such as those associated with distal renal tubular acidosis and primary hyperaldosteronism, or extrarenal losses such as those associated with gastroenteritis.

Paralysis can result from muscle ion channel mutations, or channelopathies. Mutations of sodium, potassium, and calcium ionic channels can result in several forms of episodic paralysis. Familial hypokalemic periodic paralysis, the autosomal dominant form associated with low serum potassium concentration during paralytic attacks, is due to dysfunction of sodium or calcium channels. Most cases are inherited; however, one third are sporadic. Attacks are precipitated often by carbohydrate-rich meals and result in flaccid paralysis. Symptoms begin early in life and rarely begin after age 25 years.

Often, weakness associated with familial hypokalemic periodic paralysis occurs with only mild hypokalemia, suggesting that ionic distribution across muscle membranes causes weakness rather than hypokalemia itself. Serum potassium concentrations are typically normal between paralytic attacks because total body potassium stores remain at normal levels. As in our patient, weakness can occur with minimal hypokalemia. This is in contrast to weakness due to potassium loss, which occurs only with profound hypokalemia (potassium concentrations <2.0 mEq/L).[6]

Thyrotoxic hypokalemic periodic paralysis is clinically similar to familial hypokalemic periodic paralysis. Paralytic attacks follow carbohydrate intake and insulin administration, and weakness occurs often out of proportion to the degree of hypokalemia. These effects of insulin and

carbohydrates have been exploited as a diagnostic tool.[4,7] Once euthyroidism is established, symptoms of thyrotoxic hypokalemic periodic paralysis do not recur, even with insulin and glucose administration.

The underlying mechanism of thyrotoxic hypokalemic periodic paralysis is poorly characterized. Thyrotoxicosis may uncouple the active transport of calcium across the membrane of the sarcoplasmic reticulum. Excess thyroxine may increase electrolyte permeability, causing potassium influx and failure of depolarization. Paralysis can be induced only in individuals with thyrotoxicosis (with carbohydrates and insulin) if there is a history of periodic paralysis, suggesting that excess thyroxine alone is not the cause; the individual must be predisposed to the condition.[7] Possible ionic channel gene mutations are being investigated. However, familial clustering is rare, suggesting that simple genetic inheritance is unlikely. One popular theory is that a predisposition to these effects of thyrotoxicosis is multifactorial, a complex interplay between multiple genes and environment.

Thyrotoxic hypokalemic periodic paralysis is more prevalent in Asian males, such as our patient, with a male-to-female ratio of approximately 20:1. One large Taiwanese study found that of 1366 patients with thyrotoxicosis, symptoms of episodic paralysis occurred in 23 (13%) of 178 males and 2 (0.17%) of 1188 females.[7] In our population (Olmsted County, Minnesota), consisting primarily of white persons of northern European descent,[2] the overall incidence of thyrotoxicosis is estimated to be 0.1% to 0.2%.

Therapies targeting thyrotoxicosis and its associated hyperadrenergic state have had excellent results. One study examined propranolol in patients with thyrotoxic hypokalemic periodic paralysis inducible with glucose and insulin.[4] Propranolol pretreatment for 6 days gave partial or complete protection from induced paralysis in 5 of 7 patients.[4] This study also examined pretreatment with acetazolamide, the mainstay of therapy for familial hypokalemic periodic paralysis, and found paralysis severity worsened in patients with thyrotoxic hypokalemic periodic paralysis. Potassium replacement therapy during attacks of thyrotoxic hypokalemic periodic paralysis is of debatable efficacy. One review of 24 episodes of thyrotoxic hypokalemic periodic paralysis found that recovery time did not correlate with potassium dose and that rebound hyperkalemia was common.[4] Researchers recommended that potassium replacement be used with caution and should not exceed 90 mEq of potassium chloride per 24 hours unless there is a reason for potassium loss (diarrhea, vomiting, diuretic use). Supportive care is typically adequate because attacks are self-limited. Avoiding carbohydrate loads such as alcohol can prevent further attacks. Correcting the thyrotoxic state is curative.

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Correct answers: 1. *a*, 2. *e*, 3. *c*, 4. *e*, 5. *b*