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Dysphagia, Hoarseness, and Weakness in a 12-Year-Old Girl

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CASE PRESENTATION

History

A 12-year-old girl was brought by her father to the emergency department (ED) with an 18-hour history of hoarseness and increased difficulty swallowing and clearing her throat. The father also noted difficulty understanding his daughter's speech. The patient denied odynophagia, difficulty chewing, diplopia, dizziness, fever, rash, headache, chills, nausea, vomiting, and diarrhea.

The father reported that his daughter's symptoms were part of an illness that began 9 months prior, while his family was living in Tijuana, Mexico. Initially, the father noticed that his daughter's smile looked different and that she was experiencing difficulty with speech. This was followed by problems at school and with extracurricular activities. The patient, who had always been an excellent student, began to struggle with her studies and her grades started to slip. She also experienced muscle fatigue while playing violin and practicing karate. She then was hospitalized for aspiration pneumonia that had been preceded by similar symptoms of hoarseness and dysphagia. The parents subsequently moved to Los Angeles to seek medical care for their daughter and to continue her education.

Following her enrollment in school, the patient reported that she would suddenly feel weak and fall down but would regain her strength after resting a few seconds and could stand up without assistance. She denied any trauma except the falls. The falls occurred spontaneously, without accompanying pre-aural symptoms, dizziness, or loss of consciousness. The recurrent falls prompted school officials to refer the patient for medical clearance prior to returning to school. This referral occurred 2 weeks before the ED visit.

The father was employed as a construction worker and the mother was a homemaker. None of the other family members reported neurologic symptoms.

Physical Examination

On physical examination, the patient was alert and awake and appeared comfortable, with her shoulders hunched forward. Her oral temperature was 37°C (98.6°F), heart rate was 84 bpm, respiratory rate was 18 breaths/min, and blood pressure was 108/62 mm Hg. Her height was 152.4 cm (60 in; 50th percentile for age), and her weight was 56 kg (123.5 lb; 90th percentile). Cranial nerves (CN) 2, 4, 6, 11, and 12 were grossly intact. She had bilateral ptosis (CN 3), decreased bite strength (CN 5), bilateral weakness of the facial muscles (CN 7), left lateralization during the Weber's test (CN 8), and an absent gag reflex (CN 9 and 10). Her pulmonary, cardiac, and abdominal examinations were unremarkable. Strength deficits were noted in the left leg flexors, left foot dorsiflexors, and right intraosseous hand muscles. All deep tendon reflexes were symmetrical and normal. Her gait was steady, without ataxia.

Laboratory Studies

Results of laboratory studies obtained in the ED are summarized in **Table 1**.

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Key Point

Parents most often request evaluation of a child for weakness or clumsiness when the child begins walking, enters school, or joins a team, as motor deficits that may have been overlooked become more apparent when a child is compared to his or her peers. Usually, a brief evaluation and parental reassurance are all that is required. However, any deterioration of motor skills or episodes of weakness or ataxia in an otherwise normal child should be investigated thoroughly.

- **What is the differential diagnosis of weakness in a 12-year-old child?**
- **How should this patient's evaluation and management proceed at this point?**

DIFFERENTIAL DIAGNOSIS

The slow onset and pattern of weakness in this patient suggest a neuromuscular defect, particularly myasthenia gravis. The physical examination revealed several features of this disorder, including ptosis and facial, oropharyngeal, and extremity weakness. Myasthenia gravis also is characterized by easy fatigability of affected muscles and recovery with rest, which the patient reported.

The patient's acute inability to clear oral secretions and her absent gag reflex require emergent evaluation, with possible intubation to protect her airway. She also should undergo emergent computed tomography (CT) of the head to exclude an intracranial hemorrhage or mass—two serious considerations in the differential diagnosis of weakness. If the sensory or motor deficits affected the lower extremities more than the upper extremities, magnetic resonance imaging of the spinal cord also would be appropriate to rule out a mass, an abscess, or a transverse myelitis.

Once these acute concerns have been addressed, potential causes of the patient's weakness and other sensorimotor deficits must be considered. Although myasthenia gravis is a strong consideration, the examiner also must assess the likelihood of several other possible causes of weakness in a child of this age.

Acute Causes of Weakness

Acute illnesses that can produce weakness include intracranial bleeding, trauma to the central or peripheral nervous system, infections (eg, polio encephalitis), inflammatory conditions (eg, vasculitis, myositis), botulism, and heavy metal or organophosphate poisoning.

This patient denied any trauma except the falls, which began occurring later in the course of her illness, and there was no history of fever, rash, headache, or diarrhea to suggest an infectious etiology. The reported absence of neurologic symptoms in other family members suggested that a toxic exposure (eg, heavy metal, organophosphate) was unlikely. Botulism produces an ascending paralysis and is caused by food contaminated with *Clostridium botulinum*, which would more likely have affected other family members and not just the patient. An inflammatory process also was unlikely, given the patient's normal erythrocyte sedimentation rate. Hence, pending results on head CT, a chronic deteriorating neuromuscular condition seemed the more likely cause of this patient's neuromuscular symptoms.[1]

Table 1. Results of Initial Laboratory Studies Obtained for Case Patient

Variable	Result	Normal Range
Hematologic values		
Leukocyte count	7.6 x 10^3/mm^3	3.4–10.8 x 10^3/mm^3
Differential		
Segmented neutrophils	47%	40%–60%
Lymphocytes	44%	40%–60%
Monocytes	7%	4%*
Eosinophils	2%	2%*
Platelets	231 x 10^3/mm^3	227–539 x 10^3/mm^3
Hemoglobin	14.5 g/dL	12.0–14.5 g/dL
Serum values		
Blood urea nitrogen	13 mg/dL	7–22 mg/dL
Electrolytes		
Sodium	138 mEq/L	135–148 mEq/L
Potassium	3.9 mEq/L	3.5–4.1 mEq/L
Chloride	103 mEq/L	96–109 mEq/L
Bicarbonate	22 mEq/L	24–30 mEq/L
Calcium	9.8 mg/dL	8.0–10.5 mg/dL
Erythrocyte sedimentation rate	15 mm/h	0–29 mm/h
Creatinine kinase	77 U/L	25–145 U/L

*Mean value.

Chronic Causes of Weakness

Evaluation of chronic causes of weakness requires further categorization as to symmetry.

Asymmetric weakness. Conditions that can cause asymmetric weakness include an intracranial mass, compression of a nerve due to a mass or chronic local inflammation, previous trauma to a nerve or muscle or to the brain, infection of the dorsal root ganglion, multiple sclerosis, vasculitis, and a transverse myelitis.

Nerve compressions often are accompanied by pain, paresthesias, or anesthesia along the affected nerve. Trauma usually is evident from the history or physical examination; however, in cases of child abuse, the examiner must look carefully for subtle signs (eg, bruises in different stages of healing, posterior rib fractures). Herpes zoster is characterized by vesicular eruptions along the affected dermatome. Multiple sclerosis is rare in children and is associated with increased deep tendon reflexes and a static or intention tremor. Vasculitic syndromes are a diverse group of disorders commonly characterized by blood vessel inflammation; most involve multiple organ systems, particularly the skin, kidneys, and respiratory tract.

Symmetric weakness. Symmetric weakness should be further categorized as distal or proximal. Distal weakness in the lower extremities manifests as foot drop due to weakness of the dorsiflexors; in the upper extremities there is a tendency to drop things because of decreased hand strength. Distal extremity strength can be tested by having the child attempt to walk on her toes and by assessing grip strength.

Neuromuscular diseases with predominantly distal symptoms include tetanus, heavy metal or organophosphate poisoning, tick paralysis, Guillain-Barré syndrome, and certain metabolic disorders (eg, the glycogen storage diseases [types I through V], lipid and mitochondrial myopathies). Tetanus is rare in the United States but may be seen in infants with an infection of the umbilical stump or after injury in an unimmunized child. Organophosphate poisoning results in weakness accompanied by fasciculations, with increased salivation and lacrimation. Tick paralysis results in an ascending flaccid paralysis; a tick often can be found along the hairline of the scalp. Guillain-Barré syndrome is characterized by a preceding viral infection with progressive motor weakness in more than one extremity and areflexia. Differentiation of the metabolic disorders requires a muscle biopsy with histologic and biochemical examination.

Proximal weakness may manifest as ataxia due to decreased pelvic girdle strength or frequent falls while running or walking. Proximal strength can be tested by having the patient attempt to rise from a chair without using her arms or by having the patient attempt to reach over her head to grab an object.

Proximal strength deficits are seen in myasthenia gravis, polymyositis, and periodic paralysis. Polymyositis can have an acute onset in children, but the muscles of the hands, feet, and face are spared, and serum muscle enzyme levels are elevated. Periodic paralysis is a rare, inherited disorder characterized by recurrent episodes of rapidly progressive paralysis. Although often difficult to diagnose, the disorder may be temporally linked to the ingestion of carbohydrates and the subsequent release of insulin (in the hypokalemic form) or the ingestion of potassium (in the hyperkalemic form). In both forms, the paralysis may occur during rest after exercise.

Key Point

A child with sudden onset of weakness should prompt an investigation for a malignancy (intracranial mass or spinal tumor), an endocrine abnormality (post-Hashimoto hypothyroidism, diabetes mellitus with magnesium depletion), a postinfectious neuropathy (Guillain-Barré syndrome), or a collagen vascular disease (systemic lupus erythematosus).

CLINICAL COURSE

The patient was admitted to a monitored area because of the potential for a compromised airway. A CT scan of the head was negative for hydrocephalus or intracranial hemorrhage or mass.

Endocrine and immunologic studies were ordered to clarify a presumptive diagnosis of myasthenia gravis. On the second hospital day, the patient had more difficulty breathing and required intubation and transfer to the pediatric intensive care unit. After the patient was stabilized, a lumbar puncture and magnetic resonance imaging of the brain and neck were performed but revealed no mass or thymoma. Results of endocrine studies revealed normal thyroid function, ruling out hypothyroidism-associated myasthenia gravis. However, a high level of acetylcholine receptor antibody (14.3 nmol/L; normal, < 0.7 nmol/L) and a positive response to edrophonium chloride (the Tensilon test) supported the diagnosis of myasthenia gravis. An electromyelogram was inconclusive.

The patient underwent plasmapheresis, with substantial improvement. Corticosteroids and cholinesterase inhibitors were initiated, and the patient was extubated 12 days after admission. She was able to return to school without any further neuromuscular problems. After 1 year, she regained full muscle strength and her energy level returned to her pre-illness level, although she developed a cushingoid appearance, facial acne,

and hirsutism. She was then slowly tapered off corticosteroids, and her neurologist was able to slowly decrease the dose of her cholinesterase inhibitors. She takes calcium supplements and weekly bisphosphonate and receives biannual bone density scans. She has had no relapse of symptoms.

- **When should the diagnosis of myasthenia gravis be considered in pediatric patients?**
- **What is the approach to diagnosis and treatment of myasthenia gravis in an adolescent patient?**

MYASTHENIA GRAVIS

Definition and Pathophysiology

Myasthenia gravis is a disorder of the postsynaptic portion of neuromuscular junction transmission. Acetylcholine is the major neurotransmitter used to stimulate the motor end plate, which results in muscle contraction. In myasthenia gravis, the number of acetylcholine receptors is decreased, with associated changes in the synapse morphology, resulting in diminished neuromuscular function. In most cases, the reduction of available receptors is due to circulating receptor-binding antibodies. These autoantibodies likely result from an aberrant lymphocyte-mediated immune response to the acetylcholine receptor. The sensitized lymphocytes subsequently differentiate into antigen-specific helper T cells, which then stimulate the production of acetylcholine receptor antibody. Thymic hyperplasia often is associated with myasthenia gravis, with improvement or resolution of symptoms with removal of the thymus. The exact role of the thymus in the pathogenesis of myasthenia gravis, however, is poorly understood.

Epidemiology

Myasthenia gravis is a rare condition in children. Its increased incidence in recent decades seems to be the result of improved diagnosis rather than increasing prevalence.[2] Three types of myasthenia gravis occur in children, two of which are acquired.

Neonatal myasthenia gravis can occur transiently in infants born to mothers who have the disorder. The infant may require supportive care but otherwise needs no intervention. Neonatal myasthenia gravis resolves spontaneously within days to weeks of onset.

Congenital myasthenia gravis is a rare, nonimmune form that occurs in infants who are born with defects in acetylcholine resynthesis, acetylcholine receptors, or acetylcholinesterase. Both males and females are equally affected. Symptoms may begin in the first year of life and include generalized weakness and delays in neuromuscular development. The disorder sometimes resolves spontaneously but may have a protracted course if left untreated.

Juvenile myasthenia gravis is essentially the same autoimmune disorder that occurs in adults, with an onset in adolescence. Like most autoimmune disorders, it primarily affects girls.

Key Point

The rapid development of an infant's neuromuscular system may mask congenital myasthenia gravis until the second year of life. Knowledge of the developmental milestones is therefore important, because a delay in motor skills (eg, crawling, sitting, walking) may be the first sign of disease.[3]

Clinical Presentation

Myasthenia gravis usually presents as fatigue that worsens with repetition or sustained effort. Symptoms may be absent in the morning or resolve with a period of rest. Usually, the symptoms have a gradual onset but may appear acutely, particularly after a viral illness.

More than half of patients have ptosis and extraocular weakness. The affected child may complain of diplopia or use her fingers to keep her eyes open. Weakness of the bulbar muscles may cause problems with speech or swallowing. Weak neck muscles may result in loss of head control, in which case the affected child may demonstrate difficulty holding her head up while lying supine. Weak facial muscles may result in unclear speech and fatigue while chewing food. The parents may report that their child fails to finish her meal because of weakness. Finally, weakness of the respiratory muscles may result in shortness of breath or respiratory failure.

Key Point

Myasthenic crisis presents as dyspnea, dysphagia, and respiratory failure. Forced vital capacity is the best way to monitor whether intubation is necessary, as arterial blood gas values may remain normal until intubation is required. The Tensilon test will help differentiate the patient having an exacerbation of myasthenia gravis from an individual in cholinergic crisis. Patients with myasthenic crisis should remain in a monitored area until forced vital capacity returns to normal.

Diagnosis

Physical examination. If ptosis is not readily apparent, the sign can be elicited by having the patient hold an upward gaze for up to 90 seconds; gradually, the eyelids will begin to droop. Grip strength can be assessed

by having the patient rapidly clench and unclench the fists, which will fatigue the hand muscles. Upper extremity fatigue can be elicited by having the patient hold her arms out in front of her chest, which will tire the deltoids and cause the arms to drop down. Lower extremity involvement can be assessed by having the patient attempt to walk on her toes or to rise out of a chair without using her arms.

Laboratory and other diagnostic tests. An electromyelogram may be diagnostic because of the decremental response to repetitive nerve stimulation. However, in contrast to other neuromuscular disorders, the motor nerve conduction velocity remains normal. Several muscles may need to be tested, because not all muscle groups may be affected.[4] Acetylcholine receptor antibody may be present in the plasma, but it can be absent in up to 44% of patients, particularly prepubertal ones.[5] The antibody level does not correlate with disease severity.[6] A thyroid function panel also should be performed because myasthenia gravis occasionally occurs secondary to hypothyroidism. Serologic markers of autoimmune disease (eg, antinuclear antibody, rheumatoid factor) should be assayed to determine whether other autoimmune disorders are present.

The administration of edrophonium chloride (the Tensilon test) can be diagnostic. The test works by temporarily inhibiting cholinesterase, which transiently raises the concentration of acetylcholine in the neural synapse. A test dose is given first to check for an allergic reaction. If no adverse effects are noted, the full dose (0.2 mg/kg) is administered and the patient is observed for improvement of ptosis, ophthalmoplegia, and fatigability, which constitutes a positive response.[4] The duration of action is short, and the child should be monitored for cholinergic crisis, which can cause extreme bradycardia and respiratory weakness. Atropine should be at the bedside and administered if cholinergic crisis does occur.

Treatment

Cholinesterase inhibitors (typically, pyridostigmine) are the primary treatment but require careful titration to prevent cholinergic crisis and/or a muscarinic reaction. Because most cases of myasthenia gravis are the result of autoimmune dysfunction, immunosuppressants (typically, corticosteroids) are often used to suppress T cell function. Intravenous immunoglobulin or plasmapheresis may be used during an acute myasthenic crisis to rapidly decrease the level of acetylcholine receptor antibody. Occasionally, thymectomy is performed, particularly in those patients with predominantly bulbar symptoms.[7]

Prognosis

Children with acquired myasthenia gravis often experience a cycle of remissions and flare-ups, with complete or partial remission often occurring within 2 years of onset. The reason for remission is not known but may be related to alterations in the immune system. Nephrotic syndrome and other autoimmune diseases have been associated with myasthenia gravis. **HP**

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