Determining the cause of generalized weakness can be a daunting task, since the differential diagnosis is vast. An overall approach to the patient who complains of generalized weakness is presented in our article. Here we offer an Algorithm that summarizes the diagnostic approach, along with 5 illustrative cases. Each demonstrates how anatomic localization, a refined differential diagnosis, and ancillary laboratory tests can be combined to help pinpoint the cause of the problem.

**Case 1**

**Progressive Weakness in a Woman With Systemic Lupus Erythematosus**

A 35-year-old woman with systemic lupus erythematosus (diagnosed 2 years earlier following an evaluation for arthralgias, adenopathy, and Raynaud phenomenon) presented with a 4-month history of progressive weakness. Initially, the patient complained of inability to walk long distances. Subsequently, she noticed that she had difficulty in climbing stairs, as well as in getting out of chairs and in getting off the toilet. Her weakness slowly progressed to the point where she required a cane to walk. During the past 4 to 6 weeks, weakness developed in the patient's arms. In particular, she described difficulty in lifting her arms to brush her teeth, comb her hair, and replace dishes in overhead cabinets. All the symptoms were equal bilaterally. The patient's weakness did not fluctuate throughout the day and was not affected by exercise. The patient denied any numbness, tingling, or pain. The family history was unremarkable.

Neurological examination revealed normal mental status; the cranial nerve examination was also normal. Bilateral mild atrophy of the shoulder girdle muscles was noted, along with symmetric weakness in the legs and arms, greater proximally than distally. Reflexes were mildly reduced but easy to elicit, and plantar stimulation produced downgoing toes. Sensory and coordination examinations were normal. The patient was able to walk only with assistance.

Laboratory studies revealed an erythrocyte sedimentation rate of 50 mm/h, a creatine kinase level of 5000 U/L, and a normal level of thyroid-stimulating hormone. Electrodiagnostic studies indicated a myopathy with muscle membrane irritability, suggesting an inflammatory, dystrophic, or toxic/metabolic myopathy. A follow-up muscle biopsy confirmed the presence of polymyositis. The patient's condition improved with corticosteroid treatment.

**Step 1. Anatomic localization (examination):** The neurological examination established the anatomic location. The presence of symmetric weakness, greater proximally than distally, in combination with the normal sensory and reflex examinations suggested the presence of a muscle disorder. This generated the initial differential diagnosis.

**Step 2. Refined differential diagnosis (history):** The history helped further refine the initial differential diagnosis. The subacute/chronic progression was consistent with an endocrine, inflammatory, toxic- or drug-induced myopathy; sarcoidosis; infectious disorder; or a late decompensation of a congenital or hereditary muscle disorder. There was no drug or toxin history. The family history was unremarkable, and the early developmental history did not suggest a congenital disorder. The history of systemic lupus erythematosus indicated the possibility of an inflammatory myopathy.

**Step 3. Ancillary laboratory studies:** The subsequent electromyographic and laboratory evaluations were consistent with an inflammatory myopathy; the follow-up muscle biopsy (with muscle selection directed by the electromyographic study) confirmed the diagnosis of polymyositis.

**Case 2**

**Double Vision and Ptosis in a Young Woman With Hyperthyroidism**

A 28-year-old woman had a 2-month history of episodic diplopia that fluctuated throughout the day.
but tended to worsen at night. She also had a 6-week history of episodic drooping of her right eyelid and instances of slurred speech. Hyperthyroidism had been diagnosed 3 years previously; the patient underwent surgery and was following a regimen of thyroid replacement therapy. The family history was unremarkable.

Neurological examination disclosed bilateral (right greater than left) ptosis, which increased with 30 seconds of sustained up-gaze. The pupils were round, measured 3 mm on both sides, and were briskly reactive. The patient was able to adduct the left eye but had limited abduction of this eye; the right eye moved only minimally in either direction. The remainder of the cranial nerve examination was normal, as were motor, sensory, and cerebellar examinations. Reflexes were present and symmetric, and toes were downgoing.

Electrodiagnostic testing revealed a postsynaptic disorder of neuromuscular transmission consistent with myasthenia gravis. This diagnosis was confirmed by detection of acetylcholine-receptor antibodies in the serum. The patient's condition improved markedly with pyridostigmine therapy.

**Step 1. Anatomic localization (examination):** The physical examination was notable for extraocular muscle and lid weakness, with additional task-specific fatigability, in the absence of sensory or reflex changes. This pattern of weakness is consistent with a neuromuscular transmission disorder or possibly an ocular or oculopharyngeal-type dystrophy (ie, myopathic disorder). The task-specific fatigability is more consistent with a neuromuscular transmission disorder.

**Step 2. Refined differential diagnosis (history):** The subacute onset and fluctuating nature of the symptoms combined with a tendency toward nighttime worsening is consistent with myasthenia gravis. The history of hyperthyroidism (seen in 5% of patients with myasthenia gravis) provides further support for this diagnosis.

**Step 3. Ancillary laboratory studies:** The electrodiagnostic examination and test for acetylcholine-receptor antibodies confirmed the diagnosis.

**Case 3**

**Progressive Numbness and Tingling in a Young Traveler**

A 24-year-old woman with no significant medical history had returned from a 5-day trip to Honolulu 2 weeks earlier. At that time, she experienced a mild upper respiratory tract infection that lasted 1 to 2 days. Two days before hospital admission, she awoke with numbness and tingling in her toes and feet. On the day of admission, tingling developed in her hands and, during the course of the day, it spread to her legs, hips, and arms. She also began to notice head instability, difficulty in walking, and dyspnea on exertion. She denied any alteration in bowel or bladder function and had no pain. There was no history of recent immunizations or surgery. The patient had no GI symptoms, and her only medication was an oral contraceptive.

On physical examination, the patient was afebrile. Her blood pressure was 158/85 mm/Hg; pulse, 78 beats/min; and respiration rate, 18 breaths/min. The general examination was unremarkable. The cranial nerve examination was notable for bilateral facial weakness. Motor examination disclosed normal tone with a quadriparesis affecting proximal muscles more than distal ones. Sensory examination revealed diminished joint position and vibration sense in both legs. Reflexes were absent. Babinski sign was equivocal. The patient's vital capacities declined significantly during the ensuing 24 hours, which prompted intubation.

Laboratory examination revealed mildly increased liver enzyme levels. Lumbar puncture showed no white blood cells, a total protein level of 74 g/dL, and a glucose level of 63 mg/dL. Electrodiagnostic studies confirmed the presence of an acquired demyelinating polyneuropathy consistent with Guillain-Barr syndrome. Plasmapheresis was initiated, and the patient had significant recovery during the subsequent 2 weeks.

**Step 1. Anatomic localization (examination):** The presence of weakness, sensory loss, and areflexia is consistent with a neuropathic disorder. Proximally predominant weakness per se is consistent with a myopathic or neuromuscular transmission disorder; however, the sensory signs and symptoms, as well as the areflexia, are atypical of a myopathic or neuromuscular transmission disorder and more suggestive of a neuropathic condition. Neuropathies typically produce distally predominant weakness; the presence of significant proximal weakness in a neuropathic setting would be suggestive of an acquired demyelinating polyneuropathy (such as Guillain-Barr syndrome), the neuropathy of porphyria, or a proximal diabetic radiculoplexopathy. The bilateral facial weakness is more consistent with Guillain-Barr syndrome; it occurs in half of patients with this disorder.

**Step 2. Refined differential diagnosis (history):** The acute to subacute time course and the history of an upper respiratory tract infection are consistent with Guillain-Barr syndrome. There was no history of diabetes.
Step 3. Ancillary laboratory studies: The electrodiagnostic studies confirmed an acquired demyelinating polyneuropathy consistent with Guillain-Barré syndrome. Porphyria neuropathies present a different electrodiagnostic pattern. The lumbar puncture disclosed the albuminocytological dissociation typically seen in Guillain-Barré syndrome.

Case 4
Gradual Onset of Hand Weakness in a Healthy Man
A healthy 37-year-old man noticed the gradual onset of left-hand weakness and difficulty with gripping, jar opening, and performance of fine finger tasks. The initial diagnosis was ulnar neuropathy, and the patient underwent an ulnar nerve transposition procedure. Despite this intervention, his left-hand weakness progressed during the ensuing few months, during which time he noticed the gradual onset of right-hand weakness. The patient denied numbness, tingling, or pain, and had no bowel or bladder symptoms.

The physical assessment disclosed a normal cranial nerve examination. There was weakness of the median, ulnar, and radial C8-T1 muscles bilaterally, with greater weakness of the left side. There was also mild weakness of the left deltoid and biceps. A detailed sensory examination was normal. Reflexes were 3+ in the legs, 2+ in the right arm, and 3+ in the left arm. The left toe was upgoing; the right toe was downgoing.

Electrodiagnostic studies confirmed the presence of a generalized disorder of the motor portions of the peripheral nervous system, probably localized to the anterior horn cells; this is consistent with the diagnosis of early amyotrophic lateral sclerosis.

Step 1. Anatomic localization (examination): The physical examination disclosed distal greater than proximal weakness affecting the arms more than the legs in an asymmetric, multifocal, myotomal distribution. The abnormalities were purely motor. This pattern is consistent with either a motor polyradiculopathy or a disorder of the anterior horn cells. The absence of sensory symptoms or pain would be unusual for neuropathic or root disease. The presence of hyperreflexia in symptomatic limbs suggested coexistent upper motor neuron pathology. The combination of upper and lower motor neuron findings would be most consistent with a motor neuron disorder. A cervical spinal cord lesion might also be considered, but the absence of sensory changes, pain, and bowel or bladder disturbance would argue against this possibility.

Step 2. Refined differential diagnosis (history): The slowly progressive subacute deterioration, particularly in the absence of sensory complaints or pain, is most indicative of a motor neuron disorder.

Step 3. Ancillary laboratory studies: The electrodiagnostic studies confirmed the diagnosis.

Case 5
Student With Weakness and Numbness
A 21-year-old college student had a 2-month history of difficulty in walking. On further questioning, she described an episode of weakness and numbness in her left arm 2 years previously and some transient visual difficulties in her left eye 1 year earlier.

On physical examination, there was pallor of the left optic disc, increased tone in both lower extremities, mild weakness of ankle dorsiflexion on both sides, pathologically brisk reflexes in the lower extremities with bilaterally upgoing toes, and finger-nose-finger dysmetria in the left arm. Sensory examination was unremarkable.

Cranial MRI disclosed multiple white matter-based lesions consistent with multiple sclerosis. A lumbar puncture disclosed a white blood cell count of 20/µL, an elevated cerebrospinal g-globulin level, and oligoclonal immunoglobulin bands. A regimen of interferon-b was begun.

Step 1. Anatomic localization (examination): The presence of weakness in the lower extremities, hyperreflexia, increased tone, and bilaterally upgoing toes suggested an upper motor neuron process. The predominance of symptoms in the legs suggested a thoracic spinal cord lesion. The dysmetria in the left arm suggested a more rostral disorder in the foramen magnum or brain stem, but the absence of other cranial nerve abnormalities argued against brain stem pathology. Alternatively, the left arm dysmetria, in conjunction with the paraparesis, might have indicated two independent lesions. The optic nerve pallor suggested an old optic neuropathy, which is evidence of a third independent lesion.

Step 2. Refined differential diagnosis (history): The absence of pain argued against a structural spinal cord lesion. The history of independent transient attacks of nervous system dysfunction, separated in time and affecting different anatomic structures within the CNS, was most consistent with a central demyelinating disorder (eg, multiple sclerosis).
Step 3. Ancillary laboratory studies: Both MRI of the brain and lumbar puncture disclosed findings typical of multiple sclerosis.

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