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Acute Nontraumatic Muscle Weakness

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Abstract

Acute nontraumatic weakness (ANTW) is defined as acute onset of weakness in any part of the body. The weakness occurs due to interruption at any point along the motor pathway. The motor pathway originates from upper motor neuron cells in the cerebral cortex and traverses through the brainstem till lower motor neurons in the spinal cord. The axon of a lower motor neuron is known as the peripheral motor nerve that synapses with muscle. ANTW is of varied etiology and presentation that may be immediately life-threatening if respiratory muscles or autonomic nervous system is involved. Involvement of respiratory muscles may be associated with respiratory failure that may require mechanical ventilation. The weakness may be localized to one limb or generalized involving several muscle groups. When bulbar muscles are involved, weakness leads to problem in swallowing and coughing that endangers the patient's airway. Similarly, the course of the disease also varies, and these patients may worsen rapidly. Hence, a comprehensive history, systematic evaluation, and a detailed neurological examination are performed to localize the disorder. There are specific clinical features peculiar to the particular location of the lesion in the body. Hence, it is possible to anatomically localize these lesions based on the clinical features. Initial laboratory tests and appropriate neuroimaging should be obtained as indicated by history and examination. The time-sensitive emergencies should be addressed immediately, as the delay in management may lead to either permanent neurological damage or may worsen the overall outcome in such conditions. The initial management should always include care of airway, breathing, and circulation (ABC). The imaging should be obtained only after initial stabilization of ABC. The definitive treatment should be done as per the etiology.

Keywords
- ► acute weakness
- ► neuromuscular weakness
- ► nontraumatic weakness
- ► respiratory failure

Introduction

Acute nontraumatic weakness (ANTW) is defined as the sudden onset of paralysis/weakness in any part of the body. The motor functions are controlled by the motor pathway involving upper and lower motor neurons (►**Fig. 1**). The upper motor neurons (UMNs) arise from the pyramidal cells of the neocortex and pass through the posterior limb of the internal capsule to enter the crus of the midbrain.[1] The motor tracts then pass through the pons and medulla as the corticospinal tract, which are also known as the pyramidal tracts.[1] The corticospinal tract divides as the lateral corticospinal tract (decussates at pyramids) and the anterior corticospinal tract (crosses at corresponding spinal cord) as these pass down in the spinal cord.[1,2] Approximately 90% of motor fibers form the lateral tract, while the rest (~10%) form the anterior tract. The lateral corticospinal tracts control the opposite side of the body, while the anterior corticospinal tract neurons control the same side of the body and trunk muscles.[1] Axons from UMNs synapse with the interneurons in the spinal cord, and occasionally directly with the lower motor neurons.[2] The lower motor neuron is located in the spinal cord, and its axon projects out of the spinal cord and controls the movement of muscles.[1] If there is a disease involving any part of the motor

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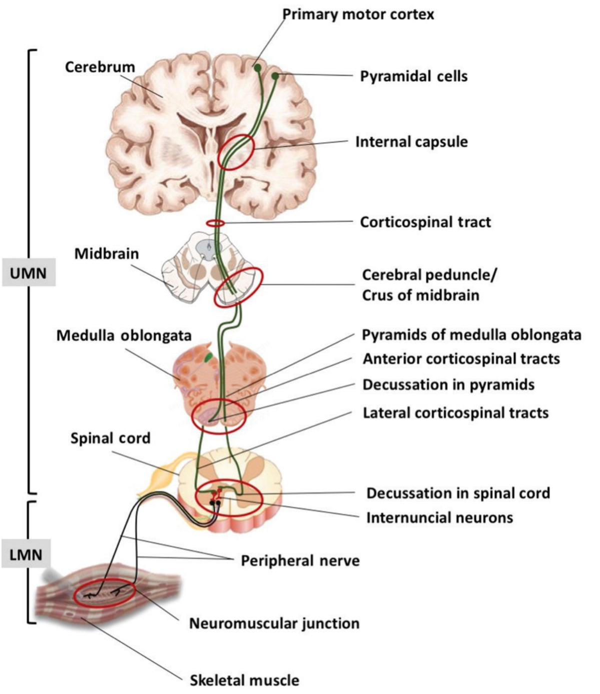

Fig. 1 Diagrammatic representation of the motor tract. It originates from pyramidal cells (motor neuron) of the cerebral cortex as the upper motor neurons (UMNs) and synapse in the spinal cord with lower motor neurons (LMNs). UMN is colored as green, internuncial neuron as red, and LMN as black.

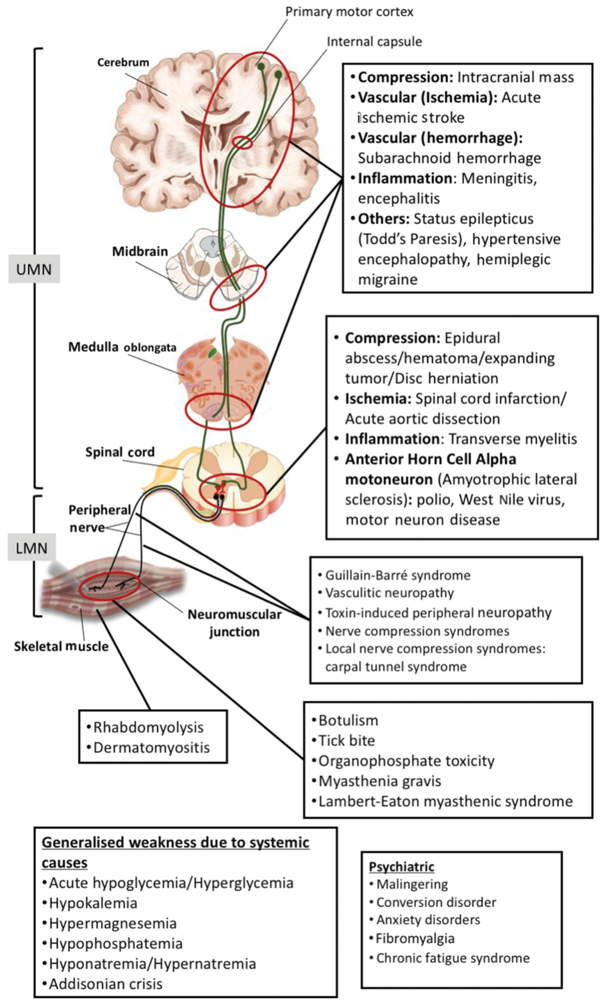

Fig. 2 Diagrammatic representation of various etiologies of acute motor weakness along the motor tract. LMN, lower motor neuron; UMN, upper motor neuron.

pathway, patients will develop weakness. ►**Figure 1** depicts the motor pathway.

The etiology of ANTW varies from immediately life-threatening conditions to minor disorders as shown in ►**Fig. 2.**[3] The weakness may be localized to one limb or may become generalized involving the respiratory and bulbar muscles. In the latter scenario, protection of airway and care of breathing become the priority. In a few cases, weakness is associated with autonomic disturbances and may lead to hemodynamic instability. Hence, the management of ANTW should include simultaneous resuscitation (care of airway, breathing, and circulation [ABC]) and evaluation of underlying disease pathology. ANTW is one of the few neurological conditions where delaying the diagnosis and initiation of treatment directly affects the outcome. With a thorough history and clinical examination, we should be able to localize the lesion in many patients or should be able to narrow down the differential diagnosis list.

Here in this review, we discuss the systematic approach to the management of patients with ANTW. Traumatic and chronic weaknesses are beyond the scope of this review.

Initial Evaluation

The initial evaluation should include the assessment of the patient's ability to protect the ABC and appropriate measures should be taken to optimize ABC before the neurological examination.[4,5] Initial neurological examination should be done quickly to rule out time-critical emergencies including acute ischemic stroke, acute spinal cord compression, status epilepticus, dyselectrolytemia, hypoglycemia, and toxin. Various assessment tools are available to assess the neurological status of the patient including the Glasgow Coma Scale, FOUR score (includes eye response, motor response, brainstem response, and respiration), and prehospital stroke scale score. Early recognition and activation of the stroke code system are necessary for optimum outcome in these patients. The acute spinal cord compression may present with flaccid paralysis below the level of insult, and a sensory deficit limited to the involved segment. There may be certain syndromes having their own specific features such as acute cauda equina syndrome that presents with lower severe back pain, sciatica, perineal hypoesthesia, bowel and bladder incontinence, and limb weakness with decreased reflexes.[3] If toxin exposure is suspected, scene safety should be ensured, and history related to amount and type toxin should be elicited. Initial biochemistry must include blood glucose, electrolytes (sodium, potassium, calcium, magnesium, and phosphorus), kidney and liver function tests, blood coagulation test, and complete blood counts. Relevant imaging should be obtained as indicated by history and examination. A detailed motor and sensory examination should be done to locate the lesion anatomically by characteristics of the weakness.

Assessment of Airway and Ventilation

Neurologically ill patients need airway protection and ventilation if their airway is at risk of aspiration or breathing is inadequate. There are various causes of the airway and respiratory compromise including pharyngeal muscle weakness, leading to the upper airway obstruction and increased risk of aspiration, and respiratory muscle weakness leading to respiratory failure.[6] Pulmonary gas exchange is usually preserved but may be affected due to atelectasis. Noninvasive ventilation may be tried if the airway reflexes are intact, but respiratory failure occurs due to respiratory muscle weakness. Patients should be monitored regularly as patient's clinical condition may deteriorate rapidly.

Besides the patient's physiology, the plan to intubate is also influenced by the clinical environment and the anticipated course of the disease. If the patient is comatose and needs to be transported to a higher center, for imaging, or other invasive intervention, it would be most appropriate to secure the airway with endotracheal intubation. The patients who are expected to deteriorate in due course of time may need intubation, such as rapidly progressing Guillain–Berré syndrome (GBS).[7,8] On the other hand, if the patient has a known illness, which is stable and expected to improve, can be managed by noninvasive ventilation.

Various predictors for the need of intubation are enumerated in ►**Table 1**. A combination of clinical signs and objective parameters should be used to predict the need for intubation rather than a single parameter alone. Rapid sequence induction is the preferred modality of emergency intubation in the neurologically ill patients who are at risk of aspiration.[9-12] Pharmacological agents must be carefully chosen as these patients may be at risk of succinylcholine-induced hyperkalemia (e.g., GBS) or resistant to it (e.g., myasthenia gravis).[13,14] The patients may be highly sensitive to the sedative-hypnotic agents due to associated autonomic nervous system disturbance.

After intubation, the goals of mechanical ventilation are to normalize oxygenation using the lowest possible inspired oxygen to achieve a hemoglobin saturation >94%, a systemic pH of 7.3 to 7.4, and partial pressure of carbon dioxide or end-tidal carbon dioxide of 30 to 40 mm Hg, to reduce the work of breathing, and to prevent ventilator-induced lung injury.[15] Once the patient's ABC are stabilized, a detailed and comprehensive neurological examination is done to localize the lesion.

Clinical and Anatomical Localization

The cause of weakness can be localized anatomically based on detailed history and examination as the patterns of weakness and associated findings are often specific for each anatomical region. Then we can make a focused differential diagnosis, and specific testing can be done to make an accurate

Table 1 Indications for intubation[2,3]

Clinical symptoms • Increasing generalized muscle weakness • Dysphagia • Dysphonia • Dyspnea on exertion and at rest • Unable to remove secretions from the throat
Subjective (clinical signs) • Tachypnea/hypopnea • Inadequate chest rise • Paradoxical respiratory pattern • Weak coughing ability • Unable to complete full sentences (gasping for air) • Inability to perform single-breath count: count from 1 to 20 in single exhalation (FVC 1.0 L is roughly equal to counting from 1 to 10) • Use of accessory muscles (cervical/trapezius/nasal flaring) • Weakness of trapezius and neck muscles: inability to lift head from bed • Orthopnea • Tachycardia/hypertension (secondary to sympathetic stimulation due to hypoxia and hypercapnia) • Sweating
Objective • Loss of consciousness • Hypoxemia (<60 mm Hg) • PFT findings –Vital capacity <1 L or 20 mL/kg, or 50% decrease in VC in a day –Maximum inspiratory pressure > −30 cm H_2O –Maximum expiratory pressure < 40 cm H_2O • Hypercarbia

Abbreviations: FVC, forced vital capacity; PFT, pulmonary function tests; VC, vital capacity.

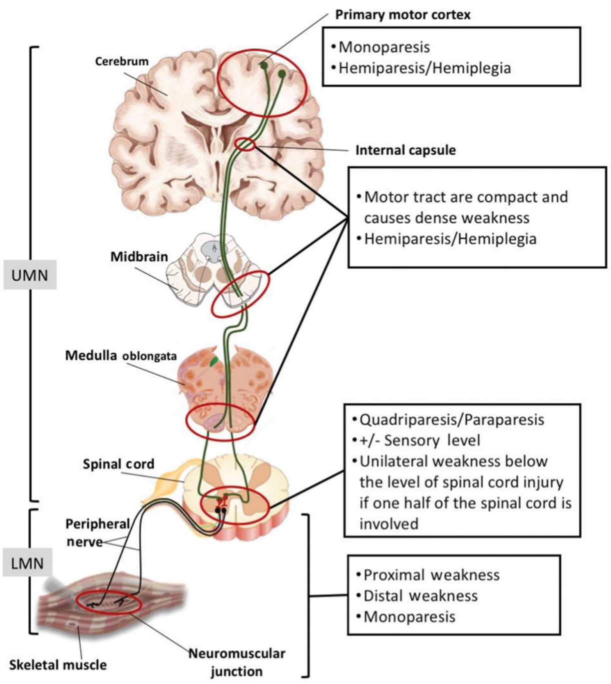

Fig. 3 Diagrammatic representation of clinical localization of the cause of acute nontraumatic muscle weakness based on the pattern of weakness. LMN, lower motor neuron; UMN upper motor neuron.

diagnosis. In an obtunded or confused patient, a good clinical history is essential, as such patients may not cooperate for examination. With history and examination, we should be able to elicit whether the weakness is unilateral or bilateral, the pattern of weakness (monoparesis, hemiparesis, paraparesis, quadriparesis or patchy involvement), associated weakness (facial, neck or truncal muscle), the tone of the involved limbs (hypertonia [spasticity or rigidity] or hypotonia), reflexes (normal, diminished or hyperreflexia), and sensory involvement. In a cooperative patient, further evaluation is done to assess the pattern of weakness (symmetrical or asymmetrical, proximal or distal extremities), and sensory modalities affected (pain, fine touch, proprioception, and vibration). The absence of sensory signs (loss of sensations) or symptoms (numbness/tingling) rule out the involvement of peripheral nerves to some extent, and a central nervous system disease should be considered. ►**Figure 3** and ►**Table 2** show the localization of various differential diagnosis depending on the clinical features.[3]

With this protocol, we can locate the following anatomical regions: brain, spinal cord, anterior horn cell (α motoneuron), peripheral nerve, neuromuscular junction (NMJ), and muscle.[3] The diseases of the brain and spinal cord (central nervous system) lead to "upper motor neuron (UMN) weakness," that is the disruption of descending motor axons or cell

Table 2 Clinical localization of weakness based on pattern of weakness

Pattern of weakness	Probable differential diagnosis
Hemiparesis/hemiplegia (partial/complete paralysis affecting only one side of the body)	• Acute stroke: ischemic, hemorrhagic, or subarachnoid hemorrhage • Intracranial mass • Meningitis/encephalitis • Hypoglycemia/hyperglycemia • Postictal Todd's paresis • Hemiplegic migraine • Brown–Sequard syndrome
Quadriparesis/paraparesis ± sensory level (symmetrical weakness of either all four limbs or both lower limbs)	• Spinal cord compression (e.g., epidural abscess, hematoma, expanding tumor, or prolapsed intervertebral disc) • Spinal cord infarction: ischemia • Transverse myelitis • Generalized weakness: electrolyte and glucose abnormalities
Proximal weakness (predominantly affecting the axial muscles, deltoid, and hip flexors)	• Acute myopathy • Guillain–Barré syndrome • Acute diabetic lumbosacral radiculoplexus neuropathy • Myasthenia gravis • Acute West Nile virus-associated paralysis • Lambert–Eaton myasthenic syndrome
Distal weakness (weakness mainly affecting the hands, wrists, and feet)	• Vasculitis neuropathy • Toxin-induced peripheral neuropathy • Nerve compression syndromes
Monoparesis (paralysis of a single muscle, muscle group, or limb)	• Acute stroke • Intracranial mass • Postictal Todd's paresis • Nerve compression syndromes • Diabetic lumbosacral radiculoplexus neuropathy • Acute poliomyelitis

Source: Modified from Caulfield et al.[3] (with permission).

bodies that innervate the lower motor neurons located in the anterior horn cells of the spinal cord. Lower motor neurons type of weakness is caused by lesions of the anterior horn cells, peripheral nerve, and NMJ. UMN lesions are usually characterized by increased muscle tone, hyperreflexia, and a positive Babinski sign (great toe extension and fanning of fingers). LMN lesions, in contrast, cause flaccidity, areflexic weakness, and fasciculations (involuntary contractions or twitching of muscle fibers). During the acute phase of weakness, the UMN lesions may mimic the LMN lesions and may present with flaccid paralysis, normal or decreased tone, unreliable reflexes, and absent atrophy and fasciculations (occurs after a longer duration of paralysis).[16,17]

The characteristic features, history, clinical examination diagnosis, and treatment of various causes are represented in ►Fig. 4.

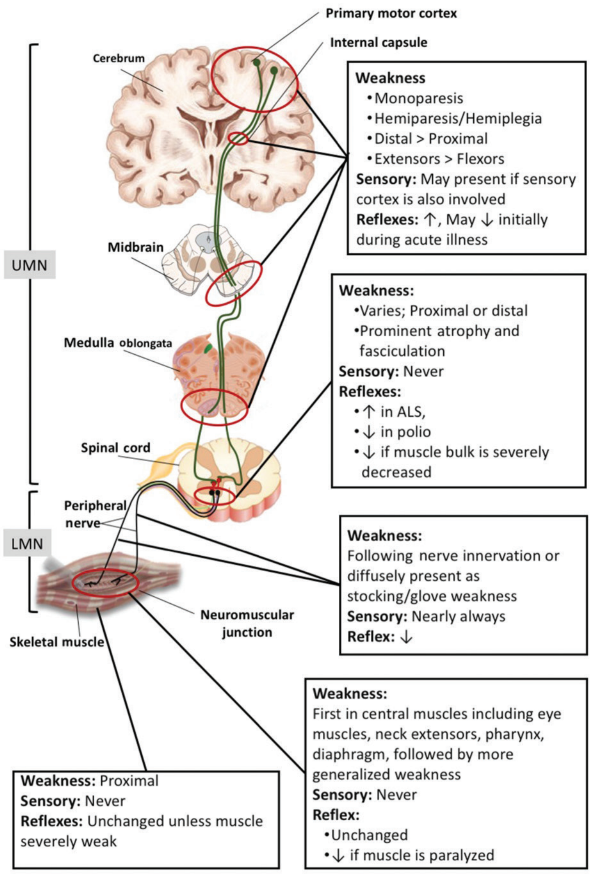

Fig. 4 Diagrammatic representation of anatomical localization of the cause of acute nontraumatic muscle weakness at various levels along the motor tract. LMN, lower motor neuron; UMN upper motor neuron.

Approach of a Patient with ANTW

Irrespective of clinical presentation, the initial management always includes care of ABC. Along with checking the vitals (pulse rate, blood pressure, and temperature), blood sugar should be checked in all patients presenting with weakness. After that, a detailed history and neurological examination are done to make the initial working diagnosis and differential diagnosis. The algorithm suggested by ENLS is shown in ►Fig. 5.[3]

The diagnostic tests and definitive management vary greatly from one patient to another and may range from an emergent stroke imaging to elective nerve/muscle biopsy for specific illnesses. Various diagnostic modalities and treatment options for major differential diagnosis are enumerated in ►Table 3. After making an initial working diagnosis and differential diagnosis, the patients are further evaluated by various investigations including initial laboratory tests such as glucose, electrolytes (sodium, calcium, magnesium, potassium, and phosphorous), blood urea nitrogen, creatinine, liver function tests, coagulation profile, complete blood counts, and arterial blood gas analysis. If history and examination suggest, certain specific tests may be performed such as thyroid function tests, creatine phosphokinase or CK, erythrocyte sedimentation rate, parathyroid hormone, gamma-glutamyl transferase, serum toxicology, and drug level. Once the patient's ABC are optimized, the relevant imaging is obtained (computed tomography/magnetic resonance imaging [CT/MRI]). Nerve conduction studies, electromyography, a biopsy of nerve and muscle, and lumbar puncture are to be done if indicated. Patients should be periodically screened for airway and ventilation as these may be involved as the disease progresses. If the examination findings, laboratory tests, and imaging are all within normal limits, then we should consider functional causes such as malingering, conversion disorder, anxiety disorders, fibromyalgia, and chronic fatigue syndrome.

Psychiatric Illnesses

Conversion disorders are a quite common cause of ANTW and constitute around 5 to 14% of the cases presenting in the emergency department.[18] The conversion symptoms may represent a form of communication where patients are not able to express their emotions otherwise, or they may intend to gain attention and rewards from others. The conversion symptoms may originate from a stressful environment where an idea or psychological conflict is converted into somatic symptoms. A detailed psychodynamic assessment helps in making the diagnosis. In psychiatric illnesses presenting as ANTW, the history, clinical examination, initial laboratory tests, and imaging all are inconclusive for any physical illness. Usually, there is a temporal association with psychosocial stressors, and symptom substitution is frequently present. On examination, there is a "La belle indifference" (the person is unconcerned with symptoms) and distribution of weakness does not follow any anatomical pattern. Various investigations, such as MRI/CT and EEG, should be done to rule out organic lesions. Visual-evoked potentials and brainstem auditory-evoked responses should be done to rule out malingering/compensation neurosis if affective or emotional disturbances are found on clinical examination.

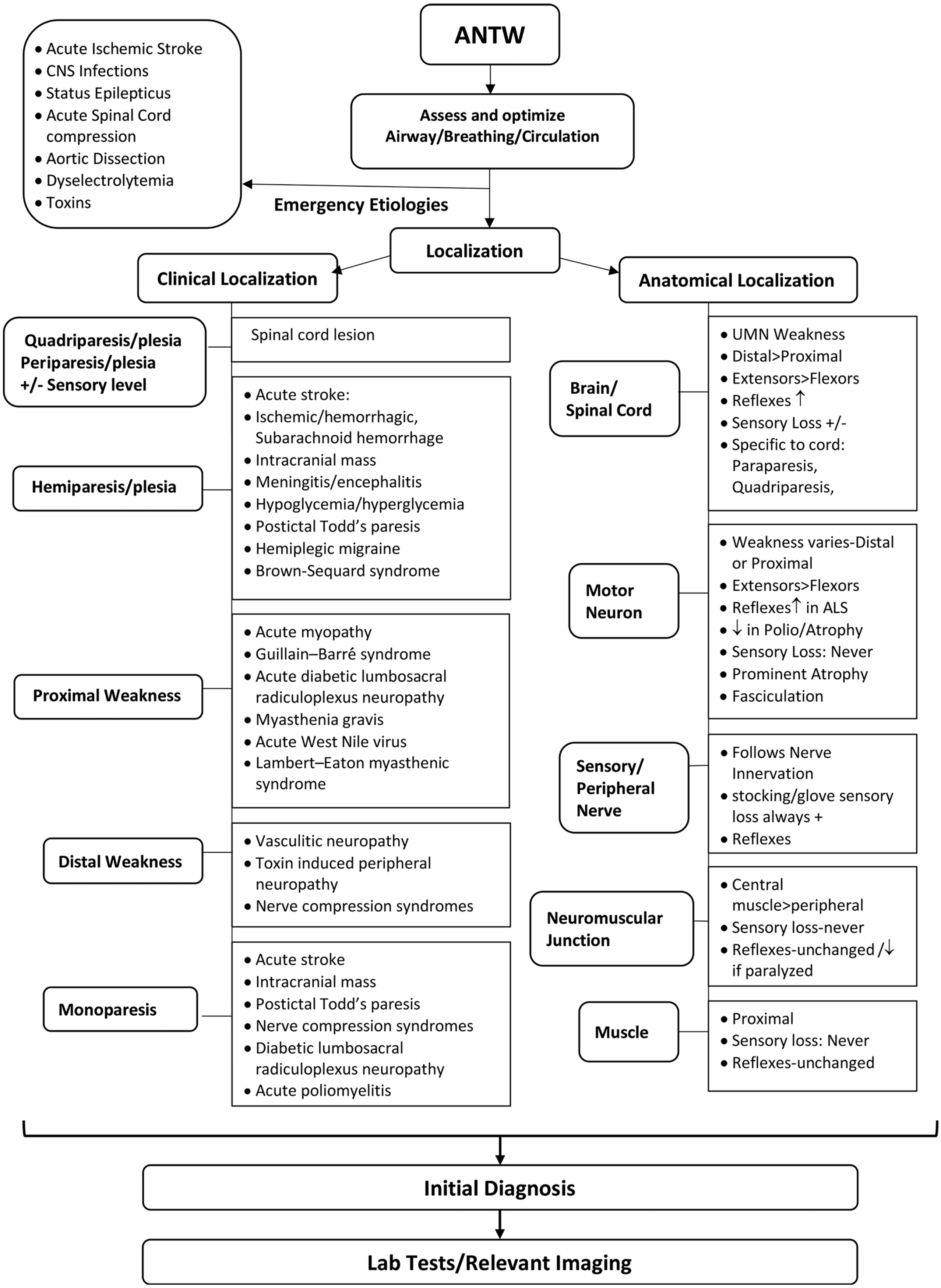

Fig. 5 Algorithm for the management of acute nontraumatic weakness. ANTW, acute nontraumatic weakness; ALS, amyotrophic lateral sclerosis; CNS, central nervous system; UMN, upper motor neuron. Source: Adapted with permission from Caulfield et al.[3]

Table 3 Clinical characteristics of various differential diagnosis of acute nontraumatic weakness

Disease	History	Examination	Investigation	Treatment
Brain lesions				
Intracranial mass[24,25]	• Associated symptoms of brain tumors vary widely depending up location and size of tumor • Symptoms and signs of increased ICP • Local mass effect causes headaches, seizures, nausea, ataxia, and cognitive dysfunction, focal neurological deficits • Generalized mass effect presents as headache, nausea and vomiting, blurring of vision • Weakness is UMN/spastic pattern (upper limb extensors, lower limb flexors) • Brain abscess also presents with similar features along with fever	• Pupillary asymmetry • Papilledema on fundus examination • UMN type of weakness • Extensor plantar reflex	• CT head to rule out other causes to localize the lesion • MRI for detailed morphology	• Consider steroids for peritumoral vasogenic edema • Manage raised ICP in the standard stepwise approach • Manage blood pressure and treat coagulopathy if there is intracranial bleed • Brain abscesses require targeted antimicrobial treatment and sometimes drainage • Surgical evacuation and excision of lesion if indicated
Acute ischemic stroke	• Sudden onset hemiparesis/monoparesis • Faciobrachial syndrome	• UMN type • On the opposite side of lesion • Extensor > flexors in UL • Flexors > extensors in LL • Reflexes increased and plantar extensors on the side of hemiparesis	• CT head • MRI brain (diffusion-weighted images) • Angiogram of neck and intracranial vessels • ECG/Echocardiography to rule out cardio-embolic cause	• Stroke protocol • In acute phase: thrombolysis/thrombectomy • In later phase: antiplatelets/statins/anticoagulants
Postictal Todd's paresis[26,27]	• More common after prolonged seizures (status epilepticus) • Self-limiting and lasts for seconds or up to hours	• Transient weakness • Weakness varies widely in location, severity, duration, tone reflexes, and sensory involvement	CT head to exclude other causes of weakness	• Supportive

(continued)

Table 3 *(Continued)*

Disease	History	Examination	Investigation	Treatment
Hypertensive encephalopathy[28,29]	• Long standing, poorly controlled hypertension • Poor compliance with antihypertensive agents, • Headaches, confusion, visual disturbances, nausea, and vomiting	• Severe, sustained hypertension • Transient, migratory neurological non-focal deficits, ranging from nystagmus to weakness, and an altered mental status, ranging from confusion to coma • Funduscopic may reveal f/s/o HTN retinopathy—papilledema, hemorrhage, exudates, and cotton wool spots	• CT head • Urine toxicology screen • Coagulation profile	• Invasive BP monitoring • IV antihypertensive agent • Aim to reduce initial MAP by no more than 25% • Avoid lowering BP too much, too quickly, as it may lead to cerebral ischemia
Hemiplegic migraine[30,31]	• Start in the first or second decade of life as sporadic or familial • Most patients also have attacks of migraine with typical aura without weakness • Aura consists of a fully reversible motor weakness • Weakness may resolve before the headache starts or may persist for days • May be accompanied by ipsilateral numbness or tingling, with or without a speech disturbance • In familial hemiplegic migraine (FHM), there is positive family history in at least one first- or second- degree relative	• Neurological examination assessing for other causes of hemiplegia • The short time course and full reversal spontaneously	• Diagnosis of exclusion • CT or MRI to exclude other etiologies • Angiography to rule out transient ischemic attacks and vascular abnormality • SPECT scan may show hypoperfusion during the aura phase • Genetic testing is available for FHM	• Early neurologist involvement • Antiemetics, nonsteroidal anti-inflammatory drugs, and nonnarcotic pain relievers • Prophylactic treatment may include lamotrigine and acetazolamide

(continued)

Table 3 *(Continued)*

Disease	History	Examination	Investigation	Treatment
Spinal cord lesions				
Spinal cord infarction[32]	• Acute quadriparesis or paraparesis with a sensory level corresponding with level of cord infarct • No history of trauma or infection • 60% of patients present with pain that localizes to the level of injury • May be associated with aortic surgery or procedures such as celiac ganglion ablation • May be having risk factors leading to hypercoagulable states	• May present with anterior or posterior spinal artery syndrome (A/PSAS) depending upon the portion of spinal cord involvement • **ASAS:** loss of motor power, usually bilateral weakness, occasionally unilateral Initially flaccid paralysis and loss of deep tendon reflexes Loss of pain/temperature sensation • **PSAS:** loss of proprioception and vibratory sense below the level of the injury Total anesthesia at the level of injury • Other variants possible	• **MRI:** Ischemic lesion matching an arterial territory of the cord • **Spinal angiogram:** as suggested from MRI to rule out malformations • Other investigations to rule out **hypercoagulable state:** prothrombotic and vasculitis screen Toxicology screen Electrocardiography Echocardiography Duplex ultrasonography of the cervical arteries 24-hour Holter electrocardiography	• Supportive treatment only • Corticosteroids are currently not recommended • Consider antiplatelet agents in patients with underlying vascular risk factors • Intervention directed toward the underlying lesion
Aortic dissection[33–35]	• Severe, sharp or "tearing" posterior chest or back pain • May be associated with an acute neurological deficit • Neurological features may include hemiplegia, monoplegia, and paraplegia	• One-third experiences neurological deficits[18] • 10% of type A dissections may present with only neurological manifestations • Weak or absent pulse (15.1%) (carotid, brachial, or femoral)[17] • Associated features may include acute myocardial infarction, cardiac tamponade, hemothorax, hypotension, pain, abdominal pain, back or flank pain, renal failure, or Horner's syndrome	• ECG to exclude myocardial infarction • CXR for mediastinum widening and hemothorax • Bedside echocardiogram transesophageal or transthoracic • CT aortogram • CT head	• Reduce systolic blood pressure and heart rate using IV β blocker; consider a nitroprusside infusion; avoid hydralazine • Surgical intervention as soon as possible and if indicated

(continued)

Table 3 *(Continued)*

Disease	History	Examination	Investigation	Treatment
Brown–Sequard syndrome[36,37]	• Sudden onset hemiplegia with contralateral loss of pain and temperature	• Ipsilateral weakness • Ipsilateral loss of proprioception and vibratory sensation • Contralateral loss of pain and temperature sensation • Urinary bladder and bowel involvement	• MRI • CT myelography if MRI contraindicated	• Immobilization • Surgery with spinal cord decompression
Transverse myelitis[38]	• Isolated spinal cord dysfunction over hours or days • Weakness and sensory disturbance below the level of the lesion • Back pain with bladder and bowel dysfunction is common • No evidence of compressive lesion • Segmental spinal cord injury caused by acute inflammation • Thoracic cord most commonly involved • 50% have preceding viral infection	• Evidence of myelopathy, with weakness and sensory symptoms corresponding to a specific dermatomal and myotomal level • Increased or decreased sensation with paresthesia may be present • Urinary bladder and bowel involvement	MRI is diagnostic	• IV methylprednisolone • IVIG • Plasma exchange
Amyotrophic lateral sclerosis (ALS)[39–42]	• Progressive weakness which may start in a limb • May manifest by slurred speech and dysphagia • A small percentage may have respiratory involvement initially • Other neurological symptoms: changes in mental function (e.g., dementia, pseudobulbar affect • Absence of alternative diagnosis	• A mixture of UMN signs and LMN signs • The sensory examination is usually normal • Spares urinary bladder/bowel	• Nerve conduction studies • Electromyography (EMG) • MRI (to exclude other intracranial lesions) • To exclude other diagnoses: anti-GM1 antibody (multifocal motor neuropathy), SPEP (multiple myeloma, lymphoma), heavy metals, HIV, Lyme antibody, myasthenia gravis • Lumbar puncture: HIV, Lyme disease or chronic Inflammatory demyelinating	• Supportive care

(continued)

Table 3 *(Continued)*

Disease	History	Examination	Investigation	Treatment
Peripheral nerve lesions				
Guillain–Barré syndrome[7,8,42–45]	• Precedental history of mild respiratory or gastrointestinal illness (2–4 weeks prior) • Typically, **symmetrical ascending paralysis** with limb paresthesia is common (80%) and pain • Dysautonomia occurs in 70% • Upper limb/facial weakness (10%) • Respiratory failure (~10%) • Oculomotor weakness (15%)	• Symmetrical ascending paralysis • Absent deep tendon reflexes • Miller Fisher syndrome variant presents with ophthalmoplegia, ataxia, and areflexia • In acute motor axonal neuropathy variant, sensation is preserved • Acute motor and sensory axonal neuropathy has more sensory symptoms • Other rarer variants may exist[40]	• CSF analysis: elevated protein, normal cell count • Electromyography • Nerve conduction studies • Glycolipid antibodies may be present in some variants	• Supportive care • Plasma exchange • IVIG • No benefit for corticosteroids[41]
Vasculitic neuropathy[46,47]	• May be part of systemic vasculitis or a nonsystemic vasculitic neuropathy • Asymmetric or multifocal painful sensorimotor neuropathy • May present as mononeuritis multiplex or a sensorimotor neuropathy • Sensory symptoms of pain, burning, or paresthesias precede and virtually always present • Weakness of muscles supplied by the affected nerve • Constitutional symptoms, including weight loss, anorexia, fatigue, arthralgia, myalgia, and fever, occur in approximately two-thirds of patients	• Flaccid asymmetric paresis with sensory abnormalities in variable distributions • Lower limbs are more commonly involved • Distal involvement is more frequent than proximal • Cranial nerve (facial) may be involved in 8% of patients	• **Vasculitic screen:** – Erythrocyte sedimentation rate – Antinuclear antibodies – Extractable nuclear antigens – Rheumatoid factor – Antineutrophil – cytoplasmic antibodies Serum complement – Serum immunofixation/ immunoelectrophoresis – Quantitative immunoglobulins Cryoglobulins • Hepatitis B/C antigen and antibody • Nerve conduction studies • EMG • Nerve and muscle biopsy	• Combination therapy with steroids and cyclophosphamide • Treat neuropathic pain with agents such as – Pregabalin – Gabapentin – Amitriptyline – Nortriptyline – Carbamazepine

(continued)

Table 3 *(Continued)*

Disease	History	Examination	Investigation	Treatment
Toxin-induced peripheral neuropathy[48] (alcohol, amiodarone, chloramphenicol, disulfiram, isoniazid, lithium, metronidazole, nitrofurantoin, nitrous oxide, thalidomide, vincristine, thallium, etc.)	• Many drugs and industrial chemicals may cause distal axonopathy • Dose, duration of exposure, and host factors affect outcome • Presentation with pain, paresthesia, and hypoesthesia in the feet and distal weakness and gait disturbance • Autonomic dysfunction may be present	• Sensory changes in glove and stocking distribution • Distal weakness that progresses proximally • Hyporeflexia, symmetrical loss of ankle jerks first • CNS may be involved	• EMG (electromyography) • Nerve conduction study • Serum levels for suspected toxin • Consider nerve/muscle biopsies	• Prevent ongoing exposure • Supportive care
Heavy metal toxicity[49–51]	• Peripheral neuropathies may occur within a few hours to days of acute high dose exposure, especially lead, arsenic, and thallium[47] • Common presentation: nausea, persistent vomiting, diarrhea, and abdominal pain, with encephalopathy, cardiomyopathy, dysrhythmias, acute kidney injury, and metabolic acidosis	• Lead neuropathy initially affects motor fibers in radial and peroneal distributions • Mees lines (horizontal hypopigmented lines across all nails) • Evidence of anemia and other major organ failures	• CBC (anemia) with blood film analysis for basophilic stippling (lead/arsenic toxicity), • Kidney and liver function tests and coagulation studies • Serum and urine metal levels of suspected metal	• Stop further exposure • Consult toxicologist/poison center • Symptomatic treatment • Consider chelation therapy
Nerve compression syndromes[52,53] (median nerve at wrist, ulnar nerve at elbow and wrist, radial nerve in proximal forearm, scapular nerve, lateral femoral cutaneous nerve, common peroneal nerve, tibial nerve, and lower brachial plexus)	• History of acute or prolonged neural pressure • History depends on the region involved • Pain and paresthesias typically precede hypoesthesia and weakness/atrophy • May be caused by systemic conditions such as pregnancy, obesity, hypothyroidism, and diabetes • Local causes such as prolapsed intervertebral disc produces symptoms in the affected dermatome and myotome	• Weakness in the muscles supplied by the affected nerve • Flaccid, hypotonic, hyporeflexic paralysis • Sensory symptoms include pain, paresthesias, and hypoesthesia • Wasting and atrophy if long standing • Skin changes include dry, thin, hairless skin; ridged, thickened, cracked nails; and recurrent skin ulceration	• Nerve conduction studies • MRI • EMG	• Treat or remove precipitants • Decompressive surgery if conservative management fails

(continued)

Table 3 *(Continued)*

Disease	History	Examination	Investigation	Treatment
Neuromuscular junction				
Botulism[53–55,56]	• **Descending symmetrical paralysis** with a clear sensorium and no fever • No sensory deficits other than blurred vision • **Foodborne** Seen after 12–36 hours of ingestion Prodromal symptoms including nausea, vomiting, abdominal pain, diarrhea, and dry mouth with sore throat[42] • **Wound botulism** Follow deep infected regions with the presence of spores • **Infantile botulism** Occurs from 1 week–1 year in infants who are formula fed • May present with constipation, weakness, feeding difficulties, descending or global hypotonia, drooling, anorexia, irritability, and weak cry[43]	• Cranial nerves first affected: fixed dilated pupils (causing blurred vision), diplopia, nystagmus, ptosis, dysphagia, dysarthria, and facial weakness • Descending flaccid paralysis • May cause bladder and bowel dysfunction	• Stool, vomit, suspected food and wound debridement looking for *C. botulinum* spores • Serum assay for botulinum toxin • Pulmonary function tests	• Adults/Children >1 year: Equine serum heptavalent • Infants < 1 year: Human-derived botulism immune globulin • Penicillin G (or metronidazole) for wound
Tick paralysis[57,58]	• Presents with unsteady gait followed by an ascending symmetrical flaccid paralysis 2–6 days post tick attachment • Sensory symptoms: paresthesias and hypoesthesia • Anorexia, lethargy, drowsiness, and confusion may precede weakness • Ataxia may be only symptom • No fever	• Tick found attached to patient • Ascending symmetrical flaccid paralysis • Hypotonic, hyporeflexic • Progresses to affect all cranial nerves including pupillary dilatation • Sensory function is generally preserved other than mild paresthesias and hypoesthesia	• Locate tick • EMG shows reduced amplitude of compound muscle action potentials • Labs, CSF analysis, and MRI are typically normal	• Paralyze tick with insecticide and remove with forceps • Supportive care
Organophosphate toxicity[59,60]	• Insecticide exposure (e.g., malathion, parathion, diazinon, fenthion, dichlorvos, chlorpyrifos, ethion) • Nerve gas exposure (e.g., sarin, VX, soman, tabun) • Ophthalmic agents (e.g., echothiophate, isoflurophate) • Antihelminthics (trichlorfon)	• Fasciculations with paralysis • Cholinergic symptoms: Bronchospasm, bradycardia, miosis, lacrimation, salivation, bronchorrhea, urination, emesis, and diarrhea • Decreased deep tendon reflexes, • cranial nerve abnormalities including bulbar palsy • Respiratory insufficiency • Delayed ascending flaccid paralysis may develop	• History of exposure • RBC acetyl cholinesterase (if available) for severity and to guide oxime therapy	• Remove contaminated clothes • Care of airway, breathing, and circulation • Atropine 2–3 mg IV stat, then double the dose every five minutes until symptoms are controlled • Pralidoxime • Consider benzodiazepines for the prevention and treatment of seizures

(continued)

Table 3 *(Continued)*

Disease	History	Examination	Investigation	Treatment
Myasthenia gravis[61,62]	• History of myasthenia gravis • Acute decompensation (myasthenic crisis) may be spontaneous or precipitated by infection, surgery, or tapering of immunosuppression, certain antibiotics and other precipitating factors • Excessive treatment with cholinesterase inhibitors may paradoxically cause weakness (Cholinergic crisis)	• 85% of patients have involvement of the eyelids and extra-ocular muscles, resulting in ptosis and/or diplopia[23] • Fatiguability • Flaccid muscles weakness • Central muscles are predominantly involved such as bulbar muscles • Neck and proximal limb weakness may occur • Respiratory failure occurs in 1% • Weakness increases after exertion	• Ice pack test (e.g., ice on affected eyelid improves ptosis) • ACh receptor antibodies if diagnosis uncertain • Pulmonary function tests • Consider arterial blood gas • Consider CT chest (thymoma may affect breathing)	• For acute decompensation, admit to ICU • Airway and ventilation should be assessed and managed with either non-invasive ventilation or intubation • Withdraw anticholinesterase medications • Plasmapheresis or IVIG • High-dose steroids • Consider other immunosuppressants
Lambert–Eaton myasthenic syndrome (LEMS)[63,64]	• In 40% of patients, small cell lung cancer is present • Progressive proximal lower limb weakness • Ptosis, diplopia, and dysarthria as cranial nerves become involved, (less common than myasthenia gravis) • Autonomic dysfunction • Exacerbated by heat or fever and certain drugs	• Proximal muscle weakness, lower limbs more than upper • Depressed tendon reflexes • Post-tetanic potentiation • Sensation preserved • Respiratory failure rare	• Voltage gated calcium channel antibodies • AChR antibodies • Repetitive nerve stimulation • EMG • Look for malignancy with imaging/ Bronchoscopy	• Confirm diagnosis and distinguish from myasthenia gravis before starting treatment • Supportive treatment • Treat underlying malignancy • Consider 3,4-diaminopyridine • IVIG • Plasma exchange
Muscle				
Dermatomyositis[65]	• May present with skin and/or muscle involvement • Proximal muscle weakness • Characteristic rash • Systemic symptoms include arthralgia, arthritis, dyspnea, dysphagia, arrhythmia, and dysphonia	• Heliotrope rash (blue-purple discoloration on the upper eyelids) • Raised, violaceous, scaly eruption on the knuckles (Gottron's papules) • Proximal symmetrical muscle weakness • Muscle pain and tenderness • Normal sensation and tendon reflexes • Joint swelling (particularly of the hand) may occur occasionally in some patients	• Elevated CK, aldolase, lactate dehydrogenase, or alanine aminotransferase • Auto-antibody serology • Skin biopsy • Muscle biopsy • NCS/EMG	• Corticosteroids • Consider immunosuppressive or cytotoxic steroid sparing agents • IVIG in refractory cases

(continued)

Table 3 *(Continued)*

Disease	History	Examination	Investigation	Treatment
Generalized weakness due to systemic causes				
Hyperglycemia[66,67]	• History of diabetes • Possible precipitating events (e.g., infection, myocardial infarction, surgery, critical illness) • Neurological symptoms primarily occur when plasma osmolality is greater than 320 mOsmol/L • Neurological symptoms may include hemiparesis, focal motor deficits, decreased consciousness, and seizures • May have polyuria, polydipsia, and weight loss for several days before presentation	• Level of consciousness may be reduced • Focal motor and sensory deficits including aphasia, hyperreflexia, hemianopia, and brainstem dysfunction • Other findings associated with DKA or HHS include evidence of volume depletion, hyperventilation and abdominal pain	• Serum glucose • Plasma osmolality • Serum electrolytes (with anion gap), urea, and creatinine • Urinalysis, and urine/ serum ketones by dipstick • Blood gas • Electrocardiogram • CT head to exclude other causes	• Fluid replacement to correct hypervolemia and hyperosmolality • Insulin infusion • Close monitoring of urine output and electrolytes (potassium, magnesium, and phosphate) • Treat precipitating cause
Hypoglycemia (serum glucose<3 mmol/L; <50 mg/dL)[68]	• Diabetes • Insulin regimen • Oral hypoglycemics • Alcohol • Sepsis • Liver disease • Hypocortisolemia	• Decreased consciousness • Many forms of focal neurological deficit possible, which may mimic • Dysphoria • Seizures stroke • Tremor, palpitations, anxiety, sweating, hunger, and paresthesia	• Blood glucose level • CT head to rule out intracranial causes	• IV dextrose • Oral if patient is conscious • Alternatively, 1 mg glucagon IM or IV
Hyponatremia, hypernatremia[69,70]	• **Hyponatremia:** diuretic overdose, hypervolemia, CHF, cirrhosis, SIADH, cerebral salt wasting and water intoxication • **Hypernatremia**: dehydration, pituitary insufficiency, iatrogenic sodium supplementation • Lethargy and confusion are most common followed by seizures and coma in both extremes	• Depressed level of consciousness or delirium	• Serum sodium levels	• **Hyponatremia:** fluid restriction, stop diuretics, avoid rapid correction • **Hypernatremia:** IV fluids if hypovolemic, prefer hypotonic solutions (5D, 0.45% NS), avoid rapid correction • if urine specific gravity is low (pituitary insufficiency): administer desmopressin
Hypermagnesemia[71]	• Typically follows excessive magnesium administration (e.g., management of pre-eclampsia) in context of renal impairment • Lethargy and confusion are most common neurologic manifestations followed by generalized weakness, and respiratory failure	• **Hyporeflexia:** (early sign) loss of deep tendon reflexes • Flaccid tetraparesis involving all muscle groups • Lethargy, confusion	Serum magnesium levels	• Stop magnesium administration • IV calcium gluconate/chloride • IV fluids • Consider dialysis

(continued)

Table 3 *(Continued)*

Disease	History	Examination	Investigation	Treatment
Hypophosphatemia[72,73]	• **Causes** of hypophosphatemia include: – **Intracellular shift:** refeeding syndrome, respiratory alkalosis, diabetic ketoacidosis, rapidly growing malignancies, osmotic diuresis, malabsorption, renal tubular acidosis – **Increased urinary excretion:** primary or secondary hyperparathyroidism, osmotic diuresis, renal tubular acidosis, transplanted kidneys, Fanconi syndrome, etc. – **Decreased intestinal absorption:** diarrhea, malabsorption syndromes, phosphate binders – **Decreased dietary intake:** anorexia nervosa or chronic alcoholism, Hypothermia • Painful proximal myopathy • Other symptoms: changes in mental function, seizures, neuropathies, arrhythmias, skeletal muscle weakness, respiratory failure, rhabdomyolysis, leucocyte dysfunction, sepsis, and sudden death	• Proximal muscle weakness is common • Any muscle group may be involved in various combinations, ranging from ophthalmoplegia to proximal myopathy to dysphagia or ileus • Weakness may be so profound as to mimic Guillain–Barre syndrome • Neurological features: Confusion, seizures, and coma • Cardiac contractility may be impaired leading to global myocardial depression	• Serum phosphate • Hypercalcemia or Hypomagnesemia is commonly associated • Other electrolytes • Rhabdomyolysis screen	• Correct precipitant • Replace total body phosphate with careful IV sodium or potassium phosphate
Periodic paralysis (PP)[74]	• Repeated episodes of flaccid muscle weakness occurring at irregular intervals with normal strength between episodes • Usually hereditary • Various types of periodic paralysis exist, including: – Hyperkalemic PP – Hypokalemic PP – Paramyotonia congenita – Thyrotoxic PP – Andersen-Tawil syndrome • Look for precipitating factor (e.g., post exercise, fasting, cold alcohol, stress, and duration of episode)	• All forms usually exhibit: – Interictal lid lag and eyelid myotonia – Normal sensation – Fixed proximal weakness – Diminished reflexes during episode – Normal power in between the episodes	• Serum potassium • Elevated creatine kinase (CK) • Potassium: creatinine ratio • Blood gas analysis for evidence of concomitant metabolic acidosis or alkalosis • ECG • EMG • Nerve conduction studies	• **Hyperkalemic PP:** – High carbohydrate food – Thiazide or acetazolamide • **Hypokalemic PP:** – Potassium supplementation – Acetazolamide • **Thyrotoxic PP:** – Beta blockers – Treat thyrotoxicosis • **Andersen–Tawil syndrome:** • Acetazolamide

(continued)

Table 3 *(Continued)*

Disease	History	Examination	Investigation	Treatment
Miscellaneous				
Envenomation[75,76]	• Snake bite[16] • Scorpion sting • Marine envenomation • Ingestion of puffer fish	• **Snake bites**[16]: Cardiovascular: hypotension, shock, arrest – Neurological: paralysisptosis, diplopia, bulbar palsy, dysarthria; respiratory muscle paralysis Coagulopathy: intracranial hemorrhage, bleeding from bite site, ecchymoses, bleeding gums, hemarthroses Rhabdomyolysis: tender muscles • **Scorpion sting**: cranial nerve and somatic skeletal neuromuscular dysfunction, with pain and paresthesia • **Blue-ringed octopus** and **puffer fish** envenomation: descending symmetrical flaccid paralysis with clear sensorium, nausea, and vomiting, blurred vision, ataxia, respiratory failure • **Stonefish** envenomation: weakness in the affected limb, severe pain, shock	• Serial bedside pulmonary function tests if descending paralysis • Other investigations as CBC, LFTs, CK, whole blood clotting time, coagulation, screen, D-dimer, fibrinogen levels, urinalysis for blood (myoglobin), • Head-CT if decreased GCS • Use venom detection kit for bite swab and urine	• Supportive care of airway, breathing, and circulation • Pressure immobilization bandage • Specific antivenom
Locked-in syndrome[77]	• Sudden onset tetraplegia, facial weakness, and horizontal gaze palsy • Causes ischemic stroke (most common), central pontine myelinolysis, encephalitis, or tumor	• **Flaccid symmetrical tetraparesis** • **Consciousness preserved** or may be affected initially but returns to normal • Voluntary vertical eye and eyelid movements preserved • Hearing, vision, pupillary reflexes, and sensation all normal	• CT brain with spiral CT angiography[35] • MRI/MRA	Follow acute stroke protocol

(continued)

Table 3 *(Continued)*

Disease	History	Examination	Investigation	Treatment
Acute porphyria[78]	• Abdominal pain: may begin in chest or back and move to abdomen • Gastrointestinal symptoms such as vomiting, diarrhea, and constipation are common • Psychiatric symptoms • Acute weakness (early or late) • May develop seizures • Certain medications are known to exacerbate	• Muscle weakness usually begins proximally and more often in upper limbs • Symmetrical hypotonia • Hyporeflexic • Flaccid paralysis • No rash unlike other forms of porphyria • Tachycardia and hypertension may be present	• Hyponatremia • Urine: dark/reddish • Urine analysis: increased porphobilinogen	• IV hemin • Manage hyponatremia • Consider antiepileptic drugs • Supportive management
Diabetic lumbosacral radiculoplexus neuropathy[79]	• Diabetes mellitus with proximal weakness • Asymmetrical pain in the hip, buttock, or thigh • Associated with poor glycemic control • Patients without distal symmetrical polyneuropathy most often have sudden, unilateral onset • Occasionally may be initial presentation of diabetes mellitus	• Proximal lower limb muscle weakness and wasting • Minimal sensory loss is observed • Knee-jerk reflex is absent, with commonly preserved ankle jerks • Ankle jerks may also be absent, with underlying distal symmetrical polyneuropathy	• Fasting blood glucose and glycated hemoglobin • Imaging of lumbo-sacral spine to exclude other causes • EMG • Nerve conduction studies	• Optimize glycemic control • Physical and occupational therapy
Psychiatric illness	• No history suggestive of any physical illness • Temporal associations with psychosocial stressors • Symptom substitution frequently present • Primary psychological or personal gain present	• La belle indifference present • Distribution does not follow anatomical pattern • Presence of affective or emotional disturbances on mental status examination	• Relevant investigations to rule out organic lesions like (MRI/CT, EEG). • Visual-evoked potentials and brainstem auditory evoked responses to rule out malingering/compensation neurosis	• Minimize and stop further investigations • Decrease secondary gains • Increase functioning • Refer for specialist psychiatric interventions

Source: Adapted with permission from Caulfield et al.[3]

Abbreviations: AChR, acetylcholine receptor; ASAS, anterior spinal artery syndrome; BP, blood pressure; CBC, complete blood count; CHF, congestive heart failure; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; DKA, diabetes ketoacidosis; ECG, electrocardiography; EEG, electroencephalogram; EMG, electromyography; GCS, Glasgow Coma Scale; HHC, hyperosmolar coma; HIV, human immuno-deficiency virus; HTN, hypertension; ICP, intracranial pressure; IV, intravenous; IVIG, intravenous immunoglobulin; LL, lower limb; LMN, lower motor neuron; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NCS, nerve conduction study; PSAS, posterior spinal artery; SIAD, syndrome of inappropriate antidiuretic hormone secretion; SPECT, single-photon emission computed tomography; UL, Upper limb; UMN, upper motor neuron.

Special Consideration in Pediatric Patients

The basic principles of assessment of the airway/ventilation and localization are the same as in adults. The major differences are in the presentation, and the common etiologies leading to weakness are highlighted here. In children, the presenting symptoms may be mutable such as irritability, agitation, restlessness, refusal to walk, frequent awakening from sleep, willingness to be held frequently, or regression of milestones. The history should focus on the evaluation of various risk factors such as congenital heart diseases, sickle cell anemia, and prothrombotic states. The examination of reflexes, signs of bulbar weakness, and assessment of sensory level are as critical as in adults, but it may be difficult in very young children. In children, it is difficult to distinguish the various causes of difficulty in walking such as weakness, pain, and ataxia.

The common causes of ANTW in children include Todd's paresis, acute demyelinating encephalomyelitis, acute transverse myelitis, GBS, and myasthenia gravis.[19-23] Stroke is a rare presentation in children but may occur in various conditions including sickle cell, congenital heart disease, prothrombotic disorder, and Moyamoya disease. The aortic dissection is quite common ischemic spinal cord injury in children leading to spinal artery infarcts. If reflexes are intact, then consider transverse myelitis, Todd's paresis, myasthenia gravis or stroke, while in patients with reduced or absent reflexes, consider early transverse myelitis with spinal shock or GBS. Imaging modalities and laboratory tests should be directed as per the differential diagnosis.

Referral to a Higher Center

Healthcare providers should provide the following details including patient's age, history of present illness, complete details of patient's initial assessment (ABC), salient history, examination findings, laboratory reports, imaging results, and treatment provided. The further plan about a pending investigations, list of potential considerations, and management (if the diagnosis of acute weakness is known) should also be provided.

Conclusion

Acute nontraumatic muscle weakness occurs due to a lesion in the motor tract anywhere from pyramidal cells to peripheral muscles. These may prove to be life threatening if airway, breathing, or circulation is affected. Care of ABC takes priority over managing and localizing the weakness. We should focus on a detailed history and examination to localize the lesion quickly, make an initial working diagnosis, and screen the patients for time-sensitive emergencies. The laboratory tests and neurological imaging are done to make the diagnosis. A systematic algorithm/protocol should be followed so that we do not miss any important cause of weakness.

Conflict of Interest

None declared.

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