Differential Diagnosis of Progressive Generalized or Symmetrical Flaccid Paralysis

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Progressive flaccid paralysis occurring over a period of hours or days is usually associated with the Landry-Guillain-Barré-Strohl syndrome.[1,2,3] This symptom complex is often accompanied by a history of a previous flu-like illness, antecedent myalgias, and subjective sensory complaints of tingling or simply a "tight" sensation in hands and feet. The paralysis that ensues either ascends from the feet and legs or descends from the facial muscles to involve all or most of the voluntary skeletal musculature. Along with paralysis of the intercostal and diaphragmatic musculature, severe cases may also involve other cranial nerves as well as the autonomic nervous system. In all cases the deep tendon reflexes are markedly diminished or absent early in the course of the disease. Sensory abnormalities are usually mild or absent. Confirmatory diagnostic studies include examination of the cerebral spinal fluid (CSF) which shows no or few mononuclear cells and an elevated protein. Nerve conduction studies may show prolonged distal latencies, slowing of nerve conduction velocities, and prolonged F responses which measure the radicular segments of the nerve. Overall prognosis is difficult to predict, with recovery taking weeks to months. Fatalities can occur despite optimal care in an intensive care unit. Electromyographic evidence of denervation suggests a more prolonged course with a greater chance of residual weakness. Atypical forms of this syndrome are more difficult to diagnose as can be illustrated by the following case history:

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The patient was a 15-year-old boy with a progressive flaccid paralysis which began with leg pains and a gait disturbance; he required tracheostomy 72 hours later. Two weeks prior to this he suffered a flu-like illness and the day before he became weak he had been mowing a field freshly sprayed with insecticide. Initial examination showed a flaccid paraplegia and absent deep tendon reflexes, but the CSF was normal with no cells and a protein less than 50 mg/100 ml. Nerve conduction studies done on arrival at the hospital and the next day showed normal distal latencies, nerve conduction velocities, and F wave latencies. In some of the severely weakened distal muscles no compound action potential could be elicited and in others these potentials were of low amplitude and not augmented by 30 Hz trains of supramaximal stimulation. During the second week of total paralysis, distal latencies were slightly prolonged and conduction velocities had decreased. The spinal fluid remained normal. After the third week, the patient began to recover, initiating movements in arms and legs. Nerve conduction studies now showed definite prolongation of distal latencies and prolonged F wave latencies. The spinal fluid now had an elevated protein and no cells. By the fifth week strength had returned and the patient was weaned from the respirator.

Discussion

The absence of the early electromyographic and spinal fluid changes[1] usually associated with a post-infectious polyradiculopathy instigated a search for other disorders which may present in a similar fashion. In devising a systematic approach towards a differential diagnosis in this atypical case, it was help-

ful to consider the component parts of the motor unit, specifically the anterior horn cell, axon (peripheral nerve), neuromuscular junction, and the muscle fibers innervated by that anterior horn cell.

Anterior Horn Cell Disease

Most of the anterior horn cell diseases that are encountered today are chronic and progressive and are not likely to be confused with the clinical presentation under discussion.[4,5] However, there remains the possibility of the emergence of a new neurotrophic virus or the occurrence of acute poliomyelitis in the uninoculated. Poliomyelitis presents as a biphasic illness beginning as a flu-like syndrome which remits within 48 hours. Headache, severe myalgias and meningismus mark the next phase, with the spinal fluid showing a pleocytosis of 50 to 250 cells, an elevated protein (100 to 250 mg/100 ml), and a normal glucose. Some cases may then progress with muscle fasciculations and paralysis. If mild, the paralysis can be quite asymmetrical, but if severe, it may appear symmetrically and involve bulbar musculature. Deep tendon reflexes may be exaggerated early, but these are lost in the paralytic stage of the disease.

Peripheral Nerve

Acute polyneuropathies or polyradiculoneuropathies most often fall within the symptom complex of the Guillain-Barré syndrome.[1,2] A wide variety of infective agents are capable of producing a state likened to experimental allergic neuritis with monocytic infiltration, edema, and demyelination of the peripheral nerve as the common pathological reaction. Such agents appear to combine with cell membranes, triggering an aberrant immune response which is directed towards cell membrane and, consequently, myelin. Generalized inflammatory states as seen with systemic lupus erythematosus are capable of producing a syndrome indistinguishable from the postinfectious variety. Furthermore, this syndrome has also been caused by infiltrations of plasma cells in association with multiple myeloma.

In some patients there is a tendency to suffer from a chronic relapsing steroid-dependent form of a polyradiculoneuropathy.[6,7] In these patients the onset is usually more gradual, over one to two weeks, and usually does not involve cranial nerves or respiratory muscles. With the use of steroid medication, the patients become asymptomatic, although nerve conduction studies still remain abnormal. In the event of steroid withdrawal there is an exacerbation of all symptoms with a progressive paralysis.

Diphtheria toxin, although rapidly fixing to peripheral nerve, has a delayed effect as it appears to block myelin production.[8] Consequently, the turnover of new myelin is inhibited, resulting in progressive demyelinization of the peripheral nerve weeks to months later. Despite the characteristic clinical features of diptheria, long delays between the time of the initial infection and the subsequent neuropathic complications may make the association difficult. Paralysis begins and may be localized to cranial nerves involving, in particular, the palate and the pupil with a characteristic fatigue of accommodation. More rarely, facial and extraocular muscles are also involved. A certain number of patients then develop a generalized peripheral sensori-motor neuropathy with loss of reflexes, mild sensory loss, and peripheral weakness. A tachycardia is oftentimes associated with the peripheral neuropathy, as well as spinal fluid changes of elevated protein with or without pleocytosis. A similar onset and cause have also been described in the neuropathy associated with extra faucial diphtheria.

The hepatic porphyrias,[9] especially the acute intermittent and variegated forms, can cause paralysis following the abdominal and psychic manifestations. Oftentimes, pain precedes the weakness in affected muscles, which usually involves the upper limbs first and especially proximal muscles and wrist extensors. Progression may be stepwise over one to four weeks and involves limbs, trunk, cranial, and autonomic nerves. The spinal fluid protein is slightly increased and there are few monocytes. Nerve conduction studies are frequently normal since it is the axons which suffered a primary insult and not the myelin. Other abnormal metabolic states, such as hepatic and renal failure, as well as diabetes, are more likely to cause chronic neuropathies and do not present as acute paralytic states.

Exposure to toxic substances,[10] either during their manufacture or use, can be the cause of progressive, flaccid paralysis. Cases are usually sporadic and in some this reaction seems to be determined by individual susceptibility. Cases can appear so typical that without a history of exposure to endrin, aldrin, dichloro-diphenyl-trichloroethane (DDT), or dichloro-diphenyl-dichloroethane (DDD), a diagnosis of acute, infective polyneuritis may be made. The ingestion of thallium salts[11] found in rodenticides and insectides can cause an acute polyneuropathy in addition to gastrointestinal disturbances. The neuropathy is mostly sensory, affecting the lower extremities, and is associated with migratory arthralgias. In some pa-

tients paralysis may be generalized, involving respiration and associated with circulatory difficulty as the autonomic system is involved as well. Usually, with massive doses, central nervous system symptoms predominate with hallucinations, convulsions, and death. Several weeks after the ingestion of thallium, alopecia occurs and this is what implicates thallium poisoning.

It would be an oversimplification to state that there are a wide variety of agents capable of producing polyneuropathy—heavy metals, drugs, and toxic chemicals—but for the most part these do not present as acute neuropathic polyneuropathies. New substances are found capable of producing the syndrome and isolated case reports continue to appear in the literature. Examples of this are the ascending polyradiculopathies associated with the ingestion of the fruit from poisonous shrubs[12] as well as reports of this syndrome as a complication of hyperalimentation.[13]

Neuromuscular Junction

Neuromuscular blockade can occur either presynaptically or postsynaptically and cause a rapidly progressive, generalized, or selective paralysis. Presynaptic blockade is thought to be the mechanism of action in tick paralysis.[14] Five to six days after the attachment of certain female gravid ticks, usually located on the scalp, there is a rapid ascending paralysis which may begin with a gait disturbance and myalgia. If the tick is not removed, this may proceed to respiratory embarrassment. Spinal fluid is usually normal. The substance which the tick secretes must be quite potent, but it would also seem to have a rather short half-life since symptoms improve within hours of removing the tick.

Presynaptic neuromuscular blockade appears to be the mechanism of action of botulinus toxin.[15] Twenty-four to 48 hours after the ingestion of the toxin, ocular motor weakness, pupillary paralysis, and respiratory paralysis occur, usually preceded by a gastrointestinal disturbance. Progression to generalized paralysis can also occur. Nerve conduction studies are usually normal, neuromuscular blockade being demonstrated by high frequency stimulation with subsequent augmentation in the compound action potential.

Postsynaptic neuromuscular blockade can occur due to the inability of the postsynaptic membrane to respond to acetylcholine as it would in the myasthenic crisis.[4,16,17] Occasionally myasthenia gravis may begin with an acute, generalized severe form of muscular weakness which involves cranial nerves. Deep tendon reflexes are usually preserved and there is no sensory loss. Myasthenics may develop acute paralysis due to under-medication, or as a result of exposure to drugs which have mild presynaptic blocking properties and do not ordinarily affect nonsusceptible individuals.[18] Postsynaptic blockade can also occur as in cholinergic crises when acetylcholine is not degraded at the receptor site. Such blocks can occur in the myasthenic secondary to overmedication with antiacetylcholinesterase-type drugs[4,16,17] or in individuals who have been exposed to organophosphates such as tri-orthocresyl phosphate.[10] Organophosphate compounds are not only capable of producing an acute cholinergic crisis but also cause severe demyelinating types of polyneuropathies usually after a latent period of one to three weeks after exposure.

Muscle Fibers

Primary and secondary periodic paralyses are classified as hypokalemic, hyperkalemic, and normokalemic depending upon the serum potassium at the time of the paralysis.[4,19] The onset is rapid and progressive and usually follows exercise, exposure to cold, or the ingestion of a heavy meal. During a severe attack, deep tendon reflexes are depressed and there is an inability to initiate muscle contraction by electrical stimulation. Motor nerve conduction velocity may thereby be unobtainable. Spinal fluid is normal. The diagnosis may be suspected in the hereditary forms which are recurrent and by the potassium levels during the attack. The hyperkalemic[20] and normokalemic[19] forms may be associated with the onset of myotonia after exposure to cold between attacks. The secondary periodic paralyses are usually sporadic. Hypokalemic periodic paralysis may be seen as the presenting complaint or as a complication of thyrotoxicosis in certain individuals. Hypokalemic periodic paralysis is also seen in association with hyperaldosteronism as well as a complication of thiazides and sprinolactone.[4] Hyperkalemic forms occur in association with renal and adrenal failure. It would be extremely unusual for other myopathies to present as rapidly progressive paralysis. With fulminant forms of polymyositis or in rhabdomyolysis with associated myoglobinuria, patients are extremely ill, muscles are quite painful and the serum creatinine phosphokinase levels should be very high.[19]

As with many conditions involving the nervous system, the ability to localize the site of a particular

abnormality provides a logical means for considering a differential diagnosis in terms of what can happen at that particular site. In viewing the motor unit and its component parts a similar process is useful when considering progressive paralysis.

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