Differential Diagnosis of Acute Flaccid Paralysis and Its Role in Poliomyelitis Surveillance

Arthur Marx, Jonathan D. Glass, and Roland W. Sutter

DEFINITION OF ACUTE FLACCID PARALYSIS

Acute flaccid paralysis (AFP) is a clinical syndrome characterized by rapid onset of weakness, including (less frequently) weakness of the muscles of respiration and swallowing, progressing to maximum severity within several days to weeks. The term “flaccid” indicates the absence of spasticity or other signs of disordered central nervous system motor tracts such as hyperreflexia, clonus, or extensor plantar responses (1). When applied to voluntary muscles, “paralysis” means loss of contraction due to interruption of motor pathways from the cortex to the muscle fiber. It is preferable to use the term “paresis” for slight loss of motor strength and “paralysis” or “plegia” for severe loss of motor strength (1). The differential diagnosis of AFP varies considerably with age. No single operational clinical case definition of AFP or paralytic poliomyelitis that combines both high sensitivity and high specificity has emerged (2–4). The currently used case definition increases sensitivity in detecting the existence of AFP but tends to decrease specificity in detecting paralytic poliomyelitis.

INTRODUCTION

AFP is a complex clinical syndrome with a broad array of potential etiologies. Accurate diagnosis of the cause of AFP has profound implications for therapy and prognosis. If untreated, AFP may not only persist but also lead to death due to failure of respiratory muscles. AFP, a syndrome that encompasses all cases of paralytic poliomyelitis, also is of great public health importance because of its use in surveillance for poliomyelitis in the context of the global polio eradication initiative.

In 1988, the World Health Assembly adopted a resolution calling for global eradication of poliomyelitis by the year 2000 (5). At the end of 1999, 30 countries worldwide remained polio-endemic, and intense activity is currently being directed towards interrupting virus transmission in 10 remaining high priority countries facing particular challenges (6). Despite these challenges, the goal of polio eradication appears to be within reach. AFP surveillance is a key strategy for monitoring the progress of polio eradication and is a sensitive instrument for detecting potential poliomyelitis cases and poliovirus infection. Current levels of surveillance have made it possible to document a substantial reduction in morbidity due to poliomyelitis. To ensure the success of the poliomyelitis eradication initiative, it has become critical that surveillance be intensified so that the absence of wild poliovirus circulation can be verified with confidence in countries not reporting confirmed cases of poliomyelitis.

The objectives of this review are to describe 1) the clinical characteristics, epidemiology, and differential diagnosis of potential causes of AFP, including distribution by age, gender, time, ethnicity, and geographic region; 2) the anatomic, morphologic, and pathophysiologic mechanisms associated with causes of AFP; 3) the region- or country-specific significance of these etiologies; 4) the potential of these etiologies to cause epidemics of AFP; and 5) an algorithm for determining the correct diagnosis and etiology of AFP for use in clinical examinations and laboratory studies.

This review is intended to provide greater assurance to clinicians concerning the accuracy of the diagnosis of AFP, including the rational use of limited resources when it may not be practical to conduct a detailed clinical assessment, and to raise awareness among health workers and surveillance coordinators about the importance of accurately diagnosing and differentiating AFP. The presentation of our findings and the subsequent discussion provide an overview of possible causes of AFP and focus on diagnostically helpful characteristics of AFP, as well as regional or country-specific experience.

For better understanding of the clinical characteristics and differential diagnosis of AFP, we focus in this review on grouping causes of AFP by pathophysiologic mechanisms and anatomic sites of action, an aspect incompletely...
explored in previous review articles. We discuss etiologies that have emerged or become more significant recently—for instance, neurologic complications in patients with acquired immunodeficiency syndrome (AIDS). We also provide an overview of causes of paralytic illness in developing countries that are commonly misdiagnosed as AFP.

METHODS

All available electronic databases, including Medline (1966 to date), Biosis (1969 to date), and CAB Health (1973 to date), were systematically reviewed for reports on AFP in any language available. Records in CAB Health are extracted from the Public Health and Tropical Medicine Database. Textbooks, monographs, conference proceedings, and other sources were reviewed and searched for cross-references. In addition, experts in the field, including health officials in World Health Organization regional offices and individual countries, were consulted. Our observations from clinical and epidemiologic field experience were included in this review.

CLINICAL APPROACH TO PATIENTS WITH AFP

Each case of AFP is a clinical emergency and requires immediate examination. The clinical investigation of AFP is often limited by the existing health infrastructure and available resources. For all cases, a detailed clinical description of the symptoms should be obtained, including fever, myalgia, distribution, timing, and progression of paralysis. The symptoms of paralysis may include gait disturbance, weakness, or troubled coordination in one or several extremities. Careful assessment of the patient’s personal history (recent illness, exanthem (erythema migrans in Lyme borreliosis), timing, food and water consumption, exposure to chemicals (organic solvents), insect (tick) or snake bites, family history, vaccinations, and psychogenic problems, including dementia) is crucial in order to narrow the differential diagnosis. Trauma or spinal cord compression should be kept in mind as an obvious cause of AFP. Depending on the geographic region, the skin and scalp should be carefully inspected for ticks, stings from insects, spiders, or scorpions, and snake bites.

Figure 1 shows an algorithm for the clinical evaluation of limb or respiratory weakness. The signs of AFP should be evaluated clinically by performing a comprehensive neurologic examination, including assessment of muscle strength and tonus, deep tendon reflexes, cranial nerve function, and sensation (tactile sensation, vibration, and kinesthetic perception). Particular attention should be paid to the presence of meningismus, signs of disordered central nervous system function (ataxia), or autonomic nervous system abnormalities (bowel and bladder dysfunction, sphincter tonus, neurogenic reflex bladder) (7). Fasciculation is often cited as a sign of anterior horn cell damage, but it may also be present in demyelinating neuropathies (8). Electrophysiologic studies are very important for determining the diagnosis and prognosis of lower motor neuron disease; nerve conduction velocity and electromyographic studies, for instance, are used to differentiate demyelinating neuropathies from axonal neuropathies (7).

In currently or recently polio-endemic countries, every case of AFP should be reported, regardless of its presumed etiology. Two stool specimens should be collected within 14 days after onset of paralysis, and virus isolation should be performed by a qualified laboratory (if this is not feasible, stool specimens should still be collected up to 2 months from the onset of paralysis) (9). If indicated, serologic testing, isolation, and immunologic assays should be carried out for enteroviruses, human immunodeficiency virus (HIV), Herpesviridae (cytomegalovirus, Epstein-Barr virus, herpes simplex virus types 1 and 2, varicella-zoster virus), Mycoplasma pneumoniae, Campylobacter jejuni, and Borrelia species, as well as a VDRL (Venereal Disease Research Laboratory) test. Testing for antinuclear and anti-GM1 (glycolipid ganglioside-monosialic acid) glycoconjugate antibodies may be needed to confirm diagnoses of immunologic or autoimmune disorders.

If the necessary infrastructure and resources are available, further laboratory tests may be indicated for differentiating

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**FIGURE 1.** Algorithm for the evaluation of patients with limb or respiratory weakness. NMJ, neuromuscular junction; CK, creatine kinase; AMAN, acute motor axonal neuropathy; AIDP, acute inflammatory demyelinating polyneuropathy; ICU, intensive care unit.

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<table>
<thead>
<tr>
<th>Site, condition, factor, or agent</th>
<th>Clinical findings</th>
<th>Onset of paralysis</th>
<th>Progression of paralysis</th>
<th>Fever at onset</th>
<th>Sensory signs and symptoms</th>
<th>Bowel or bladder dysfunction</th>
<th>Menin-gismus</th>
<th>Reduced or absent deep tendon reflexes</th>
<th>Residual paralysis</th>
<th>Pneumocystis in cerebro-spinal fluid</th>
<th>Nerve conduction study</th>
<th>Electromyogram*</th>
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<tr>
<td><strong>Anterior horn cells of spinal cord</strong></td>
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<td>Poliomyelitis</td>
<td>Paralysis in 1% of the infected; nonspecific prodrome (abortive poliomyelitis)</td>
<td>Incubation period 7–14 days (4–20 days)</td>
<td>24–48 hours to onset of full paralysis; proximal &gt; distal, asymmetrical</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Rare</td>
<td>+/-</td>
<td>Yes</td>
<td>Yes</td>
<td>Aspatic meningitis (moderate polymorphonuclear leukocytes at 2–3 days)</td>
<td>Reduced CMAP amplitude</td>
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<td>Nonpolio enterovirus</td>
<td>Hand-foot-and-mouth disease, aseptic meningitis, AHC†</td>
<td>As in poliomyelitis</td>
<td>As in poliomyelitis</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
<td>+/-</td>
<td>Yes</td>
<td>Yes</td>
<td>As in poliomyelitis</td>
<td>Reduced CMAP amplitude</td>
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<tr>
<td>Vaccine-associated paralytic poliomyelitis</td>
<td>As in poliomyelitis</td>
<td>As in poliomyelitis</td>
<td>As in poliomyelitis</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
<td>+/-</td>
<td>Yes</td>
<td>Yes</td>
<td>As in poliomyelitis</td>
<td>Reduced CMAP amplitude</td>
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<td><strong>Other neurotropic viruses</strong></td>
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<td>Rabies virus</td>
<td>Months to years</td>
<td>Acute, symmetrical, ascending</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>+/-</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Reduced CMAP amplitude</td>
<td>Abnormal</td>
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<td>Varicella-zoster virus</td>
<td>Exanthematous vesicular eruptions</td>
<td>Incubation period 10–21 days</td>
<td>Acute, symmetrical, ascending</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>Yes</td>
<td>Reduced CMAP amplitude</td>
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<td>Japanese encephalitis virus</td>
<td>Incubation period 5–15 days</td>
<td>Acute, proximal, asymmetrical</td>
<td>+/-</td>
<td>+/-</td>
<td>No</td>
<td>Yes</td>
<td>+/-</td>
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<td>Yes</td>
<td>Reduced CMAP amplitude</td>
<td>Abnormal</td>
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<td><strong>Guillain-Barré syndrome</strong></td>
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<td>Acute inflammatory polyradiculoneuropathy</td>
<td>Preceding infection, bilateral facial weakness</td>
<td>Hours to 10 days</td>
<td>Acute, symmetrical, ascending (days to 4 weeks)</td>
<td>No</td>
<td>Yes</td>
<td>+/-</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>+/-</td>
<td>No</td>
<td>Reduced CMAP amplitude, demyelination</td>
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<td>Acute motor axonal neuropathy</td>
<td>Fulminant, widespread paralysis, bilateral facial weakness, tongue involvement</td>
<td>Hours to 10 days</td>
<td>1–6 days</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>+/-</td>
<td>No</td>
<td>Reduced CMAP amplitude, axonal degeneration</td>
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<td>Cytomegalovirus polyradiculo-myelopathy</td>
<td>Subacute ascending hypotonic</td>
<td>+/-</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>+/-</td>
<td>Yes</td>
<td>+/-</td>
<td>Yes</td>
<td>Yes</td>
<td>Mixed axonal degeneration and demyelination</td>
<td>Denervation</td>
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<td>Acute traumatic sciatic neuritis</td>
<td>Intraocular gluteal injection</td>
<td>Acute, asymmetrical</td>
<td>Hours to 4 days</td>
<td>Complete, affected limb</td>
<td>Possible</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Axonal degeneration</td>
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<td>Condition</td>
<td>Cause</td>
<td>Primary Symptoms</td>
<td>Incubation Period</td>
<td>Latency Period</td>
<td>Onset of Illness</td>
<td>Optic Symptoms</td>
<td>Myelination</td>
<td>Demyelination</td>
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<td>Acute transverse myelitis</td>
<td>Preceding <em>Mycoplasma pneumoniae</em>, <em>Schistosoma</em> other parasitic or viral infection</td>
<td>Acute, lower limbs symmetrical, hypotonia/ lower limbs</td>
<td>Hours to days</td>
<td></td>
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<td>Epidural abscess</td>
<td>Headache, back pain, local spinal tenderness, meningismus</td>
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<td>Spinal cord compression; trauma</td>
<td></td>
<td>Complete</td>
<td>Hours to days</td>
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<td>Neuropathies</td>
<td>In severe cases, palatal paralysis, blurred vision</td>
<td>Incubation period 1-8 weeks (paralysis 8-12 weeks after onset of illness)</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Yes</td>
<td>+/-</td>
<td>Demyelination</td>
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<tr>
<td>Toxin of <em>Clostridium botulinum</em></td>
<td>Abdominal pain, diplopia, loss of accommodation, mydriasis</td>
<td>Incubation period 18-36 hours</td>
<td>No</td>
<td></td>
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<td>No</td>
<td>+/-</td>
<td>Facilitation with repetitive stimuli</td>
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<td>Karwinskia humboldtiana, K. calderoni</td>
<td></td>
<td>Acute, symmetrical, ascending</td>
<td>No</td>
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<td>No</td>
<td>+/-</td>
<td>Normal or denervation</td>
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<tr>
<td>Tick bite paralysis</td>
<td>Ocular symptoms</td>
<td>Latency period 5-10 days</td>
<td>No</td>
<td></td>
<td></td>
<td>No</td>
<td>Reduced CMAP amp.</td>
<td>Denervation</td>
<td></td>
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<tr>
<td>Lyme borreliosis (relapsing fever)</td>
<td>Erythema migrans, bilateral facial paralyis, cardiac abnormalities</td>
<td>Weeks to months after tick exposure</td>
<td>Subacute, multifocal</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>Yes</td>
<td>Yes, increased protein</td>
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<td>Myasthenia gravis</td>
<td>Weakness, fatigability, diplopia, ptosis, dysarthria</td>
<td>Multifocal</td>
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<td>No</td>
<td>Decrement on rep. stimulus</td>
<td>Normal</td>
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<td>Nondepolarizing drugs</td>
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<td>Sudden, complete</td>
<td>Hours to days: prolonged blockade</td>
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<td>No</td>
<td>Myopathic CMAP</td>
<td>Normal or reduced CMAP</td>
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<td>Disorders of muscle</td>
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<tr>
<td>Polymyositis</td>
<td>Neoplasm, autoimmune disease</td>
<td>Subacute, proximal &gt; distal</td>
<td>Weeks to months</td>
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<td></td>
<td>No</td>
<td>Normal or reduced CMAP</td>
<td>Myopathic CMAP</td>
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<td>Viral myositis</td>
<td></td>
<td>Hours to days</td>
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<td>No</td>
<td>Normal or reduced CMAP</td>
<td>Myopathic CMAP</td>
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<td>Trichinosis</td>
<td>Preceding gastroenteritis</td>
<td>Subacute myalgia and weakness</td>
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<td></td>
<td>No</td>
<td>Normal or reduced CMAP</td>
<td>Myopathic CMAP</td>
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</table>
other viral or bacterial infections. A lumbar puncture and examination of the cerebrospinal fluid may be indicated to exclude bacterial infection of the nervous system. Bacterial infections frequently demonstrate large numbers of polymorphonuclear leukocytes, with low glucose and high protein levels. Of course, culture will frequently identify the specific organism involved. Cultures for bacteria are negative, identifying the illness as "aseptic" meningitis. However, clinicians should keep in mind that intramuscular injections may aggravate the risk of paralysis in poliovirus-infected individuals (10, 11). Imaging of the spine (radiography, computed tomography, or magnetic resonance imaging (if available)) may be indicated to rule out spinal cord compression, trauma, myelopathy, spondylotic polyradiculopathy, or neoplasm. Laboratory test methods, if feasible, should include red blood cell and white blood cell differentials (e.g., nucleated and stippled red blood cells with karyorrhexis in arsenic poisoning, basophilic stippling of white blood cells in lead poisoning); determination of red blood cell sedimentation rate; and measurement of serum and urinary levels of sodium, potassium, calcium, magnesium, chloride, carbonate, creatinine, uric acid, porphyrins (porphobilinogen, 8-aminolevulinic acid), and thyroxin. Measurement of enzyme activity (e.g., serum creatine kinase, acetylcholinesterase activity in red blood cells or plasma in case of organophosphate intoxication) may be indicated. An electrocardiogram may be indicated to establish the diagnosis of electrolyte metabolism disorders, such as hypokalemic periodic paralysis.

Manifestations outside of the nervous system may include skin ("raindrop" pigmentation) and nail (Mee's lines) changes in arsenic poisoning, or abdominal colic and blue lines in the gums in lead poisoning. More extensive screening for chemical compounds in serum, urine, fingernails (arsenic), or hair (thallium) may be needed at a later time; therefore, clinical specimens should be collected and stored.

Differential Diagnosis of AFP

The list of underlying causes of AFP is broad (table 1) and may vary by age and geographic region. The etiologies of AFP are often associated with specific pathophysiologic mechanisms or anatomic-morphologic changes, which may help in establishing the correct clinical diagnosis (figure 2). The causes and differential diagnoses of AFP have been reviewed previously (8, 12–16), including reviews on paralytic illness in infants (17) and children (18–21) and in tropical regions (12, 13, 22–24).

Lesion of the Anterior Horn Cells of the Spinal Cord

Viruses targeting motor neurons

Poliomyelitis. Poliomyelitis is caused by three serotypes of poliovirus, a neurotropic RNA virus of the family Picornaviridae, genus Enterovirus (25). Poliovirus type 1 has the highest ratio of paralytic infection to subclinical infection and is the most frequent cause of epidemics of paralytic disease. Poliovirus types 2 and 3 are less neuroviral. Type 2 wild poliovirus was the first serotype to be
eradicated in the Americas; as of 1999, the only remaining foci of type 2 wild poliovirus transmission were detected in northern India (26). Type 3 wild poliovirus caused a major outbreak of paralytic disease in Angola in 1999 (27). Poliomyelitis is transmitted by person-to-person spread through fecal-oral and oral-oral routes, or occasionally by a common vehicle (e.g., water, milk). The incubation period is typically 7–14 days (range, 3–35 days). When nonimmune persons are exposed to wild poliovirus, inapparent infection is the most frequent outcome (72 percent) (25). “Abortive poliomyelitis,” also referred to as “minor illness,” is the most frequent form (24 percent) of the disease. Nonparalytic poliomyelitis (including aseptic meningitis) occurs in 4 percent of patients. Only 1/1,000 to 1/100 infected individuals develop paralytic disease (28–30). Reports of greater ratios of paralytic infection to subclinical infection in poliomyelitis are not based on consistent case ascertainment, or are not representative of the range in the majority of literature reports (30, 31). Initial clinical symptoms may include fever, fatigue, headache, vomiting, constipation (or less commonly diarrhea), stiffness in the neck, and pain in the limbs. A diphasic course featuring these relatively non-specific symptoms with acute onset of paralysis during the second phase is seen mostly in young children, and is uncommon in individuals over 15 years of age. A monophasic course, with more gradual onset of symptoms and sometimes excruciating myalgia, is seen in adults (29). Distinguishing characteristics of paralytic poliomyelitis are 1) fever at onset, 2) rapid progression of paralysis within 24–48 hours, 3) asymmetrical distribution of limb paralysis, affecting proximal limb muscles more than distal limb muscles, 4) preservation of sensory nerve function with (often severe) myalgia, and 5) residual paralysis after 60 days (16, 25). Paralytic poliomyelitis may show an early cerebrospinal fluid infiltrate of polymorphonuclear leukocytes; however, these are replaced after 2–3 days by moderate numbers of lymphocytes and monocytes (32). The protein content of the cerebrospinal fluid is elevated only slightly, but it rises gradually in paralytic cases until the third week, generally returning to normal by the sixth week. Glucose levels are usually within the normal range.

Research by Sabin (28), Bodian (33), and Horstmann and Paul (34) laid the foundation for understanding of the pathophysiologic and immunologic mechanisms leading to paralytic poliomyelitis. Mendelsohn et al. (35) developed the concept that motor neuron cells expressing a specific receptor for poliovirus are susceptible to virus adherence and multiplication, leading to the subsequent destruction of motor neurons responsible for activating muscles. Anterior horn cell disease, including the appearance of inflammatory cells and motor neuron loss in the spinal cord, normally occurs within the first 2 weeks. Affected nerve cells do not

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regenerate, which results in the inability of affected muscles to function; however, axonal sprouting may result in some recovery of function (7, 25). Poliomyelitis may lead to severe asymmetrical atrophy and skeletal deformities.

Paralytic poliomyelitis may be associated with significant mortality—the case fatality rate, which is generally 5–10 percent among polio patients, was as high as 20–30 percent during outbreaks in the early 20th century (36, 37), and it increases with age (38, 39). The case fatality rate was 12 percent in a polio outbreak among young adults in Albania in 1996 (38). Most of these patients died from complications of bulbar paralysis, i.e., respiratory failure. Although children under 5 years of age are most frequently affected, outbreaks of poliomyelitis with high attack rates among adults have been described (25, 36–38, 40). The greater severity among older patients is consistent with that observed in outbreaks among susceptible adults (38, 40, 41).

Besides age, being unvaccinated or inadequately vaccinated (42), and lower socioeconomic status (16, 43), several factors have been shown to increase the risk of acquiring paralytic manifestations, including intramuscular injections, infection, stress, strenuous exercise, surgery (e.g., tonsillectomy), trauma, and pregnancy. The term “provocation poliomyelitis” describes the enhanced risk of paralytic manifestations that follows intramuscular injection, and it occurs when inflammation in muscle coincides with poliovirus infection; entry of poliovirus to nerve endings in the muscle is facilitated, and paralysis occurs 4–30 days later (44). Aggravation occurs when signals from a particular muscle (from physical activity or inflammation) cause increased blood flow in the relevant segments of the spinal cord which have already been invaded by poliovirus; increased severity of paralysis occurs 24–48 hours later (44).

Poliomyelitis changed from a comparatively rare disease into an epidemic disease during the late 19th century and early 20th century. Epidemics in Sweden in 1887–1911 and in Vermont in 1894 preceded the great New York epidemic of 1916, in which 27,000 children and adults were affected and 6,000 (22 percent) died (36, 37). Large epidemics continued to occur around the world through the 1950s, until the Sabin-derived strain of the virus is used in oral poliovirus vaccine, the Sabin-derived virus may occasionally revert to a neurovirulent strain, potentially causing paralytic illness that is clinically identical to poliomyelitis resulting from wild-type virus. The overall risk of vaccine-associated paralytic poliomyelitis in the United States and Latin America is one case per 2.5 million oral poliovirus vaccine doses; the risk in Romania is one case per 183,000 oral poliovirus vaccine doses—a 14-fold increased risk (49, 50). Three distinct groups are at risk of vaccine-associated disease: recipients of oral poliovirus vaccine (mostly infants receiving their first dose), persons in contact with oral poliovirus vaccine recipients (mostly unvaccinated or inadequately vaccinated adults), and immunocompromised individuals (51). However, neither HIV infection nor AIDS has been associated with an increased risk of paralytic disease due to wild-type or Sabin-derived poliovirus (52). There is no long-term carrier state in infected immunocompetent persons, regardless of the clinical course. However, prolonged shedding of Sabin-derived poliovirus has been shown to occur in immunocompromised patients with B-cell deficiencies (53).

Nonpolio enteroviruses. Nonpolio enteroviruses have been associated with polio-like paralytic disease, frequently accompanied by other clinical syndromes, such as aseptic meningitis, hand-foot-and-mouth disease, and acute hemorrhagic conjunctivitis. Coxsackieviruses A and B, echovirus (54), enterovirus 70 (24, 55), and enterovirus 71 (56–65) have been implicated in polio-like paralytic disease. Outbreaks of acute hemorrhagic conjunctivitis with radiculomyelitis and paralytic illness in India, Taiwan, Thailand, and Panama were etiologically linked to enterovirus 70 (24, 55). Muscle weakness and wasting associated with enterovirus 70 is usually severe and permanent (24).

Among all known nonpolio enteroviruses, enterovirus 71 has been most strongly implicated in outbreaks of central nervous system disease and AFP, first described in California during 1969–1973 (60). Global attention focused on enterovirus 71 when severe epidemics of central nervous system disease occurred in Japan in 1973 (56) and in Bulgaria in 1975 (57). Of 705 patients infected with enterovirus 71 in Bulgaria, 149 (21 percent) developed paralysis, and 44 (29 percent) of those persons died. Young children under 5 years of age were most frequently affected. Further outbreaks were reported in Hungary in 1978 (63) and in Philadelphia, Pennsylvania, in 1987 (59). Household clusters of acute neurolologic disease associated with enterovirus 71 were reported among children in Brazil in 1988–1990 (62). The most recent outbreaks were reported in Malaysia in 1997 (66) and in Taiwan in 1998 (64, 65). Antecedent illness (7–14 days before onset of AFP) was generally characterized by fever, vomiting, diarrhea, lethargy, nuchal rigidity, irritability, and anorexia; at 60-day follow-up, these patients suffered from residual paralysis with weakness and muscle wasting (67). Although signs of polio-like illness were found less frequently in AFP patients with isolation of nonpolio enterovirus than in poliovirus-positive patients, nonpolio enterovirus infection may be
clinically indistinguishable from paralytic poliomyelitis without laboratory studies (55, 67).

Other neurotropic viruses. Rabies and rabies vaccines. Rabies manifests after an incubation period of 1–2 months (or, infrequently, years). Typical rabies includes an “excitement” phase characterized by behavioral and autonomic nervous system abnormalities. A minority of cases will progress directly to a paralytic phase (“dumb” rabies) (68). Following nonspecific prodromal symptoms with paresthesia of the bitten area, paralytic rabies manifests as ascending AFP with spinter involvement and sensory disturbances. Death from respiratory and bulbar paralysis occurs after a longer illness than is seen in furious rabies. Differential diagnoses of paralytic rabies include postvaccinal encephalomyelitis, poliomyelitis, Guillain-Barré syndrome, and other causes of Landry-type ascending paralysis (68).

Neuroparalytic post-rabies vaccine encephalomyelitis, Guillain-Barré syndrome, and allergic neuritis were described after the administration of earlier rabies vaccines, namely the Semple and Hemp types (see sections on Guillain-Barré syndrome and peripheral neuropathies below), and varied in severity from neuritic and dorsolumbar myelitic paraplegic forms to the ascending Landry-type paralytic form (69). Nerve tissue cell rabies vaccines produce a rate of one neuroparalytic adverse event per 200 vaccine recipients, whereas the complication rate is much lower in vaccines derived from cell culture (69, 70).

Herpeshviridae. Herpeshviridae (cytomegalovirus, Epstein-Barr virus, varicella-zoster virus) are a group of neurotropic DNA viruses that may cause AFP associated with Guillain-Barré syndrome, opportunistic infections of the nervous system in individuals with AIDS, and acute transverse myelitis (see sections on Guillain-Barré syndrome and peripheral neuropathies below), and varied in severity from neuritic and dorsolumbar myelitic paraplegic forms to the ascending Landry-type paralytic form (69). Nerve tissue cell rabies vaccines produce a rate of one neuroparalytic adverse event per 200 vaccine recipients, whereas the complication rate is much lower in vaccines derived from cell culture (69, 70).

Viral meningoencephalitis. Viral meningoencephalitis may be caused by neurotropic viruses (paramyxovirus (para-influenzavirus, mumps virus), togovirus, arbovirus, Herpeshviridae), parasites (Trichinella spiralis; see section below), or stroke of the spinal cord (71, 72). Both cytomegalovirus and herpes simplex virus type 2 (71) can cause polyradiculoneuropathies (see section below).

Japanese encephalitis virus. Japanese encephalitis virus, a flavivirus, is endemic in Southeast Asia, parts of China, and the Indian Subcontinent; in specific areas, it may be an important cause of AFP (73). Electrophysiologic studies suggest that Japanese encephalitis virus myelitis is caused by anterior horn cell damage, and the clinical presentation mimics poliomyelitis in many respects, including weakness and wasting beyond 60 days after onset of paralysis.

POLYRADICULONEUROPATHIES

Landry-Guillain-Barré-Strohl syndrome

Landry-Guillain-Barré-Strohl syndrome, hereafter called Guillain-Barré syndrome, is a disorder of peripheral nerves, characterized by subacute (days to weeks) progression of motor-sensory dysfunction not associated with meningitis or fever. The syndrome was first described by Landry in 1859 and by Guillain, Barré, and Strohl in 1916. The diagnostic criteria developed by Asbury and Cornblath (74), based on the pathophysiologic and morphologic understanding of Guillain-Barré syndrome, correspond to those of acute inflammatory demyelinating polyradiculoneuropathy (AIDP). There is increasing evidence that what is diagnosed as Guillain-Barré syndrome may include conditions originating from a variety of underlying pathogenic mechanisms (75). In the absence of wild virus-induced poliomyelitis, Guillain-Barré syndrome is the most common cause of AFP in many parts of the world, and it accounts for over 50 percent of AFP cases in both industrialized and developing countries (76, 77). The annual incidence globally is 1–2 per 100,000 population (78); however, there are differences by region and ethnicity. Guillain-Barré syndrome is an important cause of AFP among children (21), but the incidence increases with age, and it is most common in the elderly (77). Rarely, cases in infants have been reported (21).

Guillain-Barré syndrome occurs in 50–70 percent of its patients within 2–28 days after a gastrointestinal or respiratory infection (21). It is characterized by 1) afebrile onset, 2) ascending symmetrical paralysis progressing within days to weeks (in >90 percent of patients, the nadir occurs by 4 weeks), and 3) disturbances of sensory function (74). If respiratory muscles become involved, the patient may die of respiratory failure. Patients surviving the acute phase frequently (>80 percent) recover functionally (74). In severe cases, persistent residual paresis occurs; however, the majority of patients in this group ultimately have a good functional recovery (74). The presence of bilateral facial weakness, a normal cell count and elevated protein level in the cerebrospinal fluid, and electrophysiologic evidence of abnormal conduction support the diagnosis of Guillain-Barré syndrome.

Preceding infection with C. jejuni has been identified as the most common etiologic factor of Guillain-Barré syndrome (79). Infection with M. pneumoniae, Herpeshviridae (cytomegalovirus, Epstein-Barr virus, varicella-zoster virus), HIV, measles virus, mumps virus, rubella virus, viral hepatitis, influenza A and B viruses, vaccinia virus, and nonpolio enteroviruses (Coxsackievirus, echovirus) have been demonstrated in epidemiologic studies to precede Guillain-Barré syndrome. Malignant lymphoma, alcoholism, liver cirrhosis, and thyroid disorders (hyperthyroidism, Hashimoto thyroiditis) have been linked to Guillain-Barré syndrome (80). Preceding vaccination

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against rabies (especially with the Semple-type vaccine (69); see section on rabies vaccines above), influenza, typhoid fever, rubella, or cholera and administration of vaccines containing tetanus toxoid (Td, DT), anti-tetanus toxin serum, or plasma-derived hepatitis B virus have been associated with Guillain-Barré syndrome. A causal association between use of oral poliovirus vaccine and Guillain-Barré syndrome has been suggested but has been ruled out by more recent studies (81, 82).

Outbreaks of Guillain-Barré syndrome were reported in Colombia in 1968 and in Jordan in 1976 (83). In the United States, during 1976–1977, 516 individuals aged 18 years or older who had received the influenza A/New Jersey vaccine and 432 unvaccinated individuals developed Guillain-Barré syndrome; the swine influenza component was not added to the vaccine after 1977, and there were no further cases of Guillain-Barré syndrome (84, 85).

Understanding of the immunopathogenesis of Guillain-Barré syndrome, including the primarily demyelinating and axonal forms, is based mainly on the following: 1) preceding infection with specific organisms, most notably C. jejuni and M. pneumoniae; 2) the contribution of antibody- and complement-mediated mechanisms of immune injury; 3) glycoconjugate antigens' being likely targets of immune attack, and expression of anti-GM, glycoconjugate antibodies' possibly being associated with C. jejuni infection (86); 4) heterogeneity of immunologic targets on nerve fibers; 5) the presence of Ranvier nodes as immunologic targets; and 6) "molecular mimicry," a host-generated immune response to infectious organisms or tumor cells that share antigenic determinants with the host's tissue. C. jejuni may contain GM₁-like epitopes inducing the expression of anti-GM₁ antibodies, which cross-react with antigenic determinants on nerve fibers. High titers of immunoglobulin G and immunoglobulin M anti-GM, antibodies have been found in 5–8% of patients with Guillain-Barré syndrome, as well as acute motor axonal neuropathy and autoimmune disease, including myasthenia gravis and polymyositis (86).

AIDP with acute lymphocytic infiltration and macrophage-mediated demyelination reproduces the clinical and pathologic features of Guillain-Barré syndrome most often reported in North America, Europe, and Australia (87). In other parts of the world, it has recently become clear that some cases of Guillain-Barré syndrome have extensive axonal degeneration with only minimal evidence of demyelination (88, 89).

**Subacute and chronic inflammatory demyelinating polyradiculoneuropathy**

Subacute inflammatory demyelinating polyradiculoneuropathy (SIDP) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) may be considered variants of AIDP (90). CIDP is defined as an acquired demyelinating neuropathy with insidious onset and progression over at least 8 weeks (as opposed to AIDP, which progresses over a period of up to 4 weeks, and SIDP, which progresses over 4–8 weeks) (90). All of the clinical features reported for AIDP have been seen in CIDP, including ascending, symmetrical AFP, disturbances of sensory function, cranial nerve involvement, respiratory failure, autonomic disturbances, and albuminocytologic dissociation and dysimmunoglobulinemia in the cerebrospinal fluid (90). Electrophysiologic studies allow one to distinguish CIDP from inherited demyelinating or axonal neuropathy (91).

**Acute motor axonal neuropathy**

Acute motor axonal neuropathy (AMAN), also referred to as "Chinese paralytic syndrome," is a distinct disease entity that appears different from AIDP and poliomyelitis because of its primarily axonal involvement (88, 89, 92). Recent research documented excessive axonal degeneration without preceding demyelination and suggested that the target antigen may lie on the axon (92). AMAN has been described, particularly during the summer months, among children and young adults in northern China (88) and has also been reported in Mexico (93), Spain (94), India (recently described as "Asian paralysis syndrome") (95, 96), Pakistan (97), and South Korea (80). Characteristic features of AMAN include fulminant and widespread paralysis with slow and usually incomplete recovery, bilateral facial weakness, frequent involvement of the tongue, normal sensory perception, and normal cerebrospinal fluid cell count (88, 98). Early symptoms of this disease include leg weakness and resistance to neck flexion. The weakness ascends rapidly, affects symmetrically the arms and respiratory muscles, and progresses to the maximum extent of weakness within 6 days, on average. Electromyographic studies indicate denervation potentials in weak muscles and suggest that this entity may be a reversible distal motor nerve terminal or anterior horn lesion. Serum antibodies to C. jejuni are frequently elevated (88, 99). Acute motor-sensory axonal neuropathy (89) is seen throughout the world, is rarer than AIDP and AMAN, and probably does not have a seasonal variation.

**Neurologic disorders associated with HIV infection, AIDS, or opportunistic infections**

Neurologic disorders, including AFP, may complicate HIV infection and AIDS (100). Such disorders may be caused by 1) HIV infection or AIDS; 2) opportunistic infections (e.g., Herpesviridae (cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella-zoster virus), Giardia lamblia, Toxoplasma gondii, Mycobacterium tuberculosis, or Treponema pallidum (syphilis)); or 3) vitamin B₁₂ deficiency and other deficiencies of AIDS cachexia contributing to the neuropathic process in terminal AIDS. Nucleoside antiretroviral agents and prophylactic and therapeutic drugs used to treat HIV-associated complications may cause motor-sensory neuropathies and myopathies but are generally not associated with AFP. In the early stages of AIDS, AIDP, CIDP, isolated cranial or other mononeuropathies, and brachial plexopathy can occur. In later stages, opportunistic infection of peripheral nerves by cytomegalovirus can cause syndromes of subacute progressive polyradiculomyelopathy (cytomegalovirus-polyradiculomyelopathy) (101).
Cytomegalovirus causes meningoencephalitis, myelitis, and cytomegalovirus-polyradiculomyelopathy (101) (see section on neurotropic viruses above). Cytomegalovirus-polyradiculomyelopathy is a rare but distinctive clinical syndrome causing subacute ascending hypotonic lower extremity weakness, often preceded or accompanied by pain and paresthesia in the legs and perineum, with areflexia, urinary retention, and loss of sphincter control (101). Tactile, vibratory, and kinesthetic impairments and sensory levels are noted in certain patients. The cerebrospinal fluid typically shows prominent representation of polymorphonuclear leukocytes, elevated protein levels, and low glucose levels. Electrophysiologic studies typically demonstrate features of axonal neuropathy associated with varying degrees of demyelination. The differential diagnosis of cytomegalovirus-polyradiculomyelopathy includes the following opportunistic conditions affecting the lumbosacral nerve roots and spinal cord: herpes simplex virus type 2, varicella-zoster virus, T. gondii, T. pallidum, and other bacterial infections (101).

Varicella-zoster virus infection may cause symmetrical ascending AFP, mimicking or potentially causing Guillain-Barré syndrome (102). Frequently in zoster patients, pain and paresthesia precede the belt-like vesicular eruption following sensory dermatomes. Rarely, a somewhat similar clinical picture may be seen in patients suffering from Herpesvirus simiae infection of the central nervous system following a monkey bite (19). Varicella also has been associated with AMAN (103).

ACUTE MYELOPATHIES

Acute transverse myelitis

As a cause of AFP, acute transverse myelitis is less frequent than Guillain-Barré syndrome or paralytic nonpolio enterovirus infection; the reported annual incidence is less than one case per 2 million population (104). The common presentation includes, in the initial phase of spinal shock, weakness of the lower extremities, AFP, urinary distention (neurogenic bladder), constipation, hyporeflexia, sensory impairment (sensory level), severe pain, and paresthesia. After 2–3 weeks, hyperreflexia and spasticity appear. Among patients with acute transverse myelitis, approximately one third fully recover, one third partially recover, and the rest remain disabled or die (105).

Acute transverse myelitis has been associated with M. pneumoniae, Herpesviridae (cytomegalovirus, Epstein-Barr virus, varicella-zoster virus), rabies virus, hepatitis A virus, and enteric fever. Parasitic infection may involve the spinal cord or brain stem, including Schistosoma mansoni and Schistosoma haematobium, Cysticercus cellulosae, Taenia solium and Taenia multiceps, Echinococcus granulosus (cystic hydatid disease) and Echinococcus multilocularis, and paragonimiasis (104). Cases of acute transverse myelitis have been documented following administration of oral poliovirus vaccine, tetanus toxoid (DT, Td), and cholera, typhoid fever, and plasma-derived hepatitis B virus vaccine, but the evidence has been considered inadequate to confirm a causal relation (106). The illness may be suggestive of encephalomyelopathy or a tumor rather than poliomyelitis-like paralysis. Diagnostic testing (eosinophilia, positive parasite-specific complement fixation tests) or empirical treatment (antiparasitic agents) may provide clinical leads as to the etiology.

Acute myelopathy due to spinal cord compression (space-occupying lesions, spinal block, epidural abscess) or anterior spinal artery syndrome

Acute myelopathy may occur because of the presence of space-occupying lesions or spinal block—e.g., paraspinal or epidural abscess, tumor or hematoma, or anterior spinal artery syndrome (107). The common presentations include weakness of the lower extremities, AFP, urinary distention, constipation, hyporeflexia, sensory impairment, and paresthesia. A slightly elevated protein level in cerebrospinal fluid may be found. There have been reports of acute transverse myelitis with sensory disturbances and AFP of both lower limbs following intragluteal penicillin injection (108). These accidents were probably due to mistaken intraarterial injection of the drug, with retrograde progression through branches of the internal iliac artery up to the spinal cord.

TRAUMA

Acute traumatic sciatic neuritis associated with intramuscular gluteal injection

Administration of intramuscular injections in the gluteal region is still common practice, despite the potential risk of direct trauma or postinjection neuritis. The World Health Organization recommends that diphtheria-tetanus-pertussis vaccines and other intramuscular injections be given at the anterolateral aspect of the upper thigh (109). A history of recent injections in paralyzed limbs—for the treatment of febrile infections, for instance—provides a characteristic lead for diagnosing traumatic neuritis. Traumatic neuritis needs to be differentiated from aggravation poliomyelitis (see section on poliomyelitis above).

Spinal cord injury

Trauma should always be considered clinically as a cause of AFP. However, paralysis that is clearly associated with trauma should not be included in the AFP reporting system.

Cardiovascular disorders, surgical complications

Postoperative spinal cord damage due to ischemia may occur because of the interruption of critical radicular arteries at the lower thoracic or high lumbar vertebral levels, and may result in total paraplegia or paraparesis (107). High aortic clamping and hypotension increase the probability of this occurrence. The clinical examination in such cases reveals AFP, areflexia, sensory loss, paralysed sphincter, and reflex neurogenic bladder (107).
PERIPHERAL NEUROPATHIES

Anatomically, two broad categories of peripheral neuropathy can be distinguished in terms of the pattern of involvement of the peripheral nervous system: 1) polyradiculoneuropathies involve the spinal roots and peripheral nerve trunks, and 2) polyneuropathies, which result in bilaterally symmetrical disturbance of function, tend to be associated with agents that act diffusely on the peripheral nervous system, such as toxic substances, deficiency states, systemic metabolic disorders, and certain types of autoimmune reactions.

Toxic neuropathies are an important group of disorders in neurologic practice in the tropics. Distal axonal degeneration ("dying back phenomenon") is the neuronal dysfunction in most toxic neuropathies (13). Neuropathies may occur in the course of infectious diseases, such as diphtheria, borreliosis, and rabies. Acute peripheral neuropathy with features similar to those of Guillain-Barré syndrome can occur in acute beriberi, acute intermittent porphyria, AIDS, paralytic rabies, cytomegalovirus infection, Epstein-Barr virus infection (110), and hepatitis B virus infection, and following the administration of Sempke-type rabies vaccine (69) (see section on rabies vaccines above).

Toxic neuropathies

Diphtheria neuropathy is an infrequent complication (~10 percent) among patients infected with Corynebacterium diptheriae. Patients with more severe manifestations of diphtheria (toxic forms) are at greater risk of developing cranial and peripheral neuropathy, which makes its appearance during the initial acute phase of illness or 8–12 weeks later. The neuropathy is mostly distal and mixed motor-sensory disease (111), characterized by palatal palsy, early sensory signs and symptoms, fever, and reduced or absent deep tendon reflexes. Studies of nerve conduction velocity demonstrate prominent demyelination with signs of denervation upon electromyography.

Tick bite paralysis manifests 5–10 days after a tick attaches itself. The onset of the illness is rapid, with prodromal symptoms including irritability, anorexia, pain and paresthesia in the extremities, and ataxia and being followed by symmetrical, ascending AFP within 12–36 hours. If the tick is not removed, the illness will eventually involve bulbar musculature and will lead to a fatal outcome in up to 12 percent of patients. Paralysis usually (but not always) resolves rapidly after tick removal (13). Ocular symptoms, if present, may provide clues with which to differentiate tick paralysis from Guillain-Barré syndrome, myasthenia gravis, or botulism (112). Various Dermacenter and Ixodes species, mainly in North America and Australia but also in tropical areas, are known to produce paralysis in humans and in domestic and wild animals (13). While tick toxin was thought to block neuromuscular transmission, recent reports indicate that ticks elaborate a toxin directed at the large-diameter motor or sensory nerves, particularly the motor nerve terminals (112).

Neuropathy associated with Lyme borreliosis (113) may manifest as cranial neuropathy, most commonly facial palsy, radiculoneuropathy, or symmetrical distal neuropathy. Lyme disease, caused by the spirochete bacteria Borrelia burgdorferi, is characterized by erythema migrans, high acute-phase serum titers of immunoglobulin M and immunoglobulin G Borrelia antibodies, and lymphocytosis and increased total protein levels in the cerebrospinal fluid (113). Ixodes ticks, the vector of Lyme disease, are prevalent mainly in North America, Europe, Eastern Europe, and northeastern China. The incubation period between tick exposure and erythema migrans is 3–32 days; within weeks or months after the appearance of erythema migrans, a variety of neurologic abnormalities may occur. Lyme meningitis affects nerve roots as the spirochete bacteria pass through the subarachnoid space. AFP due to Lyme polyradiculoneuropathy may develop 6–8 weeks after the tick bite and is painful and asymmetrical. Weakness that may affect both the lower and upper limbs develops within 4 weeks after onset, much more slowly than in polioymelyitis. Deep tendon reflexes are usually depressed, and sensory loss is dermatomal (72). Lyme borreliosis also may cause facial paralysis, which is bilateral in 50 percent of cases; in the absence of other clinical systemic features, it may be indistinguishable from idiopathic facial paralysis (Bell’s palsy; see section below).

Louse- or tickborne relapsing fever caused by several Borrelia species occurs worldwide and may cause AFP (114). Borreliae in tick-borne relapsing fever more frequently cause neuroparalytic complications, while louseborne borreliae cause more severe systemic illness and greater mortality.

The ingestion of the ripe fruit of Karwinskia humboldtiana (tullidora, coyotillo, buckthorn, wild cherry), which grows in northern Mexico, Central America, and the US states of Texas and New Mexico, produces a progressive ascendent symmetrical AFP resembling Guillain-Barré syndrome that in severe cases may cause bulbar paralysis and death (115, 116). K. humboldtiana has caused outbreaks of AFP in Nicaragua (117). Wild berries of Karwinskia calderoni in El Salvador may contribute to the elevated rate of AFP (erroneously attributed to Guillain-Barré syndrome) seen among children in the Americas.

Gloriosa superba (climbing lily, glory lily), found in Africa and Asia, contains colchicine, which impairs rapid axonal transport in peripheral nerves, resulting in axonal neuropathy; it also causes myopathy (22). Other poisonous plants implicated in paralytic illness include Aconitum napellus (monkshood); Callitepsis species (daisy); Gelsemium (jasmine—blossoms); Heliotropum (bush tea shrub); Melochia species (stems); and Oenantea species (parsnip) (19).

A variety of chemicals, metals, and drugs have been associated with motor-sensory neuropathies. Exposure (often agricultural or industrial) to chemicals such as lead, arsenic (118), and thallium, as well as glue-snif ting (119), may cause peripheral motor neuropathy. Historically, epidemic neuropathies in Jamaica and England could be linked to chronic arsenic intoxication rather than nutritional deficiency. Arsenic-containing compounds such as melsarsoprol are still being used in developing countries for the treatment
of African trypanosomiasis (sleeping sickness) and may cause Guillain-Barré syndrome-like AFP (120).

Many antimicrobial or chemotherapeutic agents may cause peripheral neuropathy. Symptoms are mainly sensory, but distal weakness can occur. Antirheumatic drugs (gold, colchicine) have been associated with peripheral neuropathy (22). The number of cases involved is relatively small, and cessation of treatment with these compounds results in regression of the neurologic symptoms. This observation also applies to chemotherapeutic agents (Vinca alkaloids and platinum-containing compounds).

**DISEASES OF THE NEUROMUSCULAR JUNCTION**

The skeletal neuromuscular junction, the most exposed and most vulnerable synapse known, is the site of primary pathology in disorders such as myasthenia gravis and Lambert-Eaton myasthenic syndrome (121). Both syndromes are rare, characterized by weakness and fatigability of skeletal muscles. High titers of anti-GM, glycoconjugate antibodies in patients with myasthenia suggest an autoimmune disorder (86). Endogenous chemicals such as calcium and magnesium, when in excess or deficit, will affect the neuromuscular junction (122). Exogenous chemicals such as organophosphates inhibit acetylcholinesterase activity, leading to neuromuscular blockade and muscle paralysis. A large number of drugs also alter neuromuscular transmission, acting either directly on nondepolarizing neuromuscular blocking agents or through adverse effects (e.g., amino-glycosides, phenytoin) (23).

A variety of naturally occurring toxins of animal, plant, and bacterial origin are capable of causing disorders of neuromuscular transmission.

Botulism is caused by the exotoxin of Clostridium botulinum. Botulism toxin can cause descending paralysis—characterized by symmetrical impairment of cranial nerves, followed by a descending pattern of weakness or paralysis of the extremities and trunk (123).

Tetanus exotoxin from the spores of Clostridium tetani is a major cause of perinatal mortality, and it may also cause AFP of the muscles innervated by the affected cranial nerves (i.e., cephalic tetanus) (124). The latent period for the neurologic syndrome is 14 days in neonates and 6-10 days in adults (range, 3-21 days). Tetanus toxin is carried intraneuronally within membrane-bound vesicles to spinal motor neurons, where it causes presynaptic inhibition of spinal glycinergic neurons (22). Subclinical axonopathy has also been described in patients recovering from tetanus.

Animal toxins leading to neuroparalytic syndromes include those derived from the venom of various snakes, arthropods, and marine creatures and those derived from the skin excretions of “dart-poison” frogs, poisond fish, shellfish, and crabs (producing the active agents ciguatoxin, tetrodotoxin, saxitoxin, and domoic acid). Neurotoxins produced by elapid snakes, particularly the African and Asian cobra (Naja) and the krait of southern Asia (Bungarus), may cause acute neuroparalytic syndromes in 30-50 percent of victims, including AFP, ophthalmoplegia, and bulbar and respiratory palsy. Many elapid snakes, including the mam-

bas of Africa, Vipiridae (including rattlesnakes), and the coral snakes of America, produce neurotoxins; however, only cobra and krait bites have been associated with neuroparalytic syndromes in the absence of any other symptom except local pain. An interesting early morning syndrome of acute oculobulbar palsy with flaccid paralysis, resembling the clinical picture seen with elapid snake bite but without evidence of snake bite, has been reported in India (12, 125). The features of acute onset of ptosis, external ophthalmoplegia, and bulbar paralysis with mild to moderate weakness, in the absence of a history of snake bite, could be confused with myasthenia gravis, acute infectious polyneuritis, or poisoning because of numerous agents' acting at the neuromuscular junction, but they should be distinctive enough to differentiate this syndrome from paralytic poliomyelitis.

Tetrodotoxin poisoning from consumption of puffer fish (fugu, Sphaeroides maculatus) results in a fatality rate of up to 60 percent (126). Within several hours after consumption, individuals develop circumoral paresthesia spreading to the limbs and trunk, with AFP and difficulty in breathing (126). Tetrodotoxin may act at the motor end plate as well as on axon and muscle membranes, and patients clinically respond to treatment with anticholinesterase drugs (126).

The known plant toxins most commonly implicated in paralytic illness due to neuromuscular blockade are curare, canemethonium, and hemlock extract (127).

Organophosphorus esters are used mainly as insecticides, petroleum additives, and modifiers of plastics (128). Most inhibit acetylcholinesterase activity; some, used as pesticides, helminthicides, or war gases, are extremely potent. The main symptoms include acute weakness of the hands, calf pain preceding paresthesia and weakness of the limbs, absent ankle jerks, foot-drop, and claw-hand (13). The muscle paralysis caused by delayed neuropathy (2-3 weeks after organophosphorus exposure) should be differentiated from the intermediate syndrome (3-4 days postexposure), which affects the neuromuscular junction and carries the risk of respiratory paralysis and death (13, 22, 129).

Outbreaks of neuropathy resulting from exposure to triorthocresyl phosphate, a potent organophosphate, have occurred in Morocco, Jamaica, the United States, South Africa (“Durban mystery disease”); see “Other Clinical Syndromes Causing AFP” below) (19), India (13), and Sri Lanka (13). The consumption of accidentally contaminated or adulterated food products (Jamaican ginger tonic, Romanian liquor, or contaminated cooking oil, mustard oil, or flour) may lead to paralytic disease (130). Outbreaks in Sri Lanka were linked to sesame-derived gengili oil given to teenage girls at menarche and to adult women after childbirth; these women exhibited the characteristic wrist-drop and claw-hand (13). Triorthocresyl phosphate intoxication typically begins with aching pain in the calves, followed by paresthesia, numbness, and weakness distally in the lower extremities, along with a high incidence of pyramidal signs (13). Upon examination, ankle jerks are diminished or absent; knee jerks, however, are unusually exaggerated, suggesting upper motor neuron involvement (destruction of corticospinal tracts and the spinal cord, including anterior
horn cell damage) rather than peripheral axonal neuropathy or neuromuscular blockade (1, 13).

WEAKNESS ASSOCIATED WITH CRITICAL ILLNESS

Acute weakness syndromes in critically ill patients can be categorized into three major groups with different etiologies: 1) critical illness polyneuropathy; 2) neuromuscular junction abnormalities, subdivided into myasthenia-like syndromes and prolonged neuromuscular blockade; and 3) myopathy, including acute disuse (cachectic), necrotizing, and thick filament (myosin) loss myopathy (131). Recent data also suggest that physiologic muscular inexcitability due to sodium channel dysfunction, rather than morphologic changes of the muscle, may contribute to weakness in critically ill patients (132).

Nonpolarizing neuromuscular blocking agents, used with increasing frequency in critically ill patients, have been associated with prolonged muscle weakness (133). Individuals with status asthmaticus treated with bronchodilators, antibiotics, and high dose corticosteroids and paralyzed with vecuronium to facilitate mechanical ventilation have developed flaccid quadriplegia with areflexia. Brief weakness lasting for several hours to several days is probably the result of prolonged neuromuscular blockade, while more prolonged weakness lasting for several weeks to months is probably caused by myopathy. Clinically, patients develop AFP with intact sensation and cognition.

Neuromuscular dysfunction in patients with sepsis is increasingly being reported (131, 134). The common underlying pathogenic process in these syndromes appears to be systemic inflammatory response syndrome, induced by infection or trauma and accentuated by the administration of steroids or neuromuscular blocking agents (131). Flaccid quadriplegia with the inability to wean from ventilatory support despite full cardiopulmonary recovery is the typical presentation. Electrophysiologic studies often demonstrate the presence of axonal polyneuropathies, abnormalities of neuromuscular transmission, or acute myopathies. Recovery in strength usually occurs over a period of weeks to months. Variants of critical illness polyneuropathy may affect end-stage uremic or diabetic patients developing axonal, predominantly motor polyneuropathy.

First described by Hopkins and Shield in 1974 (135), acute postasthmatic amyotrophy (Hopkins syndrome) is characterized by sudden onset of AFP of an arm or a leg with completely preserved sensibility approximately 1 week after an asthma attack. All children in the initial case description were under 10 years of age, and most were male. To date, fewer than 30 cases have been described in the literature. The AFP is probably due to a lesion of the anterior horn cells of the spinal cord, but evidence indicates a more widespread pathologic process. The etiology is unknown, but infectious or immunologic mechanisms are likely. It has been suggested that a combination of immune suppression with the stress of an acute asthma attack, concurrent infection, or corticosteroid therapy renders patients susceptible to viral invasion of anterior horn cells. Infections with M. pneumoniae and other agents have been associated with Hopkins syndrome (136).

DISORDERS OF THE MUSCLE

Idiopathic inflammatory myopathy (polymyositis) rarely may cause Guillain-Barré syndrome-like AFP (137). The onset more frequently is subacute and insidiously progressive over weeks, months, or even years. Proximal limb muscles are mostly affected, but respiratory weakness, cardiac problems, or dysphagia may occur. The diagnosis is based on electromyographic abnormalities, elevated serum creatine kinase levels, and muscle biopsy. As in other autoimmune disorders, high titers of anti-GM, glycoconjugate antibodies are found in polymyositis patients as well (86). Polymyositis is primarily found among females aged 20–40 years. Associated conditions often include lung cancer and autoimmune disease (systemic lupus erythematosus and mixed connective tissue disorder). Inflammatory polymyositis may also be associated with viral (HIV, human T-lymphotropic virus type 1, nonpolio enterovirus), parasitic (Toxoplasma), or bacterial ( Lyme disease) infections (137).

Hereditary motor and sensory neuropathies, historically called spinal muscular atrophies or muscular dystrophies, may affect the anterior horn cells of the spinal cord. Werdnig-Hoffmann disease is a rapidly progressing, often fatal disorder with onset during the first year of life; Wohlfart-Kugelberg-Welander disease is a more benign disorder with onset in late childhood or early adolescence (138). The etiology and pathogenesis of hereditary motor and sensory neuropathies are still incompletely understood (139).

Trichinosis is characterized by painful myopathic weakness potentially mimicking poliomyelitis, periorbital swelling, splinter hemorrhages, and fever, and it also may manifest as meningoencephalitis, mononeuropathies, polymyositis, and radiculitis (140). Signs of spinal cord damage have included paraparesis, hyperalgesia and decreased deep tendon reflexes of the lower extremities, urinary retention, and bladder anesthesia. The diagnosis is based on eosinophilia, serologic testing, history of preceding gastrointestinal illness, consumption of contaminated pork or walrus meat, and the presence of larvae of the nematode helminth Trichinella spiralis upon muscle biopsy (141). Although it is prevalent in tropical and temperate areas, trichinosis is also a serious medical problem among Native populations in Arctic regions.

NEUROPATHIES OCCURRING IN SYSTEMIC OR METABOLIC DISORDERS

Acute hypokalemic periodic paralysis is a rare cause of AFP (142). Two thirds of cases are due to hypokalemic familial periodic paralysis, a disease that exhibits autosomal-dominant inheritance and mostly affects Caucasian males and adolescents (142). Familial periodic paralyses have been divided into three main forms according to precipitating factors and the patient’s potassium level at the time of an attack: 1) Hypokalemic familial periodic paralysis is usually precipitated by a meal rich in carbohydrates, and it has the tendency to manifest in the morning.
hours after rest. 2) Potassium-sensitive familial periodic paralysis usually has its onset before the age of 10 years; the attacks are less severe than those of the hypokalemic form and tend to occur during the daytime. 3) In familial adynamia episodica hereditaria, first described by Gamstorp (143), glucose prevents potassium-induced attacks of AFP. Familial periodic paralysis and other muscle disorders leading to attacks of weakness that occur intermittently in otherwise normal people have been linked to disturbed function of skeletal muscle ion channels ("channelopathies") (144). Depending on the type of familial periodic paralysis, the diagnosis is established by the demonstration of changes in serum potassium levels during the attack, the presence of electromyographic and electrocardiographic abnormalities, and the use of muscle biopsy and potassium-, glucose-, or insulin-loading tests.

Thyrotoxic periodic paralysis is a syndrome defined by characteristic clinical, electromyographic, biochemical, and microscopic features. Asian, Hispanic, and Native American males aged 30–60 years are most commonly affected. Clinical manifestations include acute-onset progressive symmetrical weakness leading to AFP of the extremities and other muscle groups (acute episodes of flaccid paraplegia or tetraplegia) which is induced by excess levels of exogenous or endogenous (Graves' disease) thyroid hormones and after high carbohydrate ingestion or heavy exertion. This syndrome is distinct from thyrotoxic myopathy and familial periodic paralysis. Because of its association with use of diuretics, the syndrome is found in older individuals and needs to be differentiated clinically from Guillain-Barré syndrome.

Acute intermittent porphyria may cause a rapidly progressing peripheral neuropathy with motor-sensory signs and symptoms and consequent AFP (145). Acute intermittent porphyria may include abdominal pain and psychological and neurologic signs (disturbances of consciousness and mentation, convulsions), but not all attacks progress to the neurologic stage. The initial episode often occurs in early adolescence. The classic ruby-red coloration or measurement of porphyrins (porphobilinogen, δ-aminolevulinic acid) in the urine helps confirm the diagnosis. Sporadic cases of hypokalemic paralysis are associated with various underlying disorders, such as renal tubular acidosis, primary hyperaldosteronism (Conn's disease) (146), and secondary hyperaldosteronism due to licorice (Glycyrrhiza glabra) ingestion (22). Barium salts contaminating table salt or flour have been associated with Chinese outbreaks of hypokalemic paralytic disease known as "Pa Ping" or "Kiating" paralysis (147) (Pa Ping and Kiating are areas in China's Szechwan Province). Gossypol, a phenolic compound present in the seeds and root barks of cotton plants (Gossypium, family Malvaceae) and used in cottonseed oil for domestic cooking, is probably also responsible for epidemics of hypokalemic paralysis in China (22). Paralysis develops within 24 hours, along with dysarthria, areflexia, and dysphagia. Disorders of muscle energy metabolism causing AFP (Leigh's and McArdle's disease) may be confounded with Guillain-Barré syndrome.

OTHER CLINICAL SYNDROMES CAUSING AFP

Other entities that have been misdiagnosed as polyomyelitis include osteoarticular trauma, acute cerebellitis, retroperitoneal tumors, infection of an intervertebral disc, scurry, Caffey's disease (infantile cortical hyperostosis), postictal hemiparesis (Todd's paralysis), and "floppy infant" syndrome (18, 20).

An important psychological element was observed in a condition known as epidemic neuromyasthenia, also referred to as "the summer grippe," "Iceland disease," or "Durban mystery disease," which has been reported in various parts of the United States, Iceland, South Africa, and England (19). Reports from South Africa suggest an association with the organic compound triorthocresyl phosphate (19) (see "Diseases of the Neuromuscular Junction"), while recent reports suggest that neuromyasthenia may be caused by a low-virulence but neuropathic type 2 poliovirus (148).

Although it is not included in the surveillance case definition of AFP, facial paralysis may be associated with poliovirus infection, Guillain-Barré syndrome, or AMAN (149). The most common form of facial paralysis, idiopathic Bell's palsy (150), is characterized by complete flaccid facial paralysis. Eighty percent of affected individuals recover within a few months. A rather typical clinical course of Bell's palsy allows one to focus differential diagnostic investigation predominantly on the rapid identification of treatable infections such as those caused by varicella-zoster virus or borreliae (149). Other causes of facial paralysis include enterovirus infection, HIV infection, Ramsay-Hunt syndrome (presumably due to varicella-zoster virus infection of the geniculate ganglion), Guillain-Barré syndrome (mainly affecting cranial nerves VII and IX–XII), AMAN, and sarcoidosis (uveoparotid fever or sarcoidosis, Heerfordt syndrome).

PARALYTIC SYNDROMES COMMONLY MISDIAGNOSED AS AFP

Conditions commonly misdiagnosed as AFP can be grouped into two broad etiologic categories: paralytic illness associated with nutritional toxins (151) and chronic central nervous system disease, frequently with dementia. The links between these two etiologic categories are influenced by postinfective tropical malabsorption and micronutrient and mineral deficiency from food and water. Cobalamin (vitamin B₁₂) deficiency causes pernicious anemia and can also result in severe polyneuropathy with symmetrical paralysis and atrophy (152). Chronic cycad poisoning (evergreens, seeds), in conjunction with deficiency syndromes, has been implicated in the etiology of these clusters of paralytic illness.

Clusters of amyotrophic lateral sclerosis, Parkinson disease, and a subacute paralytic condition reminiscent of Guillain-Barré syndrome, referred to as "poliomyeloradiculitis" because of the asymmetrical distribution of paralysis (152), must be differentiated from poliomyelitis, other non-polio enterovirus infections, and micronutrient deficiency syndromes.
Tropical myeloneuropathies, a serious health problem in tropical regions, include tropical spastic paraparesis and tropical ataxic neuropathy. Although tropical myeloneuropathies are multifactorial, specific etiologic agents—e.g., cyanogenic glycosides from cassava (129), lathyrisrn (153), postinfectious tropical malabsorption, and human T-cell lymphotropic virus (154)—have been implicated. Toxicity from cyanide or cyanoglycosides in cassava can be exacerbated by relative deficiencies of B vitamins (thiamine (vitamin B₁), riboflavin (vitamin B₂), and cobalamin (vitamin B₁₂)) and sulfur-containing amino acids, which are necessary for the detoxification of these compounds. Nutritional myelopathies have been documented in Sub-Saharan Africa.

Isolated nonprogressive spastic paraparesis of acute onset has been reported as “konzo” in the Democratic Republic of the Congo and the Central African Republic and as “manto-kassa” in Mozambique and Tanzania (22, 155). Seasonal outbreaks have been linked epidemiologically to consumption of bitter cassava (Manihot esculenta, Manihot utilissima) (13). Cassava roots contain naturally occurring cyanogens, and the plant’s toxicity is enhanced with decreased intake of foods with sulfur-containing amino acids, which promote cyanide detoxification. Acute hydrocyanide poisoning may result from consuming toxic winged beans, and chronic cyanide acid poisoning may result from consuming poorly washed manioc.

Lathyrisrn is the classic cause of epidemic outbreaks of tropical spastic paraparesis associated with excessive ingestion of certain flowering peas in times of famine (Lathyrus sativus (chickling pea), Lathyrus clymenum (Spanish vetch), Lathyrus cicera (flat-podded pea)), Phascolus, and several grasses (156). Lathyrisrn is still endemic in regions of India, Bangladesh, and Ethiopia and continues to be a public health problem. Lathyrisrn has been associated with outbreaks of paralytic illness in Myanmar (World Health Organization, unpublished data).

GEOGRAPHIC DISTRIBUTION OF PARALYTIC ILLNESSES

Host or environmental factors may considerably influence the occurrence and frequency of AFP. For instance, the ability to metabolize certain drugs or compounds may vary between certain populations (isoniazid toxicity in Japan; thyrotoxic periodic paralysis mostly among Asian, Latin, and Native American men). The spread of C. jejuni infections, in conjunction with host, dietary, and sanitary factors, may account for summertime epidemics of AMAN without geographic clustering in northern China. The spread of potential vectors determines the occurrence of tickborne paralysis or borreliosis (Lyme disease, relapsing fever) causing Guillain-Barré syndrome-like AFP. The geographic distribution of genetically determined neuromuscular diseases may be influenced by genetic factors, while environmental factors may be associated with nonhereditary immunologic myopathies and neuropathies. Exposure to manmade or naturally occurring toxins, such as those found in toxic plants (e.g., K. humboldtiana, K. calderoni), venomous animals (e.g., snakes, scorpions, frogs), contaminated water or food, or infectious agents, combined with deficiency syndromes, may lead to a wide array of toxic neuropathies, mostly in tropical areas (13).

CONCLUSIONS

AFP is a complex clinical syndrome that requires immediate and careful evaluation of the differential diagnoses. Each case of AFP is an emergency, from both a clinical perspective and a public health perspective, and precise knowledge of the etiology, underlying pathophysiologic mechanisms, and anatomic-morphologic changes involved has profound implications for prognosis and treatment. The underlying pathology, precise cellular basis, or pathophysiologic mechanisms for certain causes of AFP are not yet understood. The examples of Guillain-Barré syndrome, neurologic complications in AIDS, acute transverse myelitis, and Hopkins syndrome illustrate the complex and multifactorial interaction between different pathogenic factors, including preceding or concurrent infection with neutrotropic agents, along with inadequate immune or autoimmune responses of the nervous system. Infections with neutrotropic viruses and other infectious agents may set in motion a pathologic immune process that inappropriately targets central or peripheral myelin or peripheral axons (8, 99). The association between infection with C. jejuni, M. pneumonieae, S. monsoni, or S. haematobium and a variety of causes of AFP, such as AIDP, AMAN, Hopkins syndrome, and acute transverse myelitis, is intriguing and has drawn considerable research interest. The role of infectious agents and immune processes as significant causes of AFP may be complemented by a variety of naturally occurring or manmade toxins.

The list of underlying causes of AFP is broad, and there is substantial variation by age, ethnicity, and geographic area. In the absence of wild virus-induced poliomyelitis, the acute demyelinating form of Guillain-Barré syndrome (AIDP) accounts for at least 50 percent of AFP cases globally (16, 77), followed in frequency by paralytic nonpolio enterovirus infection, the motor axonal form of Guillain-Barré syndrome (AMAN), traumatic neuritis, and acute transverse myelitis.

The campaign to eradicate poliomyelitis is at a critical stage. The smallpox eradication program demonstrated the need for accurate surveillance, while a factor contributing to the failure of earlier eradication programs was the absence of the capacity to establish surveillance meeting these high standards. Without accurate disease surveillance, it is impossible to conduct an effective disease control or eradication program or to measure the disease burden and the effect of intervention measures.

Because poliomyelitis is on the verge of eradication, accurate surveillance for AFP must be intensified. The global incidence rate of nonpolio AFP would be expected to be 1 per 100,000 among children under 15 years of age under conditions of optimal surveillance with complete case ascertainment (78). Achieving and maintaining this detection rate is considered the most sensitive performance criterion for any AFP surveillance system. Epidemiologic and
clinical surveillance require detailed knowledge of the potential differential diagnoses of AFP. It is therefore crucial that sensitive AFP surveillance be conducted, even in the absence of wild poliovirus transmission. Clinicians must be aware of the causes of AFP and of the need to report and continuously investigate AFP cases. Virologic and case-based AFP surveillance provides a tool for identifying problem areas where previous immunization strategies have failed or wild poliovirus transmission continues, and for guiding supplementary activities.

For the eradication of poliomyelitis, a highly sensitive but relatively nonspecific case definition was selected by the World Health Organization. Officials in national poliomyelitis eradication programs first introduced highly sensitive case definitions to avoid missing true cases of the disease, though false-positive diagnostic errors could still occur because of low specificity. No single practical clinical case definition combining both high sensitivity and high specificity has become available (2—4); however, virologic isolation of poliovirus from stools of patients with AFP provides the necessary specificity for confirming poliomyelitis. An internationally concerted effort is needed to develop a global registry for the nonpoliomyelitis causes of AFP, in order to supplement poliomyelitis data banks. Such a registry has been partly established in the Americas (77).

In conclusion, health workers need to be aware of the importance of comprehensively evaluating and reporting all AFP cases, collecting stool specimens immediately, and testing for neurotropic agents, including poliovirus.

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