ACUTE ONSET FLACCID PARALYSIS

This document arises from a WHO meeting convened jointly with AIREN (a WHO Collaborating Centre). It identifies and describes the various neurological disorders that produce an acute onset flaccid paralysis (AFP), including poliomyelitis, Guillain-Barré Syndrome (GBS), Acute Motor Axonal Neuropathy (AMAN, the so-called Chinese Paralytic Syndrome, CPS).

The diagnosis of illnesses causing AFP is receiving increasing attention in the context of the campaign for the global eradication of poliomyelitis. This campaign will require intense surveillance of any reported cases of AFP to determine whether they are due to poliomyelitis. In order to minimize inefficient use of resources needed for the campaign, operational screening criteria with high specificity are needed in order to distinguish outbreaks of AFP most likely due to poliomyelitis from those due to other causes.

The document closes with three appendices. The Poliomyelitis Case Investigation Form used by the WHO Expanded Programme on Immunization; an Acute Flaccid Paralysis Case Investigation Form which the meeting participants developed as a modification of the WHO/EPI form in order to provide more detailed information to distinguish poliomyelitis from non-poliomyelitis cases; and a set of detailed criteria for the diagnosis of poliomyelitis, GBS and (briefly) acute transverse myelitis.

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## CONTENTS

### 1. Introduction

1.1 Objectives of the Meeting
1.2 Background

### 2. Differential diagnosis of acute onset flaccid paralysis

2.1 Definition of AFP
2.2 General comments on neuropathology and clinical investigation of AFP
2.3 Causes of AFP
2.4 Characteristics of conditions associated with AFP
   2.4.1 Acute anterior poliomyelitis caused by poliovirus
   2.4.2 Acute anterior poliomyelitis caused by viruses other than the poliovirus
   2.4.3 Acute myelopathies
   2.4.4 Peripheral neuropathies
   2.4.5 Neuropathies occurring in systemic diseases
   2.4.6 Disorders of the neuromuscular junction
   2.4.7 Disorders of muscle

### 3. AFP in selected countries of the world

3.1 Papua New Guinea and Micronesia
3.2 Japan
3.3 Northern China
3.4 India
3.5 Latin America
3.6 The Netherlands
4. Conclusions and Recommendations

5. References

6. Appendices

Appendix I: EPI Poliomyelitis Case Investigation Form
Appendix II: Acute Flaccid Paralysis Case Investigation Form
Appendix III: Detailed Clinical Criteria for Poliomyelitis, GBS and Acute Transverse Myelitis
ACUTE ONSET FLACCID PARALYSIS

1. INTRODUCTION

This meeting was held to review current information on AFP and formulate diagnostic criteria for its differential diagnosis.

1.1 Objectives of the Meeting:

1) review current information on AFP, formulate diagnostic criteria for its diagnosis, and develop a better understanding of the variety of causes of acute-onset flaccid paralysis;
2) increase the sensitivity and specificity of diagnostic criteria, to facilitate clear differential diagnosis between poliomyelitis and other cases of AFP non-polio, and thereupon produce specific recommendations concerning the definition of acute flaccid paralysis.

1.2 Background

From the neurologic perspective, acute-onset flaccid paralysis (AFP) represents a syndrome with multiple causes. Despite a dramatic reduction in the number of AFP cases from poliovirus, AFP continues to be a major problem worldwide. It is quite evident that in many parts of the world, most cases of this syndrome are not due to poliovirus. In the past, based on clinical criteria alone, many cases were diagnosed as Guillain-Barré syndrome (GBS). But intensive studies in several parts of the world have suggested that some of these cases may represent disorders other than classic GBS. Yet the exact proportion of patients with specific conditions among those with AFP is unknown, and diagnostic criteria for most of these disorders are presently unavailable.

In the developing world, providing a precise diagnosis for each case of AFP is very important. Although criteria and the ability to diagnose poliomyelitis are available worldwide, the ability to diagnose non-polio myelitis cases is not always present. In particular, special laboratory facilities, electrodiagnostic facilities, and the ability to examine autopsy tissue are not always available everywhere. In many countries, simple, easily reproducible and applicable measures are needed to provide a differential diagnosis of non-poliomyelitis cases. It may, however, be sufficient to have teams of individual experts available to examine cases of acute-onset flaccid paralysis to provide final diagnosis; this would require an In-depth surveillance programme and a rapid-response team. The current Poliomyelitis Case Investigation Form used by EPI only allows limited ability to distinguish the various causes of AFP; disorders must be distinguished on the basis of fever, symmetry of the weakness, and pattern of recovery. While this scheme is useful for detecting cases of polio, it cannot differentiate the large number of other, non-polio myelitis causes of AFP. Both the previous EPI Form as well as a revised version of the EPI Form (AFP Case Investigation Form) based on the experiences gathered during this meeting are given in Appendix I and in Appendix II of this report.

As the number of cases of AFP from poliovirus decreases, post-report follow-up on all cases of AFP is envisioned to obtain individual diagnoses on these cases. It is estimated that AFP affects 1/100,000 children of less than 15 years of age. Of interest is that in several parts of the world these figures are not declining with the introduction of poliomyelitis vaccination. For example, in Madras, India, where 98% of children now receive poliomyelitis vaccination, the incidence of AFP in children under 15 years of age remains at 1/100,000. This raises the important issue of the differential diagnosis of AFP. In northern China, at least three disorders make up the majority of AFP cases: classic poliomyelitis from poliovirus, demyelinating GBS, and another disorder, Acute Motor Axonal Neuropathy (AMAN), the so-called the Chinese Paralytic Syndrome. Further disorders will be characterized as individual cases are more intensively investigated. Differential features of these disorders are described in the section Differential Diagnosis of AFP below.

It should especially be noted that the disorders discussed here occur primarily in children. For many of the diseases, prior criteria have been established for diagnosis in adults and thus may not be applicable to children. Considerable variation has been noted on a geographical basis.
This Meeting was facilitated by the findings of three meetings on Guillain-Barré Syndrome (GBS) held in 1989, 1991 and 1992 and co-sponsored by the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AINEREN), Johns Hopkins University and its Kriger Mind-Brain Institute, the National Institute of Neurological Disorders and Stroke at the National Institutes of Health (NINDS-NIH), and the University of Würzburg (Asbury et al., 1990; Asbury et al., 1991). These meetings resulted in the following findings:

a. There are close similarities, clinically and pathologically, among patients with acute inflammatory demyelinating polyneuropathy or demyelinating GBS, regardless of geographic origin or location at time of onset.

b. A more clear delineation of the electro-diagnostic aspects of GBS and an emphasis on the role of conduction block in the production of symptoms and in diagnosis as well as the role of electro-diagnosis in investigating the prognosis of patients with GBS.

c. Circulating factors may play a role in peripheral nerve demyelination, leading to a variety of therapeutic interventions in GBS. Initially, two controlled studies showed plasma exchange to be effective, and more recently a single study reported that human immune globulin given intravenously was equally effective.

d. The possible etiologic relationship of Campylobacter jejuni to the flaccid paralysis cases seen in many parts of the world may have implications for our understanding of the pathogenesis of AFP.

e. A reassessment of the original NINDS criteria for the diagnosis of GBS found them to be valid in both epidemiologic studies and research trials.

f. A number of cases of AFP are neither demyelinating GBS nor related to poliovirus, but form a distinct pattern that can be distinguished clinically, electro-diagnostically, and pathologically from demyelinating GBS and may be referred to as "acute motor axonal neuropathy" (AMAN).

2. DIFFERENTIAL DIAGNOSIS OF ACUTE ONSET FLACCID PARALYSIS

2.1 Definition of AFP

AFP syndrome is characterized by rapid onset of weakness of an individual's extremities, often including weakness of the muscles of respiration and swallowing, progressing to maximum severity within 1-10 days. The term "flaccid" indicates the absence of spasticity or other signs of disordered central nervous system (CNS) motor tracts such as hyperreflexia, clonus, or extensor plantar responses. Although AFP may affect individuals of any age, it is particularly the affliction of children, which is important in poliomyelitis surveillance.

2.2 General comments on neuropathology and clinical investigation of AFP

The designation of a disorder as a neuropathy is to some extent arbitrary. Considerable (and justifiable) confusion exists regarding the distinction between motor neuropathies and motor-neuron disease (Thomas, 1991). The peripheral nerves consist of those parts of the nervous system in which the axons are associated with the peripheral satellite cells, e.g., Schwann cells. Included are the cranial nerves, with the exception of the second, the spinal roots and peripheral nerves, and the sensory and autonomic ganglia. However, the spinal and brainstem motor neurons and the preganglionic sympathetic and parasympathetic neurons, their cell bodies and proximal axons are situated within the CNS. Destruction of motor-neuron cell bodies will obviously lead to loss of motor axons in the peripheral nerves. If the cell bodies remain intact, but the peripheral axons degenerate as a result, for example, from axonal transection or ischaemic damage, this can be referred to as an axonopathy. Nevertheless, axon damage can lead to secondary loss of the cell bodies, as may occur with proximal axotomy. Conditions in which there appears to be a primary loss of lower motor neurons in toto, such as amyotrophic lateral sclerosis (ALS), are referred to as neuropathies. Yet, even in ALS in some motor neurons there is a distal degeneration, an axonopathy, presumably before complete loss
of the neuron (Bradley et al., 1983). The terms *neuropathy* and *axonopathy* are descriptions of pathology, and both may occur in the same disease in differing proportions.

At times the terms *neuropathy* and *axonopathy* have been employed to indicate the primary site of the pathologic process. This is unsatisfactory because of our lack of available information in many instances. Thus, uraemic polyneuropathy is an example of an *axonopathy*: this is a distal degeneration of axons with relative preservation of anterior horn cells which show chromatolysis (Asbury et al., 1963). Yet it is not established whether the metabolic effect of uraemia acts directly on the axons or on the neuronal perikarya with a secondary effect on the axons.

Conditions that affect myelin directly (myelopathies) or Schwann cell function leading to demyelination ("Schwannopathies") can clearly be categorized as neuropathies, though even here problems arise because of the close functional relationships between the axon and the Schwann cell. The term *primary demyelination* is employed to designate myelopathies and Schwannopathies. If myelin breakdown is the consequence of axonal disease, this is categorized as *secondary demyelination*, a result of axonal atrophy, having first been recognized in uraemic neuropathy (Dyck et al., 1971; Thomas et al., 1971) or axonal enlargement, as in giant axonal neuropathy (Spencer & Schaumburg, 1978; Donaghy et al., 1988). However, it is not always easy to establish the sequence of events. Reduction in axonal calibre is known to occur in peripheral nerve fibres in experimental allergic encephalomyelitis (EAE) in association with inflammatory demyelination, although its mechanism has yet to be established. In type I hereditary motor and sensory neuropathy (HMSN), the demyelination was considered to be of the secondary type since the length of the myelin spiral exceeded axon calibre (Nukada et al., 1983), suggesting axonal atrophy and a primary neuronal disorder. Xenograft studies involving transfer of peripheral nerve from patients with HMSN I into immunosuppressed mice have yielded conflicting results. One study suggested that the disorder is primarily of Schwann cells (Aguayo et al., 1978), whereas the other exonerated them (Dyck et al., 1978). There is now evidence, derived from the Trembler mouse, that Schwann cells are involved in the determination of axonal calibre by modulating neurofilament spacing (deWaegh et al., 1992). This could provide a mechanism for reducing axonal calibre in demyelinating neuropathies.

A further question requiring resolution is the explanation for axonal loss in demyelinating neuropathies. In inflammatory neuropathy, such as GBS, in which the immunologic process is directed against myelin, the axonal loss could represent a "bystander effect." How far loss of Schwann cells, leading to persistent denudation of axons, may be responsible for axonal loss, is uncertain.

Clinical features may indicate whether the patient has a demyelinating neuropathy, on the one hand, or a neuropathy or axonopathy on the other. In someone in whom weakness has been present for longer than three weeks, the presence of substantial muscle wasting would indicate denervation atrophy and therefore a neuropathy or axonopathy. If muscle bulk has been maintained, this would suggest conduction block (or a central lesion) as the cause of the weakness with preservation of axonal continuity.

Fasciculation is often cited as a sign of anterior horn cell disease and helpful in distinguishing it from neuropathy. This is not always true: fasciculation can sometimes be pronounced in demyelinating neuropathy, for example, in the proximal demyelinating neuropathy that may occur in the lumbosacral plexus after X-irradiation for malignancy (Stohr, 1980). It can also be a feature of localized demyelinating neuropathies (Mitsumoto et al., 1990).

Widespread loss of the tendon reflexes in the absence of severe weakness favours a diagnosis of demyelinating neuropathy rather than a neuropathy or axonopathy.

Electro-diagnostic studies are generally not helpful in distinguishing between neuropathies and axonopathies, but are crucial in establishing the presence of a demyelinating neuropathy. Demyelination is indicated by finding a reduction in nerve conduction velocity greater than what would be produced by a
selective loss of larger fibres, by the detection of focal conduction block in motor fibres, or by the detection of abnormal temporal dispersion (Comblath et al., 1991).

Demyelination can selectively involve spinal roots or the limb girdle plexuses. Here, P wave latency or recordings from distal upper limb muscles with high-voltage stimulation over spinal roots may be informative.

2.3 Causes of AFP

- Acute anterior poliomyelitis
  - Caused by poliovirus
  - Caused by other neurotropic viruses, e.g., coxsackie virus, echoviruses, and enteroviruses 70 and 71
- Acute myelopathy
  - Space-occupying lesion; spinal block, e.g., due to paraspinal abscess or hematoma
  - Idiopathic acute transverse myelopathy
- Peripheral neuropathy
  - Guillain-Barré syndrome
  - Acute demyelinating neuropathy
  - Acute axonal neuropathy
  - Post-rabies vaccine
- Neuropathies in the course of infectious diseases such as diphtheria.
  - Lyme borreliosis and rabies and in the course of intoxications with heavy metals and biological toxins
- Systemic diseases
  - Acute intermittent porphyria
  - Critical illness neuropathy
- Disorders of neuromuscular transmission due to
  - Myasthenia gravis
  - Snake bite
  - Botulism
  - Insecticide intoxication
  - Tick paralysis
- Disorders of the Muscle
  - Idiopathic inflammatory myopathy (polymyositis)
  - Trichinosis
  - Hypokalemic and hyperkalemic paralysis, including familial periodic paralysis

2.4 Characteristics of conditions associated with AFP

It is of practical and theoretical importance to distinguish between several conditions accompanied by AFP. These are discussed below.

2.4.1 Acute anterior poliomyelitis caused by poliovirus

The epidemiology of poliomyelitis has been well-studied. It is a seasonal disease, occurring especially in hot, wet seasons. In polio-endemic countries, it usually affects young children, mostly those less than 36 months old. In the current era in which many people receive poliomyelitis vaccination, unusual outbreaks of
Poliomyelitis occur differing from the statements above in both age and season. For example, recent winter outbreaks of poliomyelitis have been reported in Bulgaria and Jordan. In the 1991 Bulgarian outbreak, all but one case was less than 18 months old. Both outbreaks were rapidly controlled with nationwide mass immunization programmes.

Poliomyelitis continues to be a disease of the unvaccinated or inadequately vaccinated population. In the developing world, three doses of oral poliovirus vaccine (OPV) provide a poliomyelitis protection efficacy of 85%. In the developed world, three doses of OPV provide an efficacy close to 100%.

Annually, thousands of children around the world develop AFP resulting in considerable morbidity and mortality. In the developing world, AFP caused by poliovirus is a major health problem. In 1988, the World Health Assembly committed the WHO to the global eradication of poliomyelitis by the year 2000. The success of the initiative has been well documented, with no case of AFP in the Americas being confirmed as caused by wild poliovirus since August 1991 despite excellent surveillance. The number of cases of AFP caused by wild poliovirus has fallen markedly in recent years, although improved surveillance is now detecting a higher percentage of true incidence (WHO, 1992c). As the number of detected cases declines, it becomes increasingly important to develop more specific criteria for diagnosis, so that cases of AFP not due to wild poliovirus - although still being intensively investigated - do not lead to unnecessarily intensive and extensive control measures for polio. The issues of the specificity and sensitivity of diagnostic criteria are crucial: one desires a high sensitivity while increasing the specificity in individual cases.

Three basic strategies are available to eradicate Acute Flaccid Paralysis (AFP) resulting from poliovirus. The first is to increase immunization coverage to 80% of the population. The second is to build an effective surveillance system, and the third is to implement supplemental immunization activities (WHOa,b; 1992).

In most countries, immunization coverage of 80% or greater can be achieved through the routine immunization system. The Expanded Programme on Immunization's routine schedule is a dose of OPV at birth (the zero dose) and 3 doses given at 6, 10, and 14 weeks of age. If the zero dose is not given at birth, it should be given with measles vaccine at 9 months of age. In countries where infrastructure is so weak that routine services are unable to reach 80% coverage, mass immunization campaigns may be used to rapidly increase coverage.

An effective surveillance system for poliomyelitis requires rapid and complete reporting of all AFP cases. Once a report is received, the case is investigated with collection of clinical history, epidemiologic and demographic information, a physical examination by a physician experienced in poliomyelitis diagnosis and collection of stool samples for laboratory diagnosis. Additional cases are sought in the same locality. A reverse cold chain must be established to ensure refrigeration of specimens during transport to the laboratory. A network of laboratories, highly proficient in viral culture techniques, must be available to ensure reliable analysis of stool specimens.

Effective surveillance systems will have clear delineation of authority, with one person responsible at each level. Official case definitions are adopted and widely circulated. AFP cases are line listed and spot mapped. Immediate reporting of AFP cases is a necessary condition for rapid case investigation. Immediate reports should be made by the best means available to the level at which competent case investigation can be conducted. Routine reports should be received promptly from all reporting stations on a weekly or monthly basis and must include a zero report when no cases of AFP are recognized. Eventually, the reporting system will be expanded to include all sites, government and private, likely to see AFP cases. A mechanism for providing feedback to the reporting stations is important for maintaining motivation. There are 3 supplemental immunization activities:

1) **National immunization days** are mass campaigns administering OPV to all children less than 5 years of age, regardless of prior immunization status. Two doses of OPV are administered, at least one month
apart. By rapidly increasing population immunity and flooding the environment with vaccine virus, these mass campaigns have been effective in interrupting circulation of wild poliovirus. Seroconversion to OPV may also be improved during mass campaigns. National immunization days will be required for several years to achieve poliomyelitis eradication in most poliomyelitis endemic countries.

2) Outbreak response immunization is a localized campaign conducted in the vicinity of AFP cases. Once an AFP case is detected, all children less than 5 years of age residing near the case are immunized with 2 doses of OPV given at least a month apart.

3) Mopping up immunization is a localized, house to house campaign conducted in high risk areas. All children less than 5 years, regardless of immunization status, are given 2 doses of OPV at least one month apart. High risk areas are geographic/political divisions where poliomyelitis cases have occurred in the last 3 years, population groups with demographic characteristics consistent with increased risk for poliomyelitis or areas of known low immunization coverage. Mopping up immunization should be well-planned, based on surveillance data. The definitions used in the EPI are as follows:

A. Poliomyelitis case definition
   A suspected case of poliomyelitis is any case of AFP (including GBS) in a child less than 5 years of age for which no other cause can be found.

B. Polio-compatible case definition
   A polio-compatible case is any case of AFP with residual paralysis at 60 days, or death or loss to follow-up in which there were not at least two adequate stool specimens obtained within two weeks after onset of symptoms and examined in a network laboratory. This should be a very small proportion of cases.

C. Vaccine-associated poliomyelitis
   This term refers to acute paralytic illness in which vaccine virus is believed to be the cause of the disease. Vaccine-associated cases are reported separately from those caused by the wild virus and, in order to be classified as vaccine-associated, they must have a history of receipt of OPV or have been in contact with a recently immunized individual and have had vaccine virus and not wild virus recovered from faecal specimens.

D. Not poliomyelitis
   This means acute paralytic illness in which at least two adequate stool specimens have been obtained within two weeks after onset of symptoms and have been found to be negative for poliovirus. Aliquots of the original samples should be held at the laboratory for possible future use. To ensure the accuracy of this categorization, aliquots of the original specimens of any patient who dies, is lost to follow-up, or who has residual paralysis at 60 days should be examined in two other laboratories in the network, using all appropriate techniques. If the specimens were adequate and all are negative, even these patients will be considered as "not polio" and will be "discarded."

Acute anterior poliomyelitis caused by poliovirus typically follows a prodrome of systemic symptoms and signs that include fever, vomiting, diarrhoea or constipation, muscle pain, and headache. In polio-endemic countries, it occurs primarily in children less than 3 years old, but in the continued absence of circulating wild poliovirus or individual immunization, it can occur at any age. Rapidly progressing flaccid paralysis begins while the individual is still febrile and reaches maximum involvement within two or three days. The anatomic distribution of weakness is usually asymmetric, beginning in lower or, less often, upper extremities. Bulbar paralysis occurs in 8% (Saeed et al., 1980) to 18% (Mahadevan et al., 1989) of patients in the tropics. Tendon reflexes are decreased or absent in clinically involved muscles. Sensory loss is rare, although patients often describe intense muscle pain in the acute stage. Cerebrospinal fluid (CSF) examination shows 30-100 leukocytes/dl, mostly lymphocytes; this number decreases progressively, while modest elevation of the total CSF protein increases during the first week or two following the onset of paralysis. Muscle atrophy follows, and functional recovery is minimal.
No single operational case definition of acute paralytic poliomyelitis has emerged that combines both high sensitivity and high specificity (Bellik et al., 1992). The clinical picture and CSF findings alone are not sufficient for a reliable diagnosis. Basic laboratory diagnostic support includes the ability to isolate and culture wild type poliovirus from feces. The presence of isolatable virus alone may not be sufficient for diagnosis in areas in which wild type virus is still widespread, since a patient who simply carries the virus may develop paralysis for another reason such as echovirus infection.

**Research perspectives**

New methods for poliovirus detection are becoming available and will undoubtedly increase both diagnostic sensitivity and specificity. These include:

1) The use of indirect immunofluorescence microscopy in the field for rapid identification and typing of poliovirus isolates in cell cultures from stool specimens. It may be possible to detect virus directly, without the need to use a cell culture system.

2) Polymerase chain reaction (PCR) for extremely sensitive detection and identification of polioviruses, based on the nucleotide sequence of their RNA genome. Antigen-capture PCR incorporates an immunoaffinity step to further increase sensitivity in analyzing clinical specimens directly.

3) New methods for determining the intratypic differentiation of poliovirus strains in order to determine whether field isolates are vaccine-derived or wild virus, include enzyme-linked immunosorbent assays (ELISA) using polyclonal antibodies, monoclonal antibody panels, plasmid generation of riboprobes that permit virus identification by blot hybridization, and PCR analysis of restriction fragment length polymorphism (RFLP) patterns derived from different virus strains.

These new approaches are currently being field-tested and validated. Thus, molecular biology will almost certainly enhance the clinician's ability to diagnose acute paralytic poliomyelitis accurately.

**2.4.2 Acute anterior poliomyelitis caused by viruses other than the poliovirus**

Enteroviruses other than poliovirus have been isolated from children with poliomyelitis-like acute paralysis. These include echovirus-3 in England (Stevenson & Hambling, 1968), enterovirus type 71 in a 1975 epidemic of paralytic disease in Bulgaria (Melnick, 1984), and isolations of other enteroviruses in 5 of 18 children with Hopkins' syndrome, denoting paralytic disease complicating childhood bronchial asthma (Shahar et al., 1991). In Scotland, an anterior horn cell paralytic disease that followed immunization with Salk and Sabin poliomyelitis vaccines was associated primarily with Coxsackie viruses and enteroviruses (Crist & Bell, 1970).

These reports raise important questions. When one considers that it is possible to isolate and culture poliovirus from only a fraction of reported AFP cases, e.g., in 300 of 1620 patients in a recent study from Brazil (Bellik et al., 1992), one must ask what caused the paralysis in the other 1320 individuals. Some might be accounted for by enteroviruses or coxsackie viruses, but the paucity of virologic data leaves open the possibility that still other viruses could be the cause of some instances of AFP. The occurrence of non-poliomyelitis motor-neuron infections in immuno-compromised individuals, such as in corticosteroid-treated bronchial asthma, may be important epidemiologically. Related reports have described paralytic infections by these viruses in children with hypo- and agammaglobulinemia (Wilfert et al., 1977; McKinney et al., 1987). Do the combined effects of malnutrition, anemia, and the occurrence of frequent bacterial and viral infections produce a similar, but much more prevalent, susceptibility to CNS invasion by viruses that are not ordinarily neurotropic? Clearly, careful virologic and immunologic assessment of children affected by what may prove to be non-poliomyelitis AFP, is needed to address these issues. This requires prospectively planned surveys with appropriate laboratory support.

Crawford and Hobbs (1991) asked whether some of the children thought to have poliomyelitis may instead suffer from diplegia from cerebral palsy (CP). The term CP denotes static brain or spinal-cord
dysfunction - or both - noted from birth through the first or second year of life, arising from any of a variety of known causes, such as intrauterine viral infection, bilirubin encephalopathy, or unknown causes. Several communications that followed made it clear that clinicians working in countries where poliomyelitis is endemic are skilled in distinguishing CP from paralytic poliomyelitis or the other disorders that closely resemble poliomyelitis (Wyatt, 1991; Kirkpatrick, 1991; Cross, 1991; Bhutta, 1991; Inman, 1991).

2.4.3 Acute myelopathies

The syndrome of acute transverse myelopathy in children poses a more realistic differential diagnostic problem. While one expects to see hyperreflexia, extensor plantar signs, and spasticity, these may not be present acutely. Myelopathies that occur abruptly may produce spinal shock, and flaccid areflexic paralysis below the level of the lesion. Causes include, for example, epidural abscess, tumours producing a block, arteriovenous malformations that have bled, post-viral disseminated encephalomyelitis (ADEM) with inflammation and demyelination, or instances in which the cause is totally obscure. However, examination of the child two or three weeks after the acute event should make it clear that the spinal cord tracts rather than motor neurons alone have been affected, because hyperreflexia and spasticity appear.

The pathogenesis of idiopathic acute transverse myelopathy, the spinal form of ADEM, may be analogous to the peripheral nerve disorders, acute idiopathic demyelinating neuropathy (GBS), or acute motor axonal neuropathy (see below). Each commonly follows a viral or bacterial infection, begins after a latency of one to three weeks, and progresses for several days to a week. Presumably, the preceding infection sets in motion an immune process that inappropriately targets central or peripheral myelin, or peripheral axons. As new understanding of any one of these disorders unfolds, the information is likely to be applicable to each of the others.

2.4.4 Peripheral neuropathies

Guillain-Barré syndrome (GBS) is the commonest example of an acute predominantly motor neuropathy. This is perhaps its best designation as it does not embody an implication of the underlying pathology, as does, for example, the title "acute inflammatory demyelinating polyneuropathy." There is uncertainty at present as to exactly what criteria should be adopted for the diagnosis of GBS to be accepted. Clinical criteria have been recommended (Asbury et al., 1978) which are useful for research purposes so that different laboratories will include similar cases in trials, particularly important when meta-analysis is undertaken. Nevertheless, there is increasing evidence that what is diagnosed clinically as GBS may include a variety of different underlying pathogenetic mechanisms (Thomas, 1992). Characteristically, the disorder involves an inflammatory demyelinating process. Some cases show excessive axonal destruction, possibly the result of a "bystander effect" related to the presence of inflammatory cells (Vallat et al., 1990). The existence of a primary axonal form (Feasby et al., 1986) is still under discussion. The nature of the disorder that affects children in China as an annual epidemic (McKham et al., 1991), and that has been considered to resemble GBS, must await detailed pathologic studies. Nevertheless, these will not necessarily indicate whether or not these children have GBS: this will depend upon how GBS is defined.

Acute motor axonal neuropathy (AMAN) in northern China has recently brought into question the depth of our understanding of acute paralytic syndromes. A seasonally epidemic disorder of children that closely resembles poliomyelitis clinically (Zhao et al., 1981), it typically does not cause a CSF pleocytosis and is not associated with fever - both features of acute paralytic polio. Reports of apparently similar disorders have come from Mexico (Ramos-Alvarez et al., 1969), Spain (Valenciano et al., 1971), and India (Wadia et al., 1979).

This syndrome is often referred to as the Chinese Paralytic Syndrome (CPS). The term AMAN refers to the pathophysiology and the fact that this disease process is present outside of China.
This disorder shares many features with GBS (McKham et al., 1991). Both affect adults and children, follow a febrile illness about 30% to 50% of the time, produce acute, usually symmetric paralysis without fever, and tend to go on to functional recovery. Both are associated with the presence of few cells in the CSF, but with a rising CSF protein. The primary difference lies in the strikingly seasonal epidemiology in the Chinese cases, whereas GBS is only slightly seasonal, although many clusters of GBS have been reported (e.g., Khouri, 1978, following infection with Shigella boydii in Jordan). Additionally, the pathology of the cases from China is a motor axonopathy without inflammation, whereas GBS results in a primary demyelinating neuropathy with lymphocytic infiltration. One can speculate that the cellular inflammatory response in GBS is consistent with the fact that whatever causes the attack on myelin produces an inflammatory response, whereas that may not be true when the axon is the primary target. Alternatively, the pathogenesis of the two disorders may be fundamentally different. GBS has been associated with many different preceding viral and bacterial infections, whereas the striking seasonal incidence in China strongly suggests an association with a single infectious agent. The possible relationship between these disorders should be the subject of continued study to unravel the etiology of either or both diseases, which represent disorders easily confused acutely with paralytic poliomyelitis.

Diphtheritic neuropathy is now rare in developed countries, although occasional cases are encountered because of failure to have children immunized. The generalized predominantly motor polyneuropathy may be preceded by pharyngeal paralysis with facial diphtheritic infection or local limb paralysis in the case of cutaneous diphtheria. There may be an accompanying cycloplegia and cardiomyopathy.

Acute polyneuropathy of toxic origin is usually a sensorimotor neuropathy, but in some instances motor involvement may predominate as in vincristine neuropathy, which often begins distally in the upper limbs. Acute neuropathy related to thallium or arsenic intoxication can mimic GBS. The loss of hair is a delayed phenomenon that, if present, suggests thallotoxicosis.

2.4.5 Neuropathies occurring in systemic diseases

Acute porphyric neuropathy is an acute motor neuropathy that can closely mimic GBS and is encountered in acute intermittent and variegated porphyria as well as in the rare coproporphyria and ALA dehydratase deficiency. As in GBS, muscle weakness may predominantly affect proximal muscles or the upper limbs. Sensory involvement is usually slight, but interestingly may also be proximal in distribution.

2.4.6 Disorders of the neuromuscular junction

A wide range of disorders produce AFP by interfering with neuromuscular junction transmission. These are distinguished clinically by relative or complete preservation of tendon reflexes; they usually produce symmetric flaccid weakness and are not associated with fever.

Disturbances of neuromuscular transmission are usually chronic disorders, but acute widespread muscle weakness resembling a motor polyneuropathy can occur from accidental or deliberate anticholinesterase poisoning, or infection with Clostridium botulinum. An associated external ophthalmoplegia and autonomic involvement in the latter, including an internal ophthalmoplegia, may be diagnostically helpful.

2.4.7 Disorders of muscle

Acute myopathies can pose a similar problem. Acute idiopathic inflammatory myopathy (often termed polymyositis) can produce muscle pain and tenderness, but the tendon reflexes are preserved initially. Myopathy due to trichinosis may be acute following massive infestation and is associated with gastrointestinal symptoms and fever, resembling polymyelitis. The periodic paralyses, with or without changes in serum potassium, or associated with thyrotoxicosis, are distinguished most easily by their rapid resolution with clinical improvement occurring within days of onset.
Table 1. Features distinguishing AFP occurring in acute anterior poliomyelitis, demyelinating GBS and AMAN, the latter two falling within the category "GBS clinically defined" (See Appendix III)

<table>
<thead>
<tr>
<th></th>
<th>Poliomyelitis</th>
<th>Demyelinating GBS</th>
<th>Acute Motor Axonal Neuropathy (AMAN)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRODROME</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>some</td>
<td>OCCAS.</td>
<td>OCCAS.</td>
</tr>
<tr>
<td>Upper resp. infection</td>
<td>no</td>
<td>some</td>
<td>some</td>
</tr>
<tr>
<td>Headache</td>
<td>common</td>
<td>rare</td>
<td>OCCAS.</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>no</td>
<td>OCCAS.</td>
<td>OCCAS.</td>
</tr>
<tr>
<td>Abd. cramps</td>
<td>no</td>
<td>?</td>
<td>OCCAS.</td>
</tr>
<tr>
<td>Fever</td>
<td>common</td>
<td>OCCAS.</td>
<td>OCCAS.</td>
</tr>
<tr>
<td>Constipation</td>
<td>no</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td>Irritability</td>
<td>no</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td><strong>SYMPTOMS/SIGNS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever at onset of weakness</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Muscle tenderness/pain</td>
<td>common</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>rare</td>
<td>frequent</td>
<td>rare</td>
</tr>
<tr>
<td>Sensory loss</td>
<td>no</td>
<td>frequent</td>
<td>no</td>
</tr>
<tr>
<td>Meningsmisis</td>
<td>yes</td>
<td>OCCAS.</td>
<td>OCCAS.</td>
</tr>
<tr>
<td>Babinski</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Swallowing (IX-X)</td>
<td>some (bulbar)</td>
<td>some</td>
<td>common</td>
</tr>
<tr>
<td>Lethargy</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Facial weakness (VII)</td>
<td>OCCAS. (unilateral)</td>
<td>common (bilateral)</td>
<td>common</td>
</tr>
<tr>
<td>Tongue weakness (XII)</td>
<td>OCCAS.</td>
<td>OCCAS.</td>
<td>common</td>
</tr>
<tr>
<td>EOM weakness</td>
<td>no</td>
<td>OCCAS.</td>
<td>OCCAS.</td>
</tr>
<tr>
<td>Symmetry</td>
<td>uncommon</td>
<td>common</td>
<td>yes</td>
</tr>
<tr>
<td>Areflexia</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Patchy hyperhydrads</td>
<td>OCCAS.</td>
<td>rare</td>
<td>some</td>
</tr>
<tr>
<td>Ascending pattern of weakness</td>
<td>OCCAS.</td>
<td>most</td>
<td>most</td>
</tr>
</tbody>
</table>

**EPIDEMIOLOGY**

<table>
<thead>
<tr>
<th></th>
<th>Mainly young</th>
<th>all</th>
<th>Predom. young; rare c/ year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunossuppressed host</td>
<td>OCCAS.</td>
<td>OCCAS.</td>
<td>no known cases</td>
</tr>
<tr>
<td>Seasonal</td>
<td>year-round in tropics; summer in non-tropics</td>
<td>year-round</td>
<td>summer</td>
</tr>
<tr>
<td>Areas</td>
<td>all</td>
<td>all</td>
<td>rural</td>
</tr>
<tr>
<td>Clusters</td>
<td>often</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Laboratory Features</td>
<td>Poliomyelitis</td>
<td>Demyelinating GBS</td>
<td>Acute Motor Axonal Neuropathy (AMAN)</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------</td>
<td>------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>Peripheral WBC count</td>
<td>increased</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>CSP cell count</td>
<td>increased early</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>CSP protein</td>
<td>increased late</td>
<td>increased late</td>
<td>Increased late</td>
</tr>
<tr>
<td>SIADH</td>
<td>no</td>
<td>occurs.</td>
<td>?</td>
</tr>
<tr>
<td>Stool cultures</td>
<td>positive (50%)</td>
<td>neg.</td>
<td>neg.</td>
</tr>
</tbody>
</table>

**Electrodiagnosis**

<table>
<thead>
<tr>
<th>Sensory action potentials</th>
<th>normal</th>
<th>abnormal</th>
<th>normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor conduction latency</td>
<td>normal</td>
<td>abnormal</td>
<td>normal</td>
</tr>
<tr>
<td>CMAP Amplitude</td>
<td>low</td>
<td>low/normal</td>
<td>low</td>
</tr>
<tr>
<td>Velocity</td>
<td>normal</td>
<td>normal/normal</td>
<td>normal</td>
</tr>
<tr>
<td>F wave latency</td>
<td>normal</td>
<td>abnormal</td>
<td>absent/normal</td>
</tr>
<tr>
<td>Denervation potentials</td>
<td>early</td>
<td>late</td>
<td>early</td>
</tr>
</tbody>
</table>

**Pathology**

| Spinal cord                | yes    | no     | no    |
| Inflammation               | yes    | no     | no    |
| Motor neuron loss          | no     | rare   | no    |
| Chromatolysis              | yes    | some   | yes   |
| Astrogliosis reaction in cord | no  | no     | no    |
| Spinal roots               | normal | demyelination; variable axonal degeneration | normal |
| Sensory                    |        |        |        |
| Motor                      | anterograde degeneration | demyelination; variable axonal degeneration | Wallerian-like degeneration |
| Peripheral nerves          | anterograde degeneration | demyelination; variable axonal degeneration | Wallerian-like degeneration |

**Pattern of Recovery**

| Symmetrical               | no     | yes    | yes   |
| Latest muscles to weaken, recover first | unknown | yes    | yes   |
| Early return of reflexes  | no     | no     | sometimes |
| Fasciculations            | common | no     | no     |
| Clinical improvement      | sometimes | yes    | yes   |
| Hyperreflexia              | no     | no     | occur, |
3. AFP IN SELECTED COUNTRIES OF THE WORLD

3.1 Papua New Guinea and Micronesia

In the past 37 years the quest for kuru-like foci of high-incidence neurodegeneration has been actively pursued throughout Melanesia and much of the rest of the South Pacific, with hundreds of physicians searching in their isolated stations for kuru-like neurodegenerative diseases (Alpers et al., 1975). There has been a high level alert for such illnesses throughout the South Pacific, particularly in remote isolated and primitive groups. As a result, Dr. Gajdusek’s epidemiological team has been summoned to see sporadic or small groups of patients ranging from stroke patients to Guillain-Barré syndrome (GBS), ALS (amyotrophic lateral sclerosis), acute hydrocyanide poisoning from toxic wined-beans and chronic cyanide acid poisoning from poorly washed manioc, lathyris, and fish poisoning outbreaks, sporadic Creutzfeldt-Jakob disease and other dementias and sporadic and familial Parkinson’s disease (PD) to muscular dystrophies in children and familial periodic paralysis in many dozens of locations in the Pacific Islands, Indonesia, New Guinea, and even Thailand, Malaysia, and the Philippines.

The high incidence ALS/PD on Guam intensified research, leading to the discovery of high incidence ALS/PD in remote villages on the Kii Peninsula of Japan and in remote populations in West New Guinea (Gajdusek and Salazar, 1982; Garutu et al., 1983; Gajdusek, 1984). The extreme awareness of these high incidence foci of paralytic and non-paralytic neurological diseases by physicians and nurses throughout the Pacific has led to the above-mentioned team of neuroepidemiologists being called to see even single sporadic cases of motor neuron disease and certainly any accumulation of paralytic disease patients. The team has conducted wide surveys in Melanesian, Micronesian, and Polynesian patient populations and in Aboriginal Australian populations for such diseases (Gajdusek, 1975).

Finally, the discovery in the past decade, that HTLV-1 causes tropical spastic paralysis (TSP) has led to a thorough investigation of every chronic or sub-acute motor neuron disease patient reported in Melanesia, and rare sporadic cases of TSP caused by HTLV-1 have been found and reported (Ajdukiewicz et al., 1989). This level of surveillance has resulted in a rather thorough knowledge of the prevalence of motor neuron disease syndromes and even peripheral neuropathies in the South Pacific and Oceania. A really high incidence of GBS would not have been missed, although a rare sporadic outbreak might have been overlooked. Only the clinical impression of neurologists in Ujung Pandang in southern Sulawesi and on Bali and in Jakarta that they see much GBS in children has been reported to Dr. Gajdusek’s team as a possibility of high incidence of such disease. GBS is not unusually frequent in Papua New Guinea or elsewhere in Melanesia and Micronesia.

3.2 Japan

The acute onset of flaccid paralysis in a previously healthy child or adult is dramatic. The clinical picture is one of a rapidly evolving disturbance, completely incapacitating the child or adult. There are many causes of AFP. Some of these disorders can be diagnosed by simple inspection or by careful physical and neurologic examination and a few relevant procedures.

Polioymelitis

Polioymelitis was formerly the most common form of viral infection of the nervous system. Prior to 1959, there were between 1,500 and 4,200 cases annually in Japan. Since the advent of an effective vaccine in early 1960, the incidence of poliovymelitis has decreased dramatically in Japan, and it appears that wild virus transmission has been interrupted.

Devic’s disease

Devic’s disease is more common in Asia or India than it is in the United States or western Europe. In 1988, the third nationwide survey of multiple sclerosis (MS) was carried out in Japan using new diagnostic
criteria in which the age of onset was not specified. By the preliminary survey, approximately 3,700 patients with MS were estimated to have been seen in Japan between 1 January and 31 December 1988. There seems to be no increase in the prevalence of MS in Japan. By the final survey using enquiry sheets for each individual patient, which were filled in by the reporting physician, clinical information on 1,270 patients were analyzed by Shibasaki and his group (Shibasaki et al., 1991). A significant female preponderance (male to female ratio, 1:2.4) was disclosed. The clinical picture does not seem to have changed except the proportion of the clinically definite cases increased from 46.9% in 1972, 55.9% in 1982, to 67.8% in 1989, whereas that of Devic's disease decreased from 7.6% in 1972, 5.1% in 1982, to 3.6% in 1989. At the time of clinical onset, 6.5% of all patients were younger than 15 years.

Nontraumatic myelopathies

In 1988, Gomibuchi reported a clinical study on acute nontraumatic myelopathies (Gomibuchi, 1988). Seventy-two cases of acute nontraumatic myelopathy in which walking became impossible within one week after the onset of paralysis were investigated. Fifty-one cases (71%) consisted of mass lesions requiring surgery, such as metastatic spine tumors, hemangioma of the spinal cord, and hematoma within the spinal canal. Others were six cases of anterior spinal artery syndrome and 15 cases of undetermined diagnosis. Pain preceding paralysis or paralysis itself was the initial symptom in 64% of the spinal metastases. In 23 of 47 cases, spinal decompression was followed by severe pain and a rapidly progressive paralysis. Post-operative recovery was especially good when the operation was done in the stage of incomplete paralysis. Locating the mass lesion and timely decompression were the most important approaches to handle these conditions.

Guillain-Barré syndrome

There are no published data on the annual incidence of Guillain-Barré syndrome in Japan. Kashihara and coworkers (Kashihara et al., 1987) reported an outbreak of 12 cases of GBS including two cases of cranial polyneuritis in Kochi during the four-month period from April to August 1985. All cases demonstrated progressive, rapidly developing weakness within 10 days of onset of GBS. A history of febrile illness was given by two patients. The first symptoms of the disease appeared in extremities as progressive weakness in five patients (lower, 4; upper, 1) and in cranial nerves in six patients. The CSP examination revealed albuminocytologic dissociation in 7 of 11 patients. The incidence of the ophthalmoplegia, including eight cases with external ophthalmoplegia and two cases with both external and internal ophthalmoplegia, was prominent in this series.

Shimazaki and coworkers (Shimazaki et al., 1990) reported two cases (14-year-old boy and 7-year-old girl) of GBS observed at the emergency department. A boy progressed to respiratory paralysis. Artificial respirator, plasma exchange, and methylprednisolone pulse treatment saved his life. A girl also received plasma exchange and prednisolone treatment and recovered.

Acute intermittent porphyria

Yano and coworkers (Yano et al., 1983) reported 123 cases of acute intermittent porphyria among 207 cases of acute porphyria in Japan.

Botulism

Taikawa and coworkers (Taikawa et al., 1989) reported 60 cases of food poisoning among 12,314 patients in survey of Hokkaido, Japan; in 1988. Botulism (Type E) was found in 3 cases.

Comments

There are many causes for AFP. There are several diagnostic possibilities and certain historical and physical findings can be helpful in the differential diagnosis. Important clues from the history are:

1) recent illness, exanthem, and immunization
2) a history of similar episodes in other members of the family
3) trauma or cancer  
4) exposure to ticks or organic solvents  
5) psychogenic problems

Thorough physical examination with special emphasis on the neurologic examination is important (e.g., severity, symmetry, and distribution of weakness, presence or absence of sensory impairment or sensory level, incoordination, ataxia, meningeal signs, and mental state). Pertinent laboratory tests include X-rays, CT and MRI of the spine, examination of the CSF, serum and urine, and electrodiagnostic data. With this information, it is possible to precisely diagnose most cases of AFP in Japan.

3.3 Northern China

Reports from China have described patients with AFP whose clinical characteristics resemble those of patients with demyelinating GBS but whose epidemiologic features differ from those of patients seen in North America and Europe (Zhao et al., 1981; Zhang and Li, 1979; Chia et al., 1979; Wu et al., 1988; Jiang et al., 1992; Li et al., 1992). The Chinese cases occur largely among rural residents of northern China, predominantly during the summer, and primarily in children. All reports have described the motor-predominant symptoms and signs.

Here the results of an intensive examination and analysis of 90 patients with neuropathic AFP, including findings from ten autopsies are presented. The results indicate that the large majority of patients with AFP have a pattern of disease best described as acute motor axonal neuropathy (AMAN). The AMAN pattern has distinctive epidemiologic, clinic, electrophysiologic, and neuropathologic manifestations (McKhann et al., 1992). Because of the large number of patients with this disorder, it is of considerable public health and neurologic interest.

Methods

Inpatient records of 1,399 cases were retrospectively reviewed from the Beijing Children's Hospital seen between 1956 and 1991 (Jiang et al., 1992), and 1,804 cases from the Second Teaching Hospital of the Hebei Medical College seen between 1972 and 1991 (Li et al., 1992). These cases were all diagnosed as GBS by clinical criteria.

In August, 1990 and September, 1991, an intensive investigation was undertaken of patients admitted with AFP to the Beijing Children's Hospital and the Second Teaching Hospital of the Hebei Medical College. Ninety patients were examined, 81 while they were acutely ill, and the remaining nine during their recovery. Seventeen of the 81 patients were examined a second time, one year after the acute illness. Electrodiagnostic studies were performed on 44. These have been reported (McKhann et al., 1991).

For classification purposes, patients were diagnosed as having demyelinating GBS using NINDS criteria, supported by electrodiagnostic studies. Of the 37 patients seen in 1990, two were diagnosed as having demyelinating GBS. The other 35 had a different pattern, AMAN (McKhann et al., 1991). In 1991, 53 additional AMAN patients were evaluated, for a total of 88 AMAN patients.

In order to confirm that the electrodiagnostic attributes of the AMAN patients differed significantly from those of patients with demyelinating GBS, GBS patients were identified from the records of the Neurology EMG Unit at The Johns Hopkins Hospital, who were more closely age-matched to the AMAN patients. Twenty-one patients less than 25-years-old were identified. To compare the AMAN and GBS patients, sensory conduction data were dichotomized into two categories, normal or abnormal/absent, and the two groups were compared using Fisher's exact test for 2 x 2 tables. Motor conduction data were analyzed with t-tests, with Bonferroni correction. Confidence intervals were derived for those parameters reaching statistical significance.
Antibody titers to *Campylobacter jejuni* were assessed by ELISA methodology (Blaser and Duncan, 1984). Sixty-eight serum samples were collected from the Chinese patients: 11 within 0-10 days of onset of clinical illness, 13 within 11-20 days, 11 within 21-30 days, 22 within 31-60 days, and 11 after 60 days. Control sera were collected from 21 inpatients at the two hospitals. Controls were from the same wards and had the same age distribution as the AMAN patients. Control patients with other neurologic diseases and non-neurologic disease were included together for the analysis. Sera from healthy individuals with neither clinical nor laboratory evidence of diarrheal illness served as normal controls to establish laboratory standards. All sera were stored at -20°C prior to testing.

**Results**

**Epidemiology.** The epidemiologic features derive from the review of over 3,200 cases (Jiang et al., 1992; Li et al., 1992). The major points are that in China AFP, which is not poliomyelitis by clinical criteria, occurs primarily in children and young adults, leads to a striking increase in hospital admissions in the summer months, and is found in rural areas of Hebei and surrounding provinces. Ninety-five percent of patients live in villages of 2,000 people or less.

Detailed histories from the 88 patients add additional points. The mean age at the Beijing Children’s Hospital was 4.5 years. The mean age at the Second Teaching Hospital of the Hebei Medical College, a hospital for adults and children, was 19 years, but 50% of the patients were under 15 years, and 33% under 7 years. A slight preponderance of male over female patients was noted (60:40 in favor of males). The disease does not "cluster"; that is, two or more cases are rarely, if ever, from the same village or attend the same school. In addition, the illness is not superimposed on a background of familial illness. Only two families of the 88 patients reported other family members with fever, diarrhea, or flu-like symptoms at the time of or before the onset of paralysis in the affected family member.

In the retrospective series, 4% of patients gave a history of some type of recent vaccination, usually for hepatitis or Japanese B encephalitis. Almost all children in China receive oral poliomyelitis vaccine (OPV) before age one; adults are less likely to have been vaccinated against poliomyelitis. Of the 88 patients, all but one child had received OPV, but none within the 2-3 months prior to onset of paralysis. One child had received one dose of OPV after onset of weakness.

**Clinical Features of the AMAN Pattern.** In the retrospective series, the incubation of illness in the two weeks before the onset of acute weakness varied from year-to-year, but about 30% of the patients had fever before the onset of paralysis; 10-12% had diarrhea (in some years this value may be as high as 30%); and 20% had symptoms of "upper respiratory infection." This was confirmed in the group of 88 patients.

In the 88 patients, onset was acute with the median time from first symptom of weakness of the legs to maximal involvement being 5.9 days. Although children under age 5 had a more acute illness (median time to maximal involvement, 4.4 days) than did older children (6-20 years; median time 8.3 days), this finding may be biased by more rapid admission of acutely ill younger children.

The pattern of progression is stereotypic. Patients are afebrile at the onset of weakness and on admission. The early symptoms are weakness of the lower extremities accompanied by falling, particularly in young children. An ascending, symmetric paralysis then develops, often accompanied by dysphagia, hoarseness, facial weakness, and difficulty speaking. In the most severely affected, there is quadriplegia and respiratory failure; 50% required tracheostomy and respiratory assistance. Only two of the 88 complained of sensory symptoms, such as paresthesias of the hands or feet. There were no symptoms of clouding of consciousness or deficits of higher cortical function.

The weakness is symmetric and flaccid, with areflexia. Involvement of muscles innervated by lower cranial nerves is frequent, with weakness of the face, jaw, tongue, and pharynx. Extraocular muscles are rarely involved. In younger children, there is an unusual pattern of severe weakness of neck flexors at a time
when flexion of the neck by the neck extensor muscles is actively resisted. Some children exhibit marked resistance of the neck and spine to passive flexion, described by one father "as if he [the son] had a poker in his spine." This stiffness, indistinguishable from meningismus, was more common in children under age 5. Sensory functions such as perception of pin, vibration, touch, and position sense are normal. Autonomic dysfunction is sometimes present, as indicated by patches of hyperhidrosis over the trunk. Cardiac arrhythmias and alterations of blood pressure occur, but their incidence is unknown.

Recovery may start within weeks. Older patients are likely to have a slower recovery than younger ones. Interestingly, deep tendon reflexes return while muscles are still weak. In some patients, reflexes are more easily elicited than normal, with spread of the myotatic reflex to other segments during early stages of recovery.

In the 25 patients examined up to one year after onset, recovery was remarkably good. All were ambulatory, but 17 of 25 had distal weakness with mild atrophy in the hands or feet. A mild degree of hyperreflexia with abnormal reflex spread was present in 12 of 25 patients. Patients examined up to one year after illness lacked sensory abnormalities.

In the retrospective series, mortality in the 1960s and 1970s was as high as 30%, but is now less than 5% (Wu et al., 1988).

Six of the 88 patients were observed during a second attack. Second attacks of this disease, which occur as discrete episodes and not as relapses of a continuous disease, may occur up to 12-15 years after the first attack. In the interval, the patient is well, although the actual recurrence rate is unknown.

Electrodiagnosis. As previously reported, sensory nerve conduction attributes in AMAN patients were normal in all sensory nerves studied, with the exception of one reduced median sensory velocity (McKhan et al., 1991).

In motor conduction studies of the AMAN patients, the principal abnormalities were reduced distal evoked amplitudes and absent F-wave responses, findings consistent with a pure motor axonopathy.

Laboratory findings. Of the 88 patients, 25 had lumbar punctures: mean cell count was 3 cells/ml (range, 0-12) and mean protein content was 0.6 g/l (range, 0.1-1.33). CSF obtained within the first week of illness revealed normal cell counts and protein content.

Sero logic studies. Serum antibodies to C. jejuni were frequently elevated, particularly in samples obtained early in the course of the illness (see below). Indeed, 91% of the sera collected from AMAN patients between 0-10 days showed positive IgG; 64% showed positive IgM titers when compared with two standard deviations from healthy young controls. Only 19% of hospital controls showed positive IgG and 29% showed positive IgM. Titers remained elevated in patient sera collected between 11-20 days (79% in IgG titers and 92% in IgM titers). Titers decreased in sera collected later in the illness.
Table 2. Serum antibodies to *Campylobacter jejuni*

<table>
<thead>
<tr>
<th></th>
<th>IgG (no. of positive samples/ no. of samples)</th>
<th>IgM (no. of positive samples/ no. of samples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Standard Deviations*</td>
<td>4/21</td>
<td>6/21</td>
</tr>
<tr>
<td>3 Standard Deviations*</td>
<td>0/21</td>
<td>2/21</td>
</tr>
<tr>
<td>CPS Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-10 days**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Standard Deviations*</td>
<td>10/11</td>
<td>7/11</td>
</tr>
<tr>
<td>3 Standard Deviations*</td>
<td>10/11</td>
<td>7/11</td>
</tr>
<tr>
<td>11-20 days**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Standard Deviations*</td>
<td>10/13</td>
<td>12/13</td>
</tr>
<tr>
<td>3 Standard Deviations*</td>
<td>8/13</td>
<td>9/13</td>
</tr>
<tr>
<td>21-30 days**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Standard Deviations*</td>
<td>6/11</td>
<td>8/11</td>
</tr>
<tr>
<td>3 Standard Deviations*</td>
<td>2/11</td>
<td>7/11</td>
</tr>
<tr>
<td>31-60 days**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Standard Deviations*</td>
<td>5/22</td>
<td>12/22</td>
</tr>
<tr>
<td>3 Standard Deviations*</td>
<td>4/22</td>
<td>9/22</td>
</tr>
<tr>
<td>60+ days**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Standard Deviations*</td>
<td>0/11</td>
<td>4/11</td>
</tr>
<tr>
<td>3 Standard Deviations*</td>
<td>0/11</td>
<td>2/11</td>
</tr>
</tbody>
</table>

* from controls (normal, healthy, Thai children)
** days from onset

Pathologic aspects

Ten autopsy cases were available for review. Four were from the Beijing Children’s Hospital (Jiang et al., 1992) and six were from the Second Teaching Hospital of the Hebei Medical College (Li et al., 1992). Of these, three died in 1991 and three in 1992. One was from the 88 patients with AMAN. For all autopsies, standard paraffin-embedded sections from spinal cords, spinal root, and cranial nerves were stained with hematoxylin and eosin and Weigert or luxol fast blue stains. Three cases from the Second Teaching Hospital of the Hebei Medical College were more intensively studied. Specimens were dissected from the lumbar and thoracic spinal cords, the lumbar dorsal and ventral roots, the lumbar dorsal root ganglia, and the sciatic and sural nerves. Each specimen was divided into three pieces, one being fixed in 5% glutaraldehyde, one in 4% paraformaldehyde, and one being snap-frozen. The paraformaldehyde-fixed specimens from roots and nerves were osmicated, and the nerve fibers incised. Portions of those samples were also embedded in paraffin, and sections were stained with Naumenko-Feigin reduced silver-luxol fast blue/PAS stain and with immunocytochemical methods for common leukocyte antigens (CLA). Anti-CLA (Dako) was used as the primary antibody, and the reaction product was developed by peroxidase-antiperoxidase techniques. The glutaraldehyde-fixed sample was post-fixed in osmium tetroxide and embedded in epon. Sections were examined at the light and electron microscopic levels.

Pathological findings. Of the 10 cases, two had inflammatory demyelinating GBS, with abundant lymphocytic inflammation and macrophage-mediated demyelination. One of these cases was a child aged 2.5 years from the city of Beijing who had become ill and died in February; the other was a 6-year-old from a village with onset in August.

Five of the cases had a distinct pattern of motor nerve fiber degeneration without inflammation, and four of them had no involvement of dorsal roots or sensory fibers. The spinal cords were remarkable only
for extensive chromatolysis of the anterior horn cells. The motor neurons were swollen, rounded, and had central dispersion of Nissl substance and eccentric nuclei. Both medial and lateral motor neuron populations were affected. Many neurons contained a "cap" of Nissl material overlying the hilum of the flattened eccentric nucleus. There was no evidence of motor neuron loss and no inflammation within the spinal cord. The dorsal columns were entirely normal, even in the cervical region, reflecting the lack of Wallerian-like degeneration within the dorsal roots.

The major pathologic finding was extensive Wallerian-like degeneration of the ventral roots and motor fibers within the peripheral nerves. The severity varied. In severe cases, the most proximal site of fiber degeneration was in the proximal or midventral root; the proportion of degenerating fibers increased distally toward the ventral root exit from the dura. At this level, up to 80% of motor fibers were degenerating. The small (gamma-efferent) fibers were more likely to survive than the large (alpha) fibers. Ventral root fibers in the exit zone and the intraparenchymal segments of the motor axons were normal. Even in these severe cases, there was variability between ventral roots and even between fascicles within a single ventral root. In contrast to the ventral roots, the dorsal roots and dorsal root ganglia were spared except for very rare degenerating fibers. In cases where extensive sampling of every cranial nerve was available, it was clear that degenerating fibers were most prevalent in those cranial nerves with a prominent motor component, including III, IV, VI, VII, IX, and XII.

Teased fiber preparations of ventral roots and peripheral nerves showed a variable degree of paranodal myelin changes. Frequently, these sites of paranodal demyelination contained osmiophilic spheres in the overlying Schwann cell cytoplasm, suggesting early myelin breakdown. Intermembrane demyelination was rare, but occasional fibers were identified in 2/5 cases.

Lymphocytic infiltrates and perivascular cuffs were not seen, even when specifically sought with immunocytochemistry and with electron microscopy. In contrast, numerous macrophages were present in regions undergoing Wallerian-like degeneration; these macrophages were both extratubal, within the endoneurial space, and intratubal, within degenerating nerve fibers. Foamy macrophages were frequently seen near vessels and in the subperineurial space.

Finally, in three of these cases the peripheral nerve changes were not sufficient to produce the paralysis. Because the distal nerves and intramuscular twigs were not sampled, it is possible that the responsible pathology was located in the distal most nerve regions.

Electrodiagnostic aspects

The role of electrodiagnostic studies, specifically nerve conduction studies (NCS), in the differential diagnosis of AFP in childhood was discussed. Three specific disorders were detailed: polio, AMAN, and GBS. Because limited NCS data are available on poliomyelitis and most of it published over 25 years ago, the NCS data from amyotrophic lateral sclerosis (ALS), a degenerative disease of the anterior horn cell, the site of the neurologic dysfunction in polio, is discussed (Crombach et al., 1992). The AMAN NCS data derive from previously published work on 37 cases of AFP seen in China in 1990 (McKlann et al., 1991). Although numerous excellent studies of the physiology of GBS are available (Albers et al., 1985; Brown and Feasby, 1984; Crombach, 1990), most include primarily, if not exclusively, adults. Since AMAN is primarily seen in children, electrodiagnostic data from a population of young GBS patients from The Johns Hopkins Hospital were reviewed, in order to compare more precisely the physiology of AMAN and GBS.

Sixty-one patients who entered a therapeutic study of ALS met rigorous entry criteria, including electrodiagnostic studies. The NCS data from these patients were analyzed, specifically the relationship between motor-evoked amplitude and parameters of conduction velocity: distal F wave latency and nerve conduction velocity. The relationship between these parameters was quantified, with the use of square root transformation of the primary data and the development of regression equations and confidence intervals for distal motor evoked amplitude versus the parameters of conduction velocity. The validity of these equations
was tested using the Wilcoxon Rank Sum test in a second population of 34 ALS patients, all of whom met the same rigorous criteria as the original 61 patients (Comblath et al., 1992).

In 1990, 37 patients with AFP in China were examined. By clinical and electrodiagnostic criteria, two were diagnosed as having acute demyelinating polyneuropathy (GBS). The other 35 had a distinctive disorder, AMAN, different from GBS seen in North America and Europe (McKhann et al., 1991). NCS were performed on 21 of the 35 with AMAN and have been previously reported (McKhann et al., 1991). In order to determine if these patients had different electrodiagnostic attributes from patients with GBS and to obtain a more closely age-matched population to the AMAN patients, a group of patients with GBS were identified who were less than 25 years old from the records of the Neurology EMG Unit at The Johns Hopkins Hospital, covering the years July 1982 to January 1992. Twenty-one patients met those criteria, and their conduction studies were analyzed.

In all patients, nerve conduction was studied with conventional surface recording techniques. The diagnosis of GBS used standard criteria (Asbury et al., 1978; Asbury and Comblath, 1990). To compare the AMAN and GBS patients, sensory conduction data were dichotomized into normal or abnormal/absent, and the two groups compared using Fisher’s exact test for 2 x 2 tables. Motor conduction data were analyzed with t-tests, with Bonferroni correction. Confidence intervals were derived for those parameters reaching statistical significance.

The results of the ALS NCS data have just been published (Comblath et al., 1992). In the entire group of 95 adult patients, the range of distal evoked amplitude was large, from 1 to 500% of the lower limit of normal. Despite this, the range of values associated with the other parameters was narrow. Combining the data from all 95 patients and all three nerves studied, distal and F wave latency rarely exceeded 1.25 x the upper limit of normal, and nerve conduction velocity rarely fell to <80% of the lower limit of normal. The regression equations derived from the 65 patients are listed below.

Table 3. Regression Equations from Group 1 Data

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Regression Equation</th>
<th>95% CI</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroneal Nerve</td>
<td>(Sqrt Latency) = 10.391</td>
<td>0.116</td>
<td>(Sqrt Amp) ± 0.9794*</td>
</tr>
<tr>
<td></td>
<td>(Sqrt Vel) = 9.868</td>
<td>0.0551</td>
<td>(Sqrt Amp) ± 0.5435*</td>
</tr>
<tr>
<td></td>
<td>(Sqrt F) = 10.179</td>
<td>0.0498</td>
<td>(Sqrt Amp) ± 0.4930*</td>
</tr>
<tr>
<td>Median Nerve</td>
<td>(Sqrt Lat) = 10.541</td>
<td>0.106</td>
<td>(Sqrt Amp) ± 0.5953*</td>
</tr>
<tr>
<td></td>
<td>(Sqrt Vel) = 9.650</td>
<td>0.0798</td>
<td>(Sqrt Amp) ± 0.5527*</td>
</tr>
<tr>
<td></td>
<td>(Sqrt F) = 9.85</td>
<td>0.0214</td>
<td>(Sqrt Amp) ± 0.4165*</td>
</tr>
<tr>
<td>Ulnar Nerve</td>
<td>(Sqrt Lat) = 11.195</td>
<td>0.1676</td>
<td>(Sqrt Amp) ± 0.7963*</td>
</tr>
<tr>
<td></td>
<td>(Sqrt Vel) = 9.887</td>
<td>0.0862</td>
<td>(Sqrt Amp) ± 0.6766*</td>
</tr>
<tr>
<td></td>
<td>(Sqrt F) = 10.286</td>
<td>0.0666</td>
<td>(Sqrt Amp) ± 0.4691*</td>
</tr>
</tbody>
</table>

*Standard error around the fitted line. Sqrt = square root; Latency = distal latency; Amp = CMAP amplitude from distal stimulation; Vel = conduction velocity; F = F wave latency.

For eight of the derived confidence intervals, the data from the 34 patients were not statistically different, confirming the validity of the confidence intervals. Only one of the regression equations, the median nerve distal latency, was statistically different than the data from the 34 patients. Thus, it can be confidently stated that the equations derived describe the values found in ALS patients, a disorder of the anterior horn cell.
The 21 AMAN patients ranged in age from 1.5 to 35 years (mean 8). Studies were performed from 5 to 365 days after onset of illness, with a median of 21 days. The severity of illness in the group varied from patients walking to those requiring ventilatory assistance. There were 21 patients with GBS whose ages ranged from 5 to 24 years (mean 14). At the time of nerve conduction study, their length of illness ranged from 3 to 30 days. Like the AMAN patients, there was a wide range of severity.

As previously reported, sensory action potentials in AMAN patients were normal in all sensory nerves studied except one (McKhann et al., 1991). This contrasts with the GBS patients, in whom sensory action potentials were frequently abnormal or absent; median nerve 63%, ulnar nerve 87%, and sural nerve 21%. By Fisher's exact test, the difference between the median and ulnar nerves was highly significant (p<0.001).

Motor conduction studies also differed significantly between the two groups. In the AMAN patients, the primary abnormalities were reductions in distal evoked amplitudes and absent F-wave responses. In contrast, evidence of demyelinating polyneuropathy was seen in all cases of GBS. Significant differences were present between the two groups in distal latencies in all three nerves, conduction velocity in the median and ulnar nerves, and F wave latency in the median nerve. Ninety-five percent confidence intervals for the values that were statistically different between AMAN and GBS patients are presented below.

Table 4. Motor Nerve Conduction Studies in GBS and AMAN.

<table>
<thead>
<tr>
<th></th>
<th>GBS</th>
<th>AMAN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>CI</td>
</tr>
<tr>
<td><strong>Median Nerve</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Distal Latency (ms)</td>
<td>8.6 (1)</td>
<td>6.6-10.7</td>
</tr>
<tr>
<td>Amplitude (mV)</td>
<td>3.5 (0.7)</td>
<td>2.1 (0.5)</td>
</tr>
<tr>
<td>CV (m/s)</td>
<td>46 (2)</td>
<td>41-50</td>
</tr>
<tr>
<td>F Latency (ms)</td>
<td>37 (3)</td>
<td>30-43</td>
</tr>
<tr>
<td><strong>Ulnar Nerve</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Distal Latency (ms)</td>
<td>5 (0.5)</td>
<td>4-6</td>
</tr>
<tr>
<td>Amplitude (mV)</td>
<td>3 (0.5)</td>
<td>1.3 (0.5)</td>
</tr>
<tr>
<td>CV (m/s)</td>
<td>48 (3)</td>
<td>43-52</td>
</tr>
<tr>
<td>F Latency (ms)</td>
<td>35 (3)</td>
<td>23 (2)</td>
</tr>
<tr>
<td><strong>Peroneal Nerve</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Distal Latency (ms)</td>
<td>9.6 (1)</td>
<td>8-11</td>
</tr>
<tr>
<td>Amplitude (mV)</td>
<td>1.2 (0.2)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>CV (m/s)</td>
<td>44 (2)</td>
<td>42 (3)</td>
</tr>
<tr>
<td>F Latency (ms)</td>
<td>52 (2)</td>
<td>42 (3)</td>
</tr>
</tbody>
</table>

*p<0.005; **p<0.02.

NCS are valuable in diagnosing certain diseases causing APP. While NCS data from patients with ALS were presented, a disease causing anterior horn cell degeneration with neurologic and physiologic similarities to polio, NCS have a very limited role in the diagnosis of polio. However, if NCS are performed in cases of polio, the results would be described by the regression equations. If a patient had multiple NCS values outside the ranges described here for ALS, the diagnosis of polio, especially if not confirmed by culture, would be suspect.

The electrophysiologic studies of AMAN describe a pure motor disorder, different from GBS. By nerve conduction studies, the primary abnormality is a reduction in distal evoked amplitude. The sensory system
is not involved physiologically as shown by the preservation of sensory action potentials at all stages of disease. This is in contrast to the findings reported here in a population of young patients with GBS. In those patients, median and ulnar nerve sensory action potentials were frequently abnormal. In the motor conduction studies, evidence of demyelination was present in all, unlike the AMAN patients. This provides further evidence of a distinction between AMAN and GBS.

The electrophysiology of the GBS patients reveals an evolving, acquired, demyelinating polyneuropathy with variable affection of individual nerves. Whereas most large studies of the electrophysiology of GBS have been in adults, there are several studies in children. In the largest, Bradshaw and Jones (1992) reported on 23 patients. The data presented here parallel theirs in that features of demyelination were prominent at all stages of disease. Specifically, sensory action potentials were abnormal in 73% of their patients, whereas in the Hopkins GBS series at least one sensory action potential was abnormal in all but two patients (87%). Motor nerve conduction abnormalities consistent with demyelination were present in 61% of the patients in their series. Depending on the criteria for demyelination, most if not all the Hopkins GBS patients had findings consistent with demyelination.

An interesting feature in this series is the frequent abnormalities in hand sensory action potentials compared to the sural sensory potential. This phenomenon was previously noted primarily in the median nerve (Albers et al., 1985) and postulated to reflect demyelination occurring across a potential entrapment site. Subsequent studies by Albers and confirmed in this study, suggest that both median and ulnar sensory action potentials are frequently abnormal in GBS, particularly at a time when sural sensory potentials are normal. The basis for this is uncertain.

In addition to providing evidence that AMAN and GBS are separate disorders, NCS provide an important potential tool for epidemiologic studies. Of the patients with AFP in northern China, a small proportion have GBS similar to that which occurs in Europe and North America. In many cases, separating these GBS patients from those with AMAN is difficult. The NCS suggest that physiologic data may provide a reliable method to separate the two disorders. In individual patients, performance of median and ulnar sensory and motor nerve conduction studies may be adequate to classify patients in whom the clinical distinction may be difficult.

Comments

These studies indicate that a common cause of AFP in children and young adults in northern China is AMAN, different from poliomyelitis and from demyelinating GBS. The prominence of the AMAN pattern in northern China complicates the use of diagnostic terms there, and potentially in other parts of the world. Guillain, Barré, and Strohl (1916) set forth clinical and spinal fluid features of one form of AFP without regard to age or for the underlying pathology or physiology. Certainly the northern China cases fit within the syndrome described in the original 1916 report. However, with further physiologic and pathologic investigation of most European and North American cases, the term "GBS" has come to connote an acute acquired demyelinating neuropathy of presumed immunopathogenesis. Problems of using the term "GBS" have recently been reviewed (Thomas, 1992), focusing on "axon GBS." This is important in case reporting and epidemiology; in much of the world, only a minority of cases of AFP will have electrodiagnostic studies. For this reason, the following terminology is suggested: cases fulfilling the clinical criteria for GBS are termed "GBS clinically defined"; cases with electrodagnostic or pathologic findings of demyelination are called "demyelinating GBS"; and other patterns, such as the AMAN pattern, are identified descriptively.

The syndrome in northern China clearly differs from acute poliomyelitis, as previously described (McKhan et al., 1991). In addition, pathologic characteristics are different: inflammatory cells and motor neuron loss in the spinal cord are not present.
Demyelinating GBS also occurs in children in northern China; whether it is seasonal remains to be determined. However, AMAN is by far more frequent pattern during the summer. As previously reported (McKhan et al., 1991), AMAN is distinct from demyelinating GBS. In demyelinating GBS, physiologic evidence of peripheral nerve demyelination is present in almost all cases (Brown and Feasby, 1984; Albers et al., 1985) especially in children (Bradshaw and Jones, 1992). In contrast, the physiology of the AMAN pattern predicts a pure motor, axonal pathology. The physiologic differences between GBS and AMAN are highlighted by comparing patients of similar ages, which suggest that the two patterns may be distinguished from one another by the performance of upper limb motor and sensory nerve conduction studies. Another major difference is the pathologic lesion. In demyelinating GBS, macrophage-associated demyelination, varying degrees of perivascular lymphocytic infiltration, and involvement of sensory roots, motor roots, and peripheral nerve are usually present (Asbury et al., 1969; Hughes, 1990; Ropper et al., 1991). In contrast, autopsy findings in five of 10 AFP cases revealed a selective, noninflammatory, axonal degeneration of motor axons. Only two cases, on a child of urban origin with disease onset in the winter, had pathologic features of inflammatory, demyelinating GBS.

Adult patients with some features similar to those patients in this report have been previously reported. Feasby and coworkers have described patients with severe GBS in whom both motor and sensory nerves were electrically inexcitable early in the illness. In contrast to the cases from northern China, however, these cases involve both motor and sensory roots, and there is no known seasonal predilection. Wadia and coworkers (Wadia et al., 1979; Wadia et al., 1982) (personal communication, RS Wadia) have noted subgroups of adult patients with GBS clinically defined in whom there appears to be a pure motor syndrome. However, in this series, seasonal and geographical predilections were not noted.

A striking feature of cases in northern China is the unusual epidemiology: the primary involvement of children from rural areas with peak incidence in the summer. Although these features suggest some type of infectious process, the lack of cellular infiltration in meninges or parenchyma of the spinal cord, and the normal dorsal roots but involved motor roots, make direct invasion by an organism unlikely. The absence of clustering argues against a toxic exposure. Compared to urban dwellers, many rural Chinese drink unboiled well water and have contact with a variety of farm animals, including chickens, pigs, goats, and dogs. Pesticides, chemical fertilizers, and human faces are often used in farming. The crops in this area of China include wheat, corn, and sorghum, but rarely rice.

In the study of antibody titers to C. jejuni, titers of IgG and IgM were significantly increased in some patients compared to hospital controls. Increases in titers were most striking in sera collected early, up to 10 days after the onset of the paralytic syndrome; after that, titers decreased over time. This is consistent with a previous study showing that the antibody titers reach a peak at 8 to 14 days after exposure and return to control level by 90 days (Blaser and Duncan, 1984). However, several factors may have affected these results. First, the hospital controls were mostly from an urban population, whereas most of the AMAN patients were from rural areas. Second, samples from occupants of the same or neighboring villages have not been available for use as controls. Third, the Thai village children who served as healthy normal controls may differ serologically from Chinese children. A prospective case-control study is needed.

This acute paralytic syndrome may not be limited to China. In 1967, Ramos-Alvarez reported virologic and clinical studies on 218 Mexican children with AFP. Of these, 74 had negative cultures and serologic tests for poliomyelitis and were afebrile at onset of disease; those who survived the acute illness had either complete or significant recovery (Ramos-Alvarez, 1967). In a subsequent publication, Ramos-Alvarez, Bessaudo, and Sabin analyzed the clinical, neuropathologic, and virologic data on 57 autopsied children from the same Mexican hospital (Ramos-Alvarez et al., 1969). Of those, 32 had poliomyelitis, 10 had GBS, and the remaining 15 were considered to have a noninflammatory process that the authors subdivided into cytoplasmic neuronopathy (8 cases) and nuclear neuronopathy (7 cases). Patients with this noninflammatory disease were afebrile at onset and had acellular CSF. These 15 cases from Mexico closely resemble the cases reported here both clinically and pathologically.
In 1971, Valenciano and colleagues reported on 25 cases of flaccid tetraplegia occurring within a five-month period in Albecete, Spain, with 21 of the patients falling ill between August and October. The age range was 20 months to 65 years, but 18 were under age 14. Like the patients with AMAN, the Spanish patients had rapidly developing tetraplegia, no fever, no sensory symptoms, normal CSF, and a symmetric recovery. Viral cultures, including for poliomyelitis, were negative. Postmortem studies of three cases revealed no inflammation or neuronal loss, but chromatolysis of spinal motor neurons in one case. Further, demyelination in caudal roots was detected in two of the three cases (Valenciano et al., 1971).

In 1989, Coe reported on the experience with GBS clinically defined in a large children's hospital in Seoul, South Korea (Coe, 1989). He reported on 132 children seen over a 12-year period and noted a seasonal distribution, with the majority of cases occurring in the summer months. Clinically, the cases also resembled those from northern China. Unfortunately, neither physiologic nor pathologic information is available from these cases. Of particular interest is the near identical latitude of Seoul to the areas in northern China studied in this report.

These reports all describe children with AFP with features similar to AMAN. Several authors have suggested that the motor neuron is the site of the primary pathology, in contrast to the findings in the Chinese patients, indicating that motor axons are primarily affected. It is conceivable, however, that AMAN represents one form of the spectrum of a more widespread non-inflammatory motor neuropathy, present in many parts of the world.

Sabin has emphasized that studies by the Pan American Health Organization of 6,859 children with AFP, recorded as "probable" poliomyelitis, found only 1% to 1.6% had "wild" poliomyelitis on stool culture, 5% had vaccine-like polioviruses, and 15% had "other entroviruses." In the remaining 75-80%, no virus was isolated (Sabin, 1991). In addition, the success of the campaign to eradicate poliomyelitis resulted in no proven cases of poliomyelitis in Latin America since 1991. However, the surveillance campaigns report a large number of children with a non-poliomyelitis form of AFP. At present, many of these children are considered to have GBS. Until clinical, epidemiologic, electrodiagnostic, and pathologic data become available in these children, they cannot be compared with the cases from China.

The large number of cases in northern China represents a significant public health problem. It is estimated that thousands of cases of AMAN occur each year. In addition, the age range of these patients and their clinical characteristics could lead to the diagnosis of poliomyelitis. Such misdiagnosis would confuse the data in a poliomyelitis surveillance programme. The predictable seasonal pattern of AMAN in northern China provides a unique opportunity to characterize the disease process in terms of its epidemiology, clinical characteristics, and pathophysiology. It is anticipated that such studies will clarify disease mechanisms and lead to either prevention or specific therapy.

3.4 India

Nationwide surveys have indicated that poliomyelitis continues to be a major public health problem in India and is perhaps the most important cause of AFP. It is estimated that 2.24 million children have been handicapped by poliomyelitis.

An interesting but uncommon disorder that has gained increasing recognition in recent years in India is "acute oculobulbar palsy with flaccid paralysis with spontaneous recovery" without evidence of snake bite, but resembling the clinical picture seen in cobra snake bite (Sahni et al., 1986; Wadia et al., 1986).

GBS and its variants, acute oculobulbar palsy with flaccid paralysis and poliomyelitis as seen in India, will be discussed. The vast majority of poliomyelitis patients are seen by the paediatricians, and therefore neurologists have limited experience in this field. This is the reason for the obvious bias in favor of GBS in
this report. The authors have drawn heavily on the published literature, information gathered through questionnaires and personal communication with other neurologists and also share their personal experience.

Guillain-Barre syndrome

There is no published information describing the annual incidence of GBS in India. An attempt was made to measure the magnitude of the problem in teaching hospitals by sending questionnaires to neurologists in 18 centers. Data received from 7 centers showed a wide variation in number of cases seen in a year (5 to 41) which may be attributed to the presence of other major hospitals in the region sharing the clinical load. On an average, 138 cases are seen annually. Adults were observed to be more frequently affected, constituting 75% of the total number of 730 cases of GBS. The percentage of children under age 15 in different centers varied from 3.2% to 38%. A noteworthy feature is that 29% of cases required ventilatory assistance with almost similar frequency among adults (28%) and children (32%). The case fatality ratio varied significantly (5.7 to 27.8%) between centers, the average figure being 12.3%. The mortality in the West has been reported to vary from 1.25% to 13% (Ropper and Shahan, 1984; Winter et al., 1983). These collective data from seven centers cannot be considered representative of the country, but a rough estimate of the magnitude of the problem and the gravity of the situation can be appreciated.

The National Institute of Mental Health and Neurosciences (NIMHANS) is a major center for referral of neurologic and mental disorders from hospitals in South India. The epidemiologic and clinical data from this institute and published reports from two other major centers, Vellore in southern India (Taoori and Chandl, 1963) and Chandigarh in northern India (Kaur et al., 1986) will highlight the profile of GBS in India as well as focus on regional differences. During the first period of 15 years from 1970 to 1984, 397 patients with GBS were seen at NIMHANS, constituting 29.2% of all peripheral neuropathies, excluding traumatic nerve injuries (Gouri-Devi, 1990). On an average, 26 cases of GBS and 91 cases of peripheral neuropathy were seen annually. During the second period of five years, from 1985 to 1989, the figures were 29 and 189, respectively. The proportional morbidity of GBS among peripheral neuropathy cases was 15.4%, which was considerably less than the first phase. Although the annual figures are almost similar, the decreased proportion of GBS may be due to a relative increase in number of cases due to other etiologic causes, particularly leprosy and hereditary neuropathy. GBS constituted 0.4% of all neurology cases seen during the period; the proportional mortality rate of GBS among all neurology deaths was also 0.4%.

The age distribution of the cumulative data of the three studies (Vellore, 44; Chandigarh, 56; and Bangalore, 144 cases) shows that the age at onset in 73% of the 244 patients was under age 40 years, similar to what is reported in other developing countries, such as China and Libya (Baoxun et al., 1981; Radhakrishnan et al., 1987), but younger than in the United States (Beghi et al., 1985). A higher proportion of patients were in the first two decades in Vellore (52%) and Bangalore (35%) compared to Chandigarh (18%). There was a preponderance of males in all three series, although the ratio of males to females varied from 1.4 to 2.6:1 (mean, 2.3:1). In the Bangalore study, a seasonal variation in the occurrence of GBS cases was seen with predilection in monsoon (July and August) and late winter (January). Sixty patients (42%) had disease onset in these three months. Weakness of all four limbs was seen in the majority of cases (86%), while weakness restricted to lower limbs was seen in a few (12%). Sluggish to absent reflexes (93%), sensory impairment (58%), cranial nerve involvement (49%), respiratory paralysis (24%), and autonomic dysfunction (20%) were seen with decreasing order of frequency. However, when special effort was made to assess the autonomic function, a higher frequency of dysfunction (67%) was observed (Singh et al., 1987). Phrenic nerve conduction studies showed prolonged conduction time in 64% of GBS patients (Gouri-Devi and Ganapathy, 1985), which was found to be a sensitive parameter in assessing ventilatory dysfunction as well as predicting impending respiratory failure. CSF cells were less than 10 leucocytes/mm3 in 93%, and protein was elevated in 75% of 228 patients in whom CSF was examined.
Diagnostic dilemmas

A diagnostic problem was encountered in two groups of patients seen in Bangalore during 1985-1989, who could not be included in the GBS group because the criteria were not fulfilled (Asbury et al., 1978; Asbury, 1981).

In the first group of eight patients, the CSF cells were more than 30 leukocytes/mm³ (45 to 170/mm³) on the first examination, and on the second or third lumbar puncture done within 1-4 weeks, there was a decrease to less than 10 leukocytes/mm³. In seven of these patients, protein was elevated and the clinical features and course were suggestive of GBS. Should these cases be included in the category of GBS? Is there a need to redefine the diagnostic criteria for GBS regarding CSF cell count, such as: "with high initial cell count of more than 30 leukocytes/mm³, a serial lumbar puncture should show a rapid decrease to less than 10 cells/mm³"? The inclusion of this criterion will help in giving a label for this group of patients as it is likely that a number of such patients are not properly diagnosed.

In the second group comprising eight children, the deficit peaked within four days from onset. The cardinal features were symmetric flaccid paralysis with no improvement over time. Axonal loss was detected electrophysiologically, and there was no evidence of demyelination on nerve conduction study. Although five of the children were immunized against polio, the diagnosis of poliomyelitis was considered on clinical grounds and it was felt that the vaccine might have been ineffective due either to break in cold-chain or to inadequate dose. The CSF findings were rather surprising as there was no increase in cell count in all the patients except in Case 7, who had an initial count of 30 cells/mm³, and three days later cells were not detected. Contrary to expectation, the CSF protein was elevated in all. This group of patients illustrates the need for improved criteria to distinguish GBS from poliomyelitis.

Japanese encephalitis virus and Guillain-Barré syndrome

In southern parts of Karnataka, outbreaks of Japanese encephalitis have occurred periodically since 1979 (Gourge-Devi, 1982); this region is recognized as being endemic for Japanese encephalitis virus (JEV). In view of this, an attempt was made to look for JEV infection as an antecedent event in GBS. During the period of study (1985-1988), serum and CSF from 33 patients were tested for JEV-specific IgM antibodies and JEV antigen. Virus isolation from CSF was also attempted. In 21 of the 33 patients (64%), evidence of JEV infection preceding the onset of GBS was demonstrated. The clinical features, duration of illness, and outcome of these 21 patients were similar to those without JEV infection. Since there have been many epidemics of Japanese encephalitis in eastern and northern India in the last 10 years, it would be worthwhile to investigate the role of JEV in the etiology of GBS in these regions as well (Chatterjee and Banerjee, 1975; Rodrigues, 1984).

Acute oculobulbar palsy with flaccid paralysis and spontaneous recovery

During the period under study (1985-1989), six patients with unusual and distinctive features of acute onset of ptosis, external ophthalmoplegia, and bulbar paralysis were seen in the morning after awakening from sleep. Mild-to-moderate weakness of limbs was observed in five of them. Tendon reflexes were preserved in all but one patient. The other features were bilateral facial muscle weakness and ventilatory failure. CSF did not show pleocytosis or elevated protein, and serum potassium was normal. Electrodiagnostic tests showed normal nerve conduction and the absence of decremental or incremental response on repetitive nerve stimulation. There was no response to neostigmine. The neurologic deficit reached a peak in a few hours to two days, followed by spontaneous dramatic recovery, complete within the next 7-10 days.

Since none of those patients had araxia, the diagnosis of Miller-Fisher syndrome (Fisher, 1956) cannot be considered. A clinical picture similar to our patients can occur due to elapid snake bite, but recently patients have been reported without a history of snake bite (Saini et al., 1986; Wadia et al., 1986). Despite the absence of snake bite, because the patients were living in areas endemic for elapidae, they were treated with antismake venum (ASV) and neostigmine with good response. It is of interest that 11 of 15 patients reported by Wadia and coworkers (Wadia et al., 1986) recovered rapidly without ASV treatment. Unlike our
experience, Wadia and coworkers (Wadia et al., 1986) observed decremental response on repetitive nerve stimulation and suggested that there may be a myoneural junction lesion due to a toxin similar to snake venom. Since there was no evidence of snake bite, a similar agent may also be postulated in our patients. Further studies are necessary to precisely delineate the site of lesion and the causative etiologic agent.

Polioymielitis

A survey of 14 states of India in 1981 observed that the annual incidence rate of poliomyelitis in children under 4 years varied from 1.5 to 1.9/1,000 children (Basu and Sorkhey, 1984). Lameness surveys have shown that the prevalence rate of 5-6/1,000 significantly decreased to 1.2-1.4/1,000 after effective implementation of the immunization programme (Tiške et al., 1986). Lameness surveys in the community have also shown that poliomyelitis was the cause of disability in 62% of children 5-9 years of age (Basu, 1991). In a community-based house-to-house survey to detect neurologic disorders in the rural population of 57,660 in Gouribidananur, Kamataka, southern India, 57 cases of poliomyelitis sequelae were detected (Gourie-Devi et al., 1987). The crude prevalence rate was 99/100,000 population. Among all neurologic disorders, it ranked fourth in order of frequency, the first three being epilepsy, headache, and mental retardation. Age-specific prevalence rate for children 0-5 years was 3.4 (29 cases) and 6-10 years was 1.5 (14 cases)/1,000 children.

It has been observed that 70-87% of those developing poliomyelitis are below 2 years of age (Basu, 1991; Mandke et al., 1991). Studies on acute poliomyelitis in immunized, partially immunized, and unimmunized children showed that there was no significant difference in clinical features, severity of paralysis, and fatality among the three groups (Delvanayagam and Nedunchelian, 1991). A disturbing feature, observed in this study and earlier reports by others, was the high proportion of unimmunized children at 6-11 months of age compared to other age groups (Sen et al., 1985; Sen et al., 1989; Pamecha, 1987). These observations have important implications for immunization schedules.

In a recent outbreak of poliomyelitis in 1981 in Kerala, southern India, viral etiology was established by serology and virus isolation in 66.4% of 119 cases, the poliovirus type I being the commonest isolate (Vijayan et al., 1985). Spinal form accounted for 86%, bulbospinal form for 13%, and encephalitis form for 1% of 119 cases. In another study from Delhi of children with poliomyelitis who had been immunized with three doses of OPV, the causative organism was poliomyelitis type II virus in 35.7% and non-poliovirus in 17.8% of 28 patients (Sen et al., 1985). In an equal number of nonimmunized children with poliomyelitis, poliovirus type I was shown in 78.5%.

The vaccination programme has received considerable impetus in recent years; it has been documented that national coverage of OPV (3 doses) increased from 15% in 1981 to 74% in 1989 (Basu, 1991). National review of EPI showed that the annual incidence rate was 0.9/1,000 children, which was significantly lower than that found in 1981 (1.5-1.9/1,000 children) (Gupta and Murali, 1989).

Comments

It is clear from the foregoing that in the community, poliomyelitis is by far the commonest cause of flaccid paralysis in children in India. There are inherent problems in differentiation of poliomyelitis from GBS based on clinical criteria and CSF examination without supportive electrophysiology and investigations to establish viral etiology. In the rural areas and even in some urban regions of India, investigative facilities are not available. Therefore, there is a need to formulate more definitive criteria that can be easily adapted in the peripheral hospitals.

A significant number of patients diagnosed clinically to have GBS have a transient increase of CSF cell count to above 30-50 leukocytes/mm³, not qualifying for inclusion according to the existing criteria (Asbury et al., 1978). The status of this group of patients needs to be defined. There are no national data on the annual incidence of GBS. Surveillance of GBS through sentinel hospitals, a simple method of collecting
basic epidemiologic data, can be considered. Such an approach has been successful in poliomyelitis surveillance.

Our preliminary data have demonstrated an association between JEV and GBS. Since epidemics and outbreaks of JEV have been reported in many regions of the country, it would be of interest to determine whether the incidence of GBS is higher in these areas compared to nonendemic zones.

The clinical syndrome of "acute oculobulbar palsy with flaccid paralysis with spontaneous recovery" merits recognition as a distinct entity. Further studies aimed at identifying the site of lesion and etiologic basis are warranted.

3.5 Latin America

A challenge to eradicate the transmission of wild poliovirus from the world, lies with how well one can distinguish "true" poliomyelitis cases, those caused by wild poliovirus, from cases of acute flaccid paralysis (AFP) due to other causes.

Poliomyelitis

In September, 1985, the PAHO initiative to eradicate the indigenous transmission of wildtype poliovirus from the Americas by the end of 1990 was officially approved. In 1986, a system for the active surveillance of AFP cases in children younger than 15 years of age was implemented. The same year, of the 1591 cases of AFP notified to the programme, 932 (58.5%) were confirmed as poliomyelitis with isolation of the virus in stools.

In 1989 in the Americas, although 2,103 reported AFP cases were investigated, 1,975 (94%) were determined not to be polio. To minimize inefficient use of limited resources needed for global eradication of polio, the use of operational screening criteria that maintain sensitivity, but achieve higher specificity was felt to be needed to focus case investigation efforts particularly upon cases of AFP most likely due to polio. To that end, the objectives of the following are to present: 1) the development of improved screening criteria, and 2) the use of these criteria as predictors of "true" paralytic poliomyelitis cases, retrospectively assessing AFP cases that have already been discarded.

The last case of poliomyelitis in the Americas was notified on 23 August 1991 in Peru.

GBS in the Americas

Between January 1, 1989 and December 31, 1991, a total of 1,342 cases of GBS were notified by the countries participating in a meeting organized by EPI, Pan American Health Organization-World Health Organization (PAHO-WHO) in collaboration with the Neuroepidemiology Branch (NEB), National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH). The annual incidence rates ranged from 0.4/100,000 children younger than 15 years of age in Brazil to 1.3/100,000 in Guatemala. The male/female rate ranges from 1.8 in Paraguay to 1.22 in Brazil. In all the countries of this area, the age group 1-4 years of age is the one most frequently affected, with a mean of 60% of all cases. The fatality rate ranged from 13% in Guatemala to 2% in Paraguay. The highest risk factor for mortality is the inappropriate management of respiratory support in Intensive Care Units, since a high percentage of children who required intubation died. Between 3.6% and 26% of the children required respiratory assistance. The highest percentage was observed in Guatemala and the lowest in Paraguay. In no case was either plasmapheresis or intravenous immunoglobulin G treatment used.

The clinical presentation of GBS in Latin America follows the pattern described elsewhere with presence of prodromata in 45% to 93% of the cases. These included fever in 29-56%, respiratory infections in 20-48%, and diarrhea in 10-41%. This information was obtained on a questionnaire given to the mother, and in the case of fever, inaccurate data may have been obtained. However, documented fever at the
beginning of the paralysis was seen in 2-8% of the cases. The only exception was El Salvador, where 55% of the cases had fever at onset. The presence of muscle and radicular pain was described in 10-82% of the cases. The onset of paralysis was acute and the time to acute ranged from 48 hours to 4 days in 60-75% of the cases. Only a minority of the cases (less than 12%) presented paralysis of asymmetric onset. The weakness was preferentially distal in 85-95% of the cases and followed an ascending progression in 69-92%. Cranial nerve lesions were observed in 9-48% of the cases with facial, oculomotor and bulbar nerves being involved more frequently.

Global areflexia was found in 93% of the cases, and the remaining presented at least global hyporeflexia. Occasionally, during the initial early evaluation normal reflexes were observed, but these rapidly evolved to hypo- or areflexia. For this reason, approximately 12% of the cases had no initial alteration of the reflexes. Sensory examination is unreliable in children and abnormalities were reported with too much variation in the values to be conclusive. The same is true for autonomic system involvement.

Follow-up could have been done for periods of up to 24 months with a progressive decrease in the frequency of motor sequelae. These ranged from 57-87% at 60 days to less than 1% at two years. Spinal tap was performed in 15-88% of all the cases, in some with two or more examinations of the spinal fluid. An initial increase in protein values between 40-71% was followed by progressive rise after the first week.

It should be mentioned that due to the different degrees of severity of GBS and the multiplicity of observers in some countries, clinical data may have high interobserver variability. This bias decreases in countries in which a single neurologist examined every suspected case.

Comments

The major conclusions of the study in Latin America are:

1) The annual incidence rate of AFP is 1.5/100,000 population younger than 15 years of age.
2) The annual incidence rate for GBS is 0.7/100,000 population younger than 15 years of age.
3) GBS in children younger that 1 year of age is rare. GBS affects predominantly males, with a male/female rate of 1.38:1.
4) The age-specific attack rate was highest in the age group 1-4 years with a mean of 0.9/100,000 population 1-to-4 years of age.
5) Clinical presentation of GBS in children in Latin America is similar to previous descriptions in other parts of the world. However, in a minority of cases, global hyporeflexia without distal areflexia was seen.
6) Onset of the paralysis was rather acute, with an average duration of 3.14 days and a mean of 2.24 days. This would indicate that in children the onset of the disease is faster than in adults.
7) In children, the presence of fever at the beginning of the paralysis appears to be higher than in adults, ranging between 2 and 32% of the cases. Several factors may account for this increase of fever in children, including delays in evaluating cases with fever secondary to infections, particularly of the respiratory tract. Other environmental and socioeconomic factors could also favor the presence of fever. In El Salvador, fever was present in 55% of the cases at onset. GBS in this country also has other clinical features which suggest the possibility of a different etiology, such as potential intoxication with wild berries (K. calderonii). This could also explain the fact that El Salvador has the highest incidence rate of GBS in children in the Americas (1.9/100,000 children younger than age 15).
8) Muscular and radicular pain was reported as a clinical manifestation in more than one half of the cases.
9) Follow-up of the cases for periods up to 24 months demonstrated the presence of late motor sequelae in a small percentage of the survivors.
10) The excessive mortality (25%) in some countries seems to be the result of deficient respiratory support in the Intensive Care Units.
Presentations from the participating countries underlined the relevance of local factors of importance for the appropriate etiologic investigation in cases of AFP. These factors include the possible and yet undefined impact of infection by human retroviruses (HIV, HTLV-1), several environmental neurotoxins, such as *K. calderoni* and *K. humboldtiana*, organophosphate pesticides, heavy metals, and several pharmacologic products, as well as less frequent causes, such as tick paralysis. It is important to recognize that traumatic neuritis, secondary to intramuscular injections, continues to be an important cause of asymmetric AFP in Latin America. Both toxic neuritis and traumatic neuritis can be prevented. The high rates of AFP in Central America could be related to the ingestion of *K. calderoni*. In each case of AFP from Central America, the specific history of contact or exposure to the above neurotoxin should be investigated.

For further information of the situation on AFP in the Americas see the final report of WHO-PAHO and NIH (1992) on Acute Flaccid Paralysis (AFP) and Guillain-Barré Syndrome (GBS) in Children of Central and South America.

3.6 The Netherlands

The general clinical characteristics of 1) GBS, clinically defined, 2) AMAN (McKhan and et al., 1991), and 3) the pathologically defined paralytic syndromes described in Mexico (Ramos-Alvarez, 1969), indicate that based on clinical characteristics alone these syndromes are difficult to distinguish. However, on the basis of other criteria, including epidemiologic, physiologic, antecedent infection, or immunologic and pathologic features, it may be possible to separate these disorders. In addition, clinical trials with immune intervention may also be able to segregate out these disorders.

Within the rubric "Guillain-Barré syndrome," clinically defined, are subsumed a number of disorders. In the original NINDS-NIH classification (Asbury et al., 1978), clinically similar syndromes produced from metabolic disorders or intoxications were specifically excluded. In addition, it was recognized that there were clinical variants of demyelinating GBS (Asbury et al., 1978). A bulbar onset instead of a beginning in the legs is the most remarkable indication that the syndrome encompasses different entities. Also, within the more classic forms, clinical variation is clearly seen. The distribution of weakness in individual limbs may be proximal, distal, or diffuse; the sensory system may or may not be involved; severe axonal degeneration occurs in some cases and not in others. Also the time course is variable. In addition to the acute form, chronic forms are regularly seen. Earlier analysis of both acute GBS and chronic inflammatory polyneuropathy using clinical and laboratory parameters such as serologic evidence for infections and antiperipheral nerve antibodies led to a subclassification (Van Doorn et al., 1991; van der Meché et al., 1991). The biologic factors may, however, add substantially to the prediction of prognosis (van der Meché et al., 1992).

Variations of the clinical deficit may be reflected in EMG studies, sometimes resulting in specific patterns of conduction block, in both acute and chronic GBS (van der Meché et al. 1988, Brown and Snow, 1991; van der Meché and Meulstee. 1988). Whether in addition to demyelination, a primary axonal form of GBS also exists or only secondary axonal damage occurs, is difficult to ascertain at present. It is clear, however, that in patients with severe axonal damage the sensory system may be spared both clinically and electrodiagnostically (Feasby et al., 1986; van der Meché et al., 1991). It is, therefore, to be expected that within the GBS group patients may be found with similar characteristics to the Chinese children, namely, a purely motor neuropathy with a monophasic course, with EMG results compatible with axonal lesions.

**Guillain-Barré patients with pure motor deficit: the Dutch trial**

In the Dutch GBS trial, sensory signs were scored in addition to motor signs. In summary, 147 patients were followed for six months. Inclusion criteria were inability to walk more than 10 meters without support within two weeks after onset of weakness. At entry, patients were asked about sensory deficit and investigated for disturbances of 2-point discrimination, position sense, and tactile function in the hands and position sense and tactile function in the feet. At all 16 follow-up visits, 2-point discrimination and tactile function in the hands and tactile function and position sense in the legs were scored. If no consistent abnormality was found,
patients were scored as purely motor GBS; 27 of 147 patients fulfilled this criterion. Analysis of EMG data in this subgroup was performed with two questions in mind: are electrodiagnostic measurements consistent with a pure motor disorder; and second, are they suggestive of demyelination or axonal degeneration using suggested criteria for demyelination from Comblath (Asbury and Comblath, 1990)? The clinical characteristics are given below.

Table 5. Dutch Guillain-Barré trial

<table>
<thead>
<tr>
<th>Pure motor GBS (n = 27/147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Mean age 42.6 years</td>
</tr>
<tr>
<td>- Below 20 years 6/27</td>
</tr>
<tr>
<td>- Paresthesia 9/27</td>
</tr>
<tr>
<td>- Distribution of weakness</td>
</tr>
<tr>
<td>&gt; distally 19/27</td>
</tr>
<tr>
<td>diffuse 5/27</td>
</tr>
<tr>
<td>&gt; proximally 3/27</td>
</tr>
<tr>
<td>- Antecedent infection</td>
</tr>
<tr>
<td>flu 7/27</td>
</tr>
<tr>
<td>diarrhea 11/27</td>
</tr>
<tr>
<td>other 5/27</td>
</tr>
<tr>
<td>none 4/27</td>
</tr>
<tr>
<td>- Campylobacter infection</td>
</tr>
<tr>
<td>5/26</td>
</tr>
<tr>
<td>- GM1 antibodies 11/23</td>
</tr>
<tr>
<td>- Campylobacter and GM1-AB  2/23</td>
</tr>
</tbody>
</table>

Age was somewhat lower compared to the whole group (mean 42.6 versus 47.5 years). GBS preceded by diarrhoea with weakness starting distally was relatively frequent and the presence of GM1 antibodies was somewhat overrepresented (48% versus 30% in the whole group).

From the six individuals younger than age 20, four had a distal onset of weakness, one a diffuse distribution of weakness, and one was tetraplegic on admission. There were no paresthesias. Any discrepancy between neck flexors and extensors or the presence of meningismus is unknown.

Recovery of the pure motor group (n=27) was compared to the other 120 patients. Pure motor patients tended to improve earlier but comparison over the whole period showed no significant difference (p = 0.5). Interesting is the effect of immunoglobulin (IgIV) versus plasma exchange (PE) in the pure motor group: 12 received PE and 15 IgIV. Despite the small numbers, the difference in favor of IgIV is almost significant (p = 0.08).

EMG data of the 27 pure motor patients were analyzed. Using conventional techniques, median, ulnar, and sometimes peroneal nerves were studied at entry, one week and four weeks later. EMG data were available for 24 of the 27 pure motor patients. It may be concluded that pure motor patients are not distinguishable from the other patients by motor nerve studies. The criteria of Asbury and Comblath were then used to find evidence of demyelination (Asbury and Comblath, 1990). Somewhat different from their approach, no distinction was made between conduction block or dispersion since both are due to demyelination and are difficult to differentiate. The more neutral term "length-dependent amplitude reduction" has been used. This approach enabled a single dividing line to be drawn for demyelination. Below a distal CMAP of 5 mV, another modification was introduced; the difference between the proximally elicited amplitude should be at least 1 mV smaller compared to the distal amplitude. With low distal CMAPs, the use of ratios and percentages may become rather meaningless (van der Meché et al., 1988).
Using the demyelination criteria for CMAP reduction, distal motor latency and nerve conduction velocity for at least two nerves (at least six items per patient), no item was found fulfilling the criteria in 11 persons, one item in nine patients, and two items in the remaining four patients. One may conclude from this that in at least 11, but presumably in 20 patients, demyelination is unclear. Also, the last four patients did not fulfill the criteria for a demyelinating polyneuropathy, but the number of nerves tested may be insufficient.

The EMG protocol, however, originally was not based on these later developed criteria. Needle myography was performed on 21 patients, usually in three muscles in all three scheduled EMGs. Abundant denervation potentials in two or more muscles in any of the three EMGs were seen in four patients and in one muscle in six additional patients and no or only sporadic denervation potentials in the other 11 patients. Rather severe axonal damage was therefore observed in 10/21 patients. Sensory conduction was normal in 19 patients. In the other five patients, two had absent median and ulnar sensory potentials; the three others had amplitudes below 0.01 mV, but normal conduction velocity. In general, therefore, the clinical sensory investigation and sensory conduction studies showed agreement. Exclusion of the clinically pure motor patients with disturbed sensory potentials did not change the findings discussed above.

It may be concluded that 15-20% of the GBS patients have a pure motor variant, usually with a predilection for distal muscles. At the nadir there is, in the majority of the patients, little or no evidence for demyelination and about one-half of them show abundant denervation. Therefore, an axonal dysfunction may be involved. Further, it has been suggested that these patients may benefit more from IgIV than from plasmapheresis.

Comments

In this survey, it has been argued that GBS has a variety of clinical and physiologic subtypes, among them a pure motor form. This form may have severe axonal damage. There was, in this study, no predilection for children. Comparing these results with the findings in the 38 Chinese children, it may be that some pure motor GBS patients could have been included in this Chinese group, but, the epidemiology sets them apart as a different group from the usual GBS. However, the Chinese syndrome may be a special variant of a post-infectious axonal neuropathy related to a specific infectious agent. The occurrence at an early age may be explained by the immune status of the individual.

Not only differences in neuronal changes, but also differences found in the peripheral nerves as recently discovered (Honavar et al., 1991), emphasize that the clinical GBS pattern is presumably the final common path of a variety of pathogenetic mechanisms.

4. CONCLUSIONS AND RECOMMENDATIONS

The current understanding of the etiology of AFP is still very incomplete. Two main observations can be made with regard to this problem. The first observation is that what appears to be acute paralytic poliomyelitis continues to occur in regions where extensive immunization against poliomyelitis has been carried out, e.g., in Saudi Arabia (Yohanan et al., 1991). This has been variously attributed to an inability to immunize all who are at risk, to a possible inadequacy of the response to trivalent OPV, and to the misdiagnosis of other disorders producing AFP as acute poliomyelitis. The second observation is the growing realization that all the disorders that cause AFP are not known. In addition to providing its own challenge, this compounds the problem of assuring the eradication of poliomyelitis.

As described in this report there are many disorders that can cause AFP. Many are uncommon individually, but in the aggregate are probably no less common than paralytic poliomyelitis and the postviral neuropathies, in countries in which the incidence of poliomyelitis has been significantly reduced by
immunization. In addition to the fact that this wide range of disorders raises a problem in poliomyelitis surveillance, the morbidity caused by many non-poliomyelitis causes of AFP is sufficient to warrant specific attempts to develop methods to prevent and/or treat these disorders as well. Some will yield to improvements in the environment, e.g., toxic neuropathies. Others, such as other virally induced anterior horn cell disorders, will benefit from research on viral pathogenesis currently underway in many centers throughout the world, and from development of new antiviral therapeutic agents in the future.

No single operational case definition of acute paralytic poliomyelitis has emerged that combines both high sensitivity and high specificity (Beilillik et al., 1992). The clinical picture and CSF findings alone are not sufficient for a reliable diagnosis. New methods for poliovirus detection are becoming available and will undoubtedly increase both diagnostic sensitivity and specificity.

Many issues remain. Above all, there is a need to (1) improve the understanding of the epidemiology of AFP, particularly in developing countries; (2) develop the most efficient ways to detect acute poliomyelitis due to the poliovirus in the course of field trials; and (3) move from epidemiologic characterization to the stage of unraveling etiology and pathogenesis, which in return may lead to successful therapy.

To achieve these goals, it will be necessary to improve the diagnostic criteria for use in case investigation of AFP cases. In addition, it should be possible to employ new specific laboratory tests to identify poliomyelitis and other viruses. A system of referral of specimens to designated laboratories might be the most efficient way to support this effort and ensure its success. But it also means developing diagnostic criteria for disorders other than poliomyelitis that cause AFP and enhancing the clinical, epidemiologic, and laboratory investigation of cases of non-poliomyelitis flaccid paralysis. Such a plan would also involve extensive testing of the AFP Investigation Form under controlled circumstances to determine its applicability and practicability. Finally, it would be useful to have an international registry for the non-poliomyelitis causes of AFP to supplement poliomyelitis data banks.

The frequency with which AFP occurs in developing countries clearly warrants further work. Its occurrence under widely differing circumstances and among individuals with varying genetic backgrounds, merits international collaboration.
REFERENCES


ACUTE ONSET FLACCID PARALYSIS

Page 30


6. APPENDICES

Appendix I: *EPI Poliomyelitis Case Investigation Form*

Country: ___________________________ Year: ___________________________

**SOURCE OF REPORT:**

Date reported: ___/___
Name and address of institution: _______________________________________
Person reporting case: _________________________________________________
Telephone number: ___________________________________________________

**CASE IDENTIFICATION:**

Name: ___________________________ Sex: ___________________________
Date of Birth: ___/___
Age at onset of symptoms: ___________________________________________
Present Address: _____________________________________________________
Village/city: ___________________________ District/country: ___________
State/Province: ___________________________
Permanent Address: _________________________________________________
Village/city: ___________________________ District/country: ___________
State/Province: ___________________________
Mother’s name: _____________________________________________________
Father’s name: _____________________________________________________

**HOSPITALIZATION:**

Hospitalized? Yes ____ No ____ Name of hospital: ___________________________
Address: ___________________________________________________________
Medical Record No: _________________________________________________
Date Hospitalized: ___/___

**SIGNS AND SYMPTOMS:**

Date of onset of symptoms: ___/___

<table>
<thead>
<tr>
<th>Symptom</th>
<th>yes</th>
<th>no</th>
<th>unk</th>
</tr>
</thead>
<tbody>
<tr>
<td>fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>irritability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>coryza</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>muscle pains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>headache</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stiff neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>weakness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sore throat</td>
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<tr>
<td>irritability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rigidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Date of onset of paralysis/paresthesias: ___/___

Fever present at onset of paralysis? Yes ____ No ____ If yes ____ degrees

<table>
<thead>
<tr>
<th>Symptom</th>
<th>yes</th>
<th>no</th>
<th>unk</th>
</tr>
</thead>
<tbody>
<tr>
<td>paralysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>flaccid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>asymmetrical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sudden onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sensation loss</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SITE OF PARALYSIS:**

left leg
left arm
right leg
right arm
respiratory muscles
face
other cranial nerves
**ACUTE ONSET FLACCID PARALYSIS**

**SITE OF PARESTHESIA:**
- left leg
- left arm
- right leg
- right arm

**IMMUNIZATION HISTORY**

**Usual Immunization Clinic:**

<table>
<thead>
<tr>
<th>OPV zero</th>
<th>OPV 1</th>
<th>OPV 2</th>
<th>OPV 3</th>
<th>OPV 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>unk</td>
<td>unk</td>
<td>unk</td>
<td>unk</td>
<td>unk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>imm. card</th>
<th>date of immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>day / month / year</td>
</tr>
<tr>
<td>no</td>
<td></td>
</tr>
<tr>
<td>unk</td>
<td></td>
</tr>
</tbody>
</table>

**PRELIMINARY CLINICAL CLASSIFICATION**

Discarded Case: ____  Probable Case: ____

If not polio, give final diagnosis and comments below.

Date __/__/__

Comments:

**TRAVEL AND CONTACT HISTORY**

Indicate all places outside present village/city (including other countries) visited by the patient 28 days prior to onset of paralysis/paresthesia.

<table>
<thead>
<tr>
<th>Location</th>
<th>Person(s) visited</th>
<th>Date visited</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>/</strong>/__ to <strong>/</strong>/__</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>/</strong>/__ to <strong>/</strong>/__</td>
</tr>
</tbody>
</table>

Did the case come in direct contact with another household or close contact who was immunized within 75 days before paralysis/paresthesia? yes __ no __ unk __

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>Date immunized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>/</strong>/__</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td><strong>/</strong>/__</td>
</tr>
</tbody>
</table>
LABORATORY DATA

Name of laboratory:  
Address:  
Country:  

Virus Isolation studies:

<table>
<thead>
<tr>
<th>Date collected from patient</th>
<th>Date sent to lab</th>
<th>Date of lab result</th>
<th>Poliovirus isolated type 1 type 2 type 3</th>
<th>Other (specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faeces/Swab 1</td>
<td>/ / /</td>
<td>/ / /</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Faeces/Swab 2</td>
<td>/ / /</td>
<td>/ / /</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Other</td>
<td>/ / /</td>
<td>/ / /</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Serologic studies:

<table>
<thead>
<tr>
<th>Date collected from patient</th>
<th>Date sent to lab</th>
<th>Date of lab result</th>
<th>Poliovirus isolated type 1 type 2 type 3</th>
<th>Other (specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Sample:</td>
<td></td>
<td></td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>S1</td>
<td>/ / /</td>
<td>/ / /</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>S2</td>
<td>/ / /</td>
<td>/ / /</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>S3</td>
<td>/ / /</td>
<td>/ / /</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Interpretation:  

CSF (Cerebrospinal fluid):

<table>
<thead>
<tr>
<th>Date</th>
<th>Red cells</th>
<th>White cells</th>
<th>% Lymphocytes</th>
<th>Glucose</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>/ / /</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>/ / /</td>
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<tr>
<td>/ / /</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Poliovirus strain characterization results:

<table>
<thead>
<tr>
<th>Poliovirus type</th>
<th>Strain characterization method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other results and/or comments:  

---

---
### ACUTE ONSET FLACCID PARALYSIS

**Page 42**

<table>
<thead>
<tr>
<th>Autopsy? yes</th>
<th>no</th>
<th>Pathology laboratory:</th>
</tr>
</thead>
<tbody>
<tr>
<td>material</td>
<td></td>
<td>date collected date sent date of result histopathology result (attach report)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CASE FOLLOW-UP:**

Was case seen 60 days after onset of paralysis? yes date / / no  
If no, why not?

---

Paralysis:
Paralysis present at 60 days or later? yes no  
If yes, check site of paralysis:
left leg |
left arm |
right leg |
right arm |

respiratory muscles |
face |
other cranial nerves |

Disability:
cannot walk | walks with assistance |
limps | walks normally |
other |

Did case die? yes date / / no  
If yes, give details:

---

Report of neurologist:
(attach if available, including electrodiagnostic results)

Summary of neurologist’s report, including final diagnosis:

---

Date / / Name of reporting physician |

Neurologist? yes no |

**CONTROL MEASURES:**

(include the date started, number of households searched, number of OPV doses given in children less than 5 years of age, date completed)
FINAL DIAGNOSIS:

Discarded: ___________ Specify diagnosis: ____________________________
Confirmed: ___________

Check all which apply:

- Laboratory confirmed-virus
- Laboratory confirmed-serology
- Laboratory confirmed-virus & serology
- Residual paralysis after 60 days
- Wild virus indigenous
- Death after compatible illness
- Epidemiologic linkage
- No follow-up
- Vaccine associated
- Imported

Observations:

____________________________________________________________________
____________________________________________________________________
____________________________________________________________________

SIGNATURE:

Name of investigator: ___________________________ Name of Surveillance Coordinator: ___________________________
Signature: ___________________________ Signature: ___________________________
Title: ___________________________ Title: ___________________________
Place of Work: ___________________________ Place of Work: ___________________________
Date: ___________________________ Date: ___________________________
Appendix II: Acute Flaccid Paralytic Case Investigation Form

Items marked (*) and in italics are those added by the working group to the EPI Poliomyelitis Case Investigation Form

**SOURCE OF REPORT:**
Date reported: __/__/____ Person reporting case: ______________________
Name and address of institution: ______________________ Telephone number: ______________________

**CASE IDENTIFICATION:**
Name *(omitted in Research Surveys):* ________________________________ Sex: ________________________________
Name: ________________________________ Sex: ________________________________
Date of Birth: __/__/____ Age at onset of symptoms: ________________________________
Present Address: ________________________________
Village/city: ________________________________ District/country: ________________________________ State/Province: ________________________________
Permanent Address: ________________________________
Village/city: ________________________________ District/country: ________________________________ State/Province: ________________________________
Mother's name: ________________________________ Father's name: ________________________________
*Rural:* ________________ *Urban:* ________________

**HOSPITALIZATION:**
Hospitalized? Yes No Name of hospital: ________________________________
Address: ________________________________
Medical Record No: ________________________________ Date Hospitalized: __/__/____
*Date Discharged: __/__/____

**SYMPTOMS:**

*1. Symptoms in the 4 weeks preceding the onset of paralysis:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
<th>unk</th>
<th>*if yes, date</th>
</tr>
</thead>
<tbody>
<tr>
<td>fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>constipation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*abdominal cramps</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>coryza</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*paraesthesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>muscle pains</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stiff neck</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>weakness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sore throat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>irritability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*diplopia (double vision)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rigidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. Symptoms at the onset of paralysis:

Date of onset of paralysis: ___/___/___

- lethargy  yes  no  unknown
- sensory system's deficit  ___  ___  ___
- muscle pain  ___  ___  ___
- headache  ___  ___  ___
- shortness of breath  ___  ___  ___
- paresthesias  ___  ___  ___
- fever  if yes: ___ degrees  ___  ___

Pattern of development of weakness:
- ascending  ___
- descending  ___
- bulbar  ___
- other  ___

*SIGNS ON INITIAL NEUROLOGIC EXAMINATION

- stiff neck  ___
- droopy lids  ___
- able to cough  ___
- diplopia  if yes: right ___ left ___ unk ___
- EOM weakness  ___
- facial weakness  ___
- difficulty swallowing  ___
- weakness neck flexors  ___
- weakness neck extensors  ___
- tongue  ___

*Chest size (cm)  inspiration ________ expiration ________

*able to walk: no: ___
- if yes: independent  ___ with help  ___

*Limb weakness:
- no: ___
- if yes:
  - right arm: no: ___
    - if yes: can lift arm above head  yes ___ no ___
    - can grip hand tightly  yes ___ no ___
  - left arm: no: ___
    - if yes: can lift arm above head  yes ___ no ___
    - can grip hand tightly  yes ___ no ___
  - right leg: no: ___
    - if yes: can raise leg of bed  yes ___ no ___
    - can bend ankle to head  yes ___ no ___
    - can wiggle toes  yes ___ no ___
  - left leg: no: ___
    - if yes: can raise leg of bed  yes ___ no ___
    - can bend ankle to head  yes ___ no ___
    - can wiggle toes  yes ___ no ___
**Fasciculation** yes ____ no ____
**Symmetric weakness** yes ____ no ____ R>L L<R
**Upper limbs** yes ____ no ____ R>L L<R
**Lower limbs** yes ____ no ____ R>L L<R

*Reflexes (3 = increased; 2 = normal; 1 = decreased; 0 = absent)*

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>biceps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>triceps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>supinator</td>
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</tr>
<tr>
<td>knee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ankle</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Babinski** up ____ down ____ no movement ____

*Sensation (2 = normal; 1 = decreased; 0 = absent)*

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>touch</td>
<td></td>
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</tr>
<tr>
<td>pin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vibration</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
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<td></td>
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<tr>
<td>pin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vibration</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>touch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Autonomic function*

<table>
<thead>
<tr>
<th></th>
<th>normal</th>
<th>abnormal</th>
<th>describe</th>
</tr>
</thead>
<tbody>
<tr>
<td>bladder</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>bowel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sweating</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HISTORY:**

*recent vaccination* no ____ yes ____ type ____ date / __________
*recent vaccination in family* no ____ yes ____ type ____ date / __________
*animal bite* describe ____________________________
*insect bite* describe ____________________________
*tick bite* describe ____________________________
*drugs* no ____ yes ____ type ____ date / __________
*exposure to animals* no ____ yes ____ type __________
*exposure to pesticides* no ____ yes ____ type __________
*intramuscular injection* date / __________ site __________
*trauma* describe ____________________________
*source of drinking water* describe ____________________________
*other member of family ill* no ____
if yes, describe ____________________________
**SIMILAR ILLNESS IN:**
- school: no ___ yes ___
- workplace: no ___ yes ___
- neighborhood: no ___ yes ___

**BLOOD TRANSFUSION**
- no ___
  if yes date __/__/__

**INTERVAL HISTORY**

*Date of maximal weakness: __/__/__
*Severity at maximal weakness:
  - quadriplegia with respirator: no ___ yes ___
  - quadriplegia without respirator: no ___ yes ___
  - paraplegia: no ___ yes ___
  - other, describe: ___________________________

*Respirator: no ___ yes ___
  if yes, date on __/__/__
  date off __/__/__

*Death: no ___ yes ___
  date __/__/__
  if yes, describe: ___________________________

**IMMUNIZATION HISTORY**

Usual Immunization Clinic: ___________________________

<table>
<thead>
<tr>
<th>OPV Zero</th>
<th>OPV 1</th>
<th>OPV 2</th>
<th>OPV 3</th>
<th>OPV 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yes</td>
<td>no</td>
<td>unk</td>
<td>yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OPV</th>
<th>imm. card</th>
<th>date of immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yes</td>
<td>day / month / year</td>
</tr>
<tr>
<td></td>
<td>no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>unk</td>
<td></td>
</tr>
</tbody>
</table>

**PRELIMINARY CLINICAL CLASSIFICATION**

Discarded Case: ___  Probable Case: ___
If not polio, give final diagnosis and comments below.
Date __/__/__

Comments: ____________________________________________

**TRAVEL AND CONTACT HISTORY**

Indicate all places outside present village/city (including other countries) visited by the patient 28 days prior to onset of paralysis/paresthesia.

<table>
<thead>
<tr>
<th>Location</th>
<th>Person(s) visited</th>
<th>Date visited</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>/</strong>/__</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>/</strong>/__</td>
</tr>
</tbody>
</table>
Did the case come in direct contact with someone who had been immunized with OPV in the previous 75 days? (This sentence has only been reworded) 

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Unk</th>
</tr>
</thead>
</table>

Name  
Address  
Date immunized  
/
/
/
/

LABORATORY DATA

Name of laboratory: 
Address: 
Country: 

Virus *and Bacterial* Isolation Studies:

<table>
<thead>
<tr>
<th>Date collected from patient</th>
<th>Date sent to lab</th>
<th>Date of lab result</th>
<th>Poliovirus isolated type 1</th>
<th>Poliovirus isolated type 2</th>
<th>Poliovirus isolated type 3</th>
<th><em>C. jejuni</em></th>
<th>Other (specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faeces/ Swab 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| /
/
/
| Faeces/ Swab 2              |                 |                   |                           |                           |                           |            |                 |
| /
/
/
| Other                       |                 |                   |                           |                           |                           |            |                 |

Serologic studies: Blood Sample (stored)

<table>
<thead>
<tr>
<th>Date collected from patient</th>
<th>Date sent to lab</th>
<th>Date of lab result</th>
<th>Poliovirus isolated type 1</th>
<th>Poliovirus isolated type 2</th>
<th>Poliovirus isolated type 3</th>
<th><em>C. jejuni</em></th>
<th><em>HIV</em></th>
<th>Other (specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
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<tr>
<td>3**</td>
<td></td>
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</table>

* acute
** convalescent (14-30 days after onset of weakness)

Interpretation:
CSF (Cerebrospinal fluid):

<table>
<thead>
<tr>
<th>Date</th>
<th>Red cells</th>
<th>White cells</th>
<th>% Lymphocytes</th>
<th>Glucose</th>
<th>Protein</th>
</tr>
</thead>
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</tbody>
</table>

Poliovirus strain characterization results:

<table>
<thead>
<tr>
<th>Poliovirus type</th>
<th>Strain characterization method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

Other results and/or comments:


Autopsy? yes no Pathology laboratory: 

<table>
<thead>
<tr>
<th>Material</th>
<th>Date collected</th>
<th>Date sent</th>
<th>Date of result</th>
<th>Histopathology result</th>
</tr>
</thead>
<tbody>
<tr>
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*Electrodiagnostic studies

Date __/__/__ attach

CASE FOLLOW-UP:

Was case seen 60 days after onset of paralysis? yes ___ date __/__/__ no ___

If no, why not?

Paralysis:

Paralysis present at 60 days or later? yes ___ no ___

If yes, check site of paralysis:

left leg
left arm
right leg
right arm

*from maximal weakness to follow-up

*improved: no ___ yes ___ if yes, comment on degree

*no change: no ___ yes ___
Reflexes (3 = increased; 2 = normal; 1 = decreased; 0 = absent)

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
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<tbody>
<tr>
<td>biceps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>triceps</td>
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<tr>
<td>supinator</td>
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<td></td>
</tr>
<tr>
<td>knee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ankle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babinski</td>
<td>up</td>
<td>down</td>
</tr>
</tbody>
</table>

Disability:
- cannot walk: __________
- limps: __________
- other: __________
  - walks with assistance: __________
  - walks normally: __________

Did case die? yes __________ no __________

If yes, give details:

Report of neurologist:

(Attach if available, summary of neurologist's report including final diagnosis)

Date __/__/__ Name of reporting physician __________

Neurologist? yes __________ no __________

CONTROL MEASURES:

(include the date started, number of households searched, number of OPV doses given in children less than 5 years of age, date completed)

FINAL DIAGNOSIS:

Discarded: __________

Specify diagnosis:

*poliomyelitis
*GBS
*transverse myelitis
*traumatic neuritis
*other, describe

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<thead>
<tr>
<th></th>
<th>yes</th>
<th>no</th>
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</table>
If polio, confirmed:

Check all which apply:

___ Laboratory confirmed - virus
___ Laboratory confirmed - serology
___ Laboratory confirmed - virus and serology
___ Residual paralysis after 60 days
___ Wild virus indigenous
___ Death after compatible illness
___ Epidemiologic linkage
___ No follow-up
___ Vaccine associated
___ Imported

Observations:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

SIGNATURE:

Name of investigator: __________________________
Signature: __________________________
Title: __________________________
Place of Work: __________________________
Date:  __/__/__

Name of Surveillance Coordinator: __________________________
Signature: __________________________
Title: __________________________
Place of Work: __________________________
Date:  __/__/__
Appendix III: Detailed Clinical Criteria for Poliomyelitis, GBS and Acute Transverse Myelitis

The following descriptions of the most common causes of AFPs were prepared to serve as the basis for the recommended protocol for field use. These case descriptions also make it clear that much work remains to be done in delineating the causes of AFP, reliably distinguishing acute anterior poliomyelitis from other causes of AFP, and in developing the surveillance systems that will provide a clearer picture of the epidemiology of these disorders.

1. Acute anterior poliomyelitis

Acute anterior poliomyelitis (polio) is a disease that gives rise to localized or widespread destruction of motor neurons in the spinal cord and brainstem. It is characterized by the appearance of flaccid paralysis of the muscles supplied by the affected motor neurons. It is most commonly caused by infection with the poliovirus, but can also result from other viral infections.

This terminology may be confusing and it should be emphasized that acute anterior poliomyelitis is not equivalent to infection with poliovirus, although this is the most frequent etiology.

Poliovirus

Three antigenically distinct types of poliovirus have been identified. All three can cause viral meningitis or paralytic polio, but type 1 appears to be most often associated with paralytic disease.

Prodromal symptoms follow, in the majority of symptomatic cases, an incubation period of 7-14 days. These symptoms - fever, headache, vomiting, and diarrhea - are followed in 1-to-3 days by symptoms related to the nervous system, including headache, irritability or drowsiness, back pain, and muscle tenderness. Pyrexia (38-40°C) is usually present. Neck stiffness and positive Kernig and Brudzinski signs are common. The flaccid paralysis is characteristically asymmetric and may be localized, such as to a single limb. In severe cases, the respiratory muscles may be affected. The paralysis usually reaches its maximal extent within 4-5 days and does not advance for more than 9 days. Sensation is normal. The CSF shows a high leukocyte count, but this may return to normal within a few days after onset of weakness. There is a normal or moderately elevated protein content; the elevation may be delayed.

A diagnosis of poliovirus infection is confirmed when a suggestive clinical picture is validated by isolation of the wild type poliovirus from fecal specimens from the patient or his or her immediate contacts.

Other neurotropic viruses

Poliomyelitis may occasionally occur as a consequence of infection by a variety of viruses other than poliovirus. These include coxsackie virus, echoviruses, and enteroviruses 70 and 71.

Enterovirus 70 causes epidemics of acute hemorrhagic conjunctivitis (AHC), which initially occurred in Asia and Africa. More recently, outbreaks of AHC have occurred in Latin America and southeastern USA. Neurologic abnormality develops in about 1 in 10,000 or 15,000 cases of AHC, primarily in adults. The most common neurologic picture is a flaccid, asymmetric, and proximal paralysis of the legs.

2. Guillain-Barré syndrome (GBS)

GBS connotes a peripheral neuropathy of acute onset recognized by a series of descriptive features and by the exclusion of other known causes of neuropathy. GBS is often considered unusual in children. However, in Latin America and in China, GBS as clinically defined, is the most frequent diagnosis made in children with AFP.
As originally described by Guillain, Barré, and Strohl in 1916, the disorder was recognized by clinical and spinal fluid criteria without knowledge of the physiology or pathology. Therefore, neither the underlying pathophysiology nor its structural basis were implied. The term as now used mainly connotes a demyelinating neuropathy with a presumed immune pathogenesis, synonymous with acute inflammatory demyelinating polyneuropathy. This view has been made explicit in the full criteria for diagnosis promulgated by the US NINDS (Asbury et al., 1978). The presence of demyelination is in most cases inferred from electrodiagnosis, and specific electrodiagnostic criteria for the diagnosis of acute demyelinating GBS are part of the full NINDS criteria.

However, for use in poliomyelitis surveillance this approach is unsatisfactory for at least two reasons. First, for many cases only clinical data will be available; such cases will not have spinal fluid analysis, electrodiagnosis, or pathology. Second, it is clear that many cases fulfilling the clinical criteria for GBS have a predominantly axonal motor neuropathy (McKhann et al., 1991; McKhann et al., 1992).

This report, therefore, uses the following terminology. Cases fulfilling the clinical criteria of the NINDS are referred to under the umbrella term, "GBS clinically defined." Cases with electrodiagnostic or pathologic criteria for demyelination are called "demyelinating GBS." Other physiologic patterns are identified descriptively: examples include "axonal GBS" (Feasby et al., 1986) and the acute motor axonal neuropathy pattern identified in northern China (McKhann et al., 1991; McKhann et al., 1992). In other words, GBS clinically defined is not a diagnosis, but rather a syndrome that undoubtedly includes disorders of diverse etiology, pathogenesis, and response to therapies. When possible, further delineation of cases included as "GBS clinically defined" will provide more satisfactory diagnosis, and is encouraged.

This approach will be especially valuable in delineating the causation of the diseases subsumed under the rubric "GBS clinically defined" (Thomas, 1992) (see also Table 1).

The clinical criteria promulgated by the NINDS were intended for field work and research case ascertainment; the recent experience in Latin America has demonstrated that they are serviceable in poliomyelitis surveillance. These criteria for a diagnosis of "GBS clinically defined" are presented here in an abridged form, with comments relevant to the specific problems of poliomyelitis surveillance.

I. Features Required for Diagnosis

A. Progressive motor weakness of more than one limb.
B. Areflexia (loss of tendon jerks)

II. Features Strongly Supportive of the Diagnosis

A. Clinical features (ranked in order of importance)
1) Progression: Symptoms and signs of motor weakness develop rapidly but cease to progress by four weeks into the illness.
2) Relative symmetry: Symmetry is seldom absolute, but usually, if one limb is affected, the opposite is as well. Comment: Minor subjective asymmetry at onset is frequently described by patients but on examination relative symmetry is the rule. Conversely, at onset, poliomyelitis may appear rather symmetric, but when fully evolved and especially during recovery most cases are asymmetric.
3) Sensory symptoms or signs: Comment: Objective sensory findings are not seen in polio.
4) Cranial nerve involvement: Facial weakness.
5) Recovery: It usually begins two to four weeks after progression stops, but may be delayed for months. Most patients recover functionally. Comment: Many patients retain findings at 60 days, and a smaller proportion have muscle atrophy.
6) Autonomic dysfunction: Tachycardia and other arrhythmias, postural hypotension, hypertension, and vasomotor symptoms, when present, support the diagnosis.
7) Absence of fever at the onset of neuritic symptoms. Comments: A few cases have fever at onset due to intercurrent infections or other causes. Fever does not exclude GBS but raises concern about polio.

B. Variants (not ranked)
1) Severe sensory loss with pain.
2) Progression beyond four weeks. Occasionally, a patient's disease will continue to progress for many weeks longer than four or the patient will have a minor relapse.
3) Cessation of progression without recovery or with major permanent residual deficit remaining.
4) Sphincter function: Usually the sphincters are not affected, but transient bladder paralysis may occur during the evolution of symptoms.
5) CNS involvement: Ordinarily, GBS is thought of as a disease of the peripheral nervous system. Evidence of CNS involvement is controversial. In occasional patients, such findings as severe ataxia interpretable as cerebellar in origin, dysarthria, extensor plantar responses, and ill-defined sensory levels are demonstrable and these need not exclude the diagnosis if other features are typical.

C. Cerebrospinal fluid features strongly supportive of the diagnosis
1) CSF protein: After the first week of symptoms, CSF protein is elevated or has been shown to rise on serial lumbar punctures.
2) CSF cells: Counts of 10 or fewer mononuclear leukocytes/mm in CSF. Comment: The CSF has normal or only slightly elevated cell counts; in most cases the count is below 10/mm³. For surveillance, any case with more than 20 cells should be reviewed especially closely, and the diagnosis should be excluded by more than 50 cells. Two specific exceptions occur in individuals with HIV infection and with Lyme borreliosis. The CSF protein content is typically elevated, as noted below, but it may be normal, particularly in the first week. It should be noted however that in polio, an elevated protein content without cells can occur after the first few days of weakness. Thus, elevated protein neither establishes the diagnosis of GBS nor excludes polio.

D. Features casting doubts on the diagnosis
1) Marked, persistent asymmetry of weakness.
2) Persistent bladder or bowel dysfunction.
3) Bladder or bowel dysfunction at onset.
4) More than 50 mononuclear leukocytes/mm³ in CSF.
5) Presence of polymorphonuclear leukocytes in CSF.
6) Sharp sensory level.

E. Features that exclude the diagnosis
1) A current history of hexachloride abuse of volatile solvents, for example, n-hexane and methyl n-butyl ketone; This includes inhaling paint lacquer vapors or addictive glue sniffing.
2) Abnormal metabolism indicating a diagnosis of acute intermittent porphyrin. This would manifest as increased urinary excretion of porphobilinogen and α-aminolevulinic acid.
3) A history of recent diphtheria infection.
4) Features clinically consistent with lead neuropathy (upper limb weakness with prominent wrist drop, may be asymmetrical) or evidence of lead intoxication.
5) The occurrence of a purely sensory syndrome.
6) A definite diagnosis of a condition such as poliomyelitis, botulism or toxic neuropathy (e.g. from nitrofurantoin, dapsone, or organophos-phorus compounds) which occasionally may be confused with GBS.

Antecedent events do not appear as criteria for GBS, but their prevalence is well known. Among the antecedent events most relevant to poliomyelitis surveillance in children are infection with EB virus (infectious mononucleosis), CMV and other herpes viruses, Campylobacter jejuni infections, and recent vaccinations against rabies with the Semple or suckling mouse brain vaccines.
In summary, the clinical and laboratory features most important in the distinction from poliomyelitis are the absence of fever at onset in most cases, the relatively acellular CSF, and the relative symmetry. In addition, age can be used as an adjunctive feature in discrimination; GBS in all parts of the world is extremely rare under one year of age, whereas in some settings up to 20% of poliomyelitis may occur in this group. When electrodiagnosis is possible, it provides additional information; for example, identification of a demyelinating pattern of neuropathy or of significant abnormalities of sensory nerve conduction exclude the diagnosis of polio. As discussed elsewhere in this report, the converse is not true; it is now clear that many children with purely motor neuropathies characterized physiologically by evidence of axonal degeneration in motor fibers, and by early appearance of denervation potentials, occur in cases of GBS as clinically defined. Thus, this pattern cannot be taken to establish the diagnosis of polio.

3. Acute transverse myelitis

Finally, acute transverse myelitis is mentioned briefly. This is a clinical syndrome with a wide variety of causes and characterized at onset by AFP or tetraplegia, loss of tendon reflexes, a sensory level, and a variable degree of bladder and bowel involvement. In the acute stage, it may be difficult to distinguish from poliomyelitis and GBS. The initial flaccid paralysis is however, replaced within days or weeks by spastic weakness with increased tendon reflexes and extensor plantar responses. Recovery is variable, depending on the severity of the spinal cord damage.

***