REVIEW ARTICLE

CHILDHOOD GUILLAIN-BARRE SYNDROME

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Abstract

Objective

The Guillain-Barre syndrome (GBS) is characterized by the acute onset of rapidly progressive, symmetric muscle weakness with absent or decreased deep tendon reflexes. GBS is the most common cause of acute flaccid paralysis in childhood, with an incidence of 0.6-4 per 100 000 population per year. The clinical features are distinct and obtaining patient's history and conducting an examination generally lead to the diagnosis that can be confirmed by supportive laboratory tests and electrodiagnostic studies. The major considerations in differential diagnosis include transverse myelities, toxic neuropathy, tick paralysis, infantile butolism and myasthenia gravis. Although most children with GBS have a relatively benign clinical course, some become quite ill and require intubation with intensive care monitoring .Immunomodulating treatment should be used for any child who loses the ability to walk.

Key words: Guillain-Barre syndrome, acute flaccid paralysis, childhood

Background

Guillain-Barre Syndrome (GBS) is an acute inflammatory polyneuropathy, most commonly characterized by rapidly progressive, essentially symmetric weakness and areflexia(1). Since the marked decline in poliomyelitis incidence, GBS has become the most common cause of acute flaccid paralysis in children. There is no distinctive test to confirm the diagnosis of GBS, and there is considerable heterogeneity in the presentation and clinical course. Further, variants of the disease have emerged to make GBS a true syndrome rather than a specific disease.

Epidemiology

GBS, reported worldwide, involves both genders and all ages. The incidence of typical GBS has been reported to be between 0.6 and 4 cases per 100000 population per year across the world (2), the incidence for children under 15 years being similar to that of adults. In a report from the northwest of Iran, the incidence rate was 2.27 per 100000 population of ≤ 15 years children (3). While the syndrome occurs at all ages, it predominantly affects children aged 1- 5 years (4-5). Although there are documented cases of GBS in newborns, the syndrome is rare in infants (6). There is a slight male predominance with male to female ratio of 1.5:1. Most cases of the syndrome occur sporadically; however occurrence of epidemic clusters of GBS has also been described. The motor axonal form of GBS occurs in epidemics during summer in northern China and predominantly affects children probably by

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campylobacter jejuni infection (7). An unexpectedly high incidence of GBS was reported in 2003 in the northwest of Iran (3). Serological evidence of recent campylobacter jejuni infection was found in about half of children with GBS in the same region (8).

Approximately half to two thirds of patients are reported to have a preceding illness, most commonly upper respiratory tract infection or gastroenteritis, within 4 weeks period before the onset of the GBS symptoms. Numerous case reports and descriptions of large series have implicated a plethora of different infections and other events as possible antecedents of GBS. Evidence from case-control studies has suggested the role of campylobacter jejuni, cytomegalovirus, Epstein-Barr virus, Mycoplasma pneumoniae, rabies vaccine and "swine flue" vaccine (9,10).

Pathophysiology

The Guillain-Barre syndrome is believed to be an autoimmune disorder based on T-cell activation with production of antibodies. Infectious agents such as Epstein-Barr virus, cytomegalovirus, mycoplasma pneumoniae and campylobacter jejuni, immunizations, surgery or parturition may trigger formation of such antibodies. Although most such antibodies are directed at myelin proteins, in some cases axonal moieties may be the primary target of immune-mediated nerve injury. Thus, while GBS is commonly known as acute inflammatory demyelinating polyneuropathy (AIDP), the primary pathologic process of this condition is axonal injury in many cases (i.e. in the GBS variants acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN)).

Specific nerve antigens have been implicated in a number of subtypes of GBS. The involvement of the cranial nerves in Miller-Fisher syndrome and polyneuritis cranialis, relates to development of antibodies to the ganglioside GQ1b, a glycolipid expressed on the axolemmal membrane of cranial nerves (11). Axonal GBS after campylobacter jejuni infection is usually mediated by antibodies to the GM1 ganglioside (12).

Antibody-mediated demyelination leads to mononuclear infiltrates around the endoneurial vessels and vesicular myelin degeneration. This demyelination may be discrete or diffuse and may affect the peripheral nerves at any point from their origin in the spinal cord to the neuromuscular junction. The muscle weakness in GBS results from conduction block and concomitant or primary axonal injury in the affected motor nerves. Pain and paresthesias are the clinical correlates of sensory nerve involvement.

Clinical features

The major clinical features are progressive muscle weakness and diminished deep tendon reflexes with symmetric distribution. Weakness typically starts in the lower extremities and ascends into the upper within days to weeks. In a significant proportion (15-20 %) of cases, weakness is primarily proximal; fifty percent of affected children reach the nadir of weakness by one week, 80% by 2 weeks, and over 90% by 3 weeks. By arbitrary definition, all children with uncomplicated GBS will reach their maximum level of weakness by 4 weeks from onset (13). In most cases, all deep tendon reflexes are eventually abolished, often early in the illness (13,14). Occasionally the proximal reflexes can be retained and rarely, in otherwise typical cases, can the reflexes be preserved throughout the illness. Although weakness is the hallmark of the disease, sensory disturbances are also quite common, as are neuropathic pain and dysesthesia. Back, buttock or leg pain which is presumed to result from nerve root and peripheral nerve inflammation is the initial manifestation in about 50% of children (13). This pain, often poorly organized, may cause marked irritability and discomfort. The diagnosis of GBS should always be considered in small children presenting with pain and decreased movement or refusal to bear weight and when testable, position and vibratory sensations are diminished. The weakness, sensory loss, and pain, whether alone or together, often present as a gait disturbance with an ataxic component out of proportion to the muscle weakness. GBS should be considered in any child who has an acute gait disturbance. Some cases of pediatric GBS present as the Miller-Fisher variants of ataxia, ophthalmoplegia and areflexia without peripheral weakness.

Other less common clinical features include cranial nerve involvement with facial weakness, difficulty in swallowing, and occasionally involvement of the cranial nerves that control ocular movements. Cranial nerve

involvement was observed in about 30-46% of patients (3,4,15). Autonomic dysfunction may occur in GBS accounting for some of the fatalities in the condition. Presentations of autonomic involvement are disturbances of sweating, heart rate and rhythm, blood pressure control, sphincter, visceral and pupillary function (16). Rarely are these symptoms the primary manifestations of childhood GBS (13).

As described above, the clinical presentation is remarkably variable. Therefore, the diagnostic criteria so far suggested for GBS, do not encompass the full spectrum of this disorder. It is important to note that diagnosis is based on consistent confirmed clinical, laboratory and neurophysiologic findings with exclusion of other diseases (table 1).

GBS has three stages, including a progressive phase lasting over several days to several weeks, a plateau phase of similar duration, and finally the recovery phase, over weeks to months. The major complications occur in the first phase which does not persist beyond 4 weeks.

There are different forms of GBS defined by their clinical manifestations and variable involvement of motor and sensory axons of peripheral nerves (table 2). The most common of these forms in the western population is AIDP. There have been some reports on the incidence of the AIDP and axonal types in childhood GBS. The incidences of documented axonal pattern, were up to 65% in China, 40% in Japan. 30% in Argentina, 35% in Turkey, 31% in Pakistan , 10% in the North America and about 40% in Iran (15,17-22), findings that suggest the variable incidence of this type in childhood GBS among countries. The reason is still unknown; however different populations have different genetic backgrounds and different exposures to inciting pathogenesis with possible differences in subtypes.

The Miller-Fisher variant is characterized by ataxia, areflexia, and ophthalmoplegia. Some cases are limited to acute pandysautonomia, pure sensory loss, or regional (pharyngeal-cervical-brachial) weakness.

Laboratory tests

An elevated level of CSF protein without an increase in the number of cells, albominocytologic dissociation, is the cardinal laboratory finding in GBS, which was first described by Guillian, Barre and Strohl in 1916, and after whom this syndrome is named. The time of the measurement of the CSF protein is critical; approximately 50% of patients demonstrate an initial elevation of CSF protein if measured in the first week of the illness, while the majority shows an increase in this protein, if measured after the first few weeks of illness. CSF protein normally peaks between 80 and 200 mg/dL at some time during the illness. The constituents of the CSF protein are similar to those of plasma, although gamma globulins with oligoclonel bands may be present, suggesting intrathecal synthesis of immunoglobulin. The CSF protein is rarely above 500 mg/dL; hence higher levels require looking for other causes. The cell count is usually under 10 cells/mm^3. A finding of more than 50 cells/ mm^3 suggests other possible diagnoses, as does a predominance of segmented neutrophils. HIV positive patients have elevated cells compared to HIV-negative patients. CSF should be analyzed before treatment with intravenous immunoglobulin (IVIG) which can cause aseptic meningitis.

Neurophysiologic studies (nerve conduction studies and electromyography) are very helpful in confirming the clinical diagnosis, establishing prognosis and categorizing GBS into its various recognized subgroups. Peripheral nerve demyelination is reflected in slowing of nerve conduction, which tends to be more profound in younger children (13). Because these changes are patchy, testing of multiple nerves reveals a non-uniform increase in distal latencies, slowing of nerve conduction, conduction block, and dispersion of motor responses. Both severe demyelination and axonal injury cause loss of amplitude of motor and sensory responses. In the pure axonal forms of GBS, conduction velocities are preserved despite loss of amplitude of motor responses. The late responses (F and H waves) which examine both distal and more proximal segments of the peripheral nerves are often more sensitive for identification of mild slowing of nerve conduction. Electromyography reveals a loss of motor unit action potentials (decreased recruitment) at early phase in the illness. Changes of acute denervation (fibrillation potentials and positive sharp waves) are not usually apparent during the first 7-10 days of the disease course. Detailed neurophysiologic study enables definitive diagnosis of GBS in as many as 90% of cases during the first week of symptoms (23).

Changes are virtually universal by the second week of illness. Electrodiagnostic studies are painful and can technically be difficult in small children, and should generally be performed only by individuals having the expertise.

In a recent research in our center (Tabriz children's hospital) of 72 children with GBS, we had 8% normal findings, following electrodiagnostic studies in the first week, although the second study yielded abnormal results. Therefore it is strongly recommended to perform a second electrodiagnostic study in such cases. In this study the most common electrophysiologic abnormalities were low amplitude CMAP (97.2%) and abnormal F-waves (88.9%) (22).

Urgent spinal magnetic resonance imaging (MRI) should be undertaken in children with severe back pain, a sensory level or prominent sphincter dysfunction in order to exclude spinal cord compression. Gadolinium enhancement of the cauda equine and lumbar nerve roots have been demonstrated on spinal MRI in children with GBS (24). These findings are not specific to GBS and their sensitivity is not very well known. Nerve biopsy is virtually never required for diagnosis of pediatric GBS.

Differential diagnosis

The differential diagnosis of childhood GBS includes spinal cord tumours and transverse myelitis. Both may produce a rapidly progressive paralysis, hyporeflexia, and back pain. Sphincter dysfunction is common with spinal cord lesions, but relatively rare, and usually transient, in GBS. Transverse myelitis may be associated with marked elevation of the CSF protein and significant CSF pleocytosis. Although neurophysiologic studies are usually normal in transverse myelitis, there may be loss of F waves corresponding with the affected spinal level(s).

Tick paralysis causes an ascending quadriparesis that may progress after tick removal. All children living in in endemic areas should be searched for ticks if they present with gait unsteadiness and progressive weakness. Internal and external ophthalmoplegia are common in tick paralysis. On nerve conduction studies, tick paralysis causes temperature sensitive loss of amplitude of the motor responses. The CSF is usually normal in this condition.

Childhood botulism is uncommon but should also be considered in the differential diagnosis of progressive symmetric weakness in infancy. Botulism is suggested by pupillary abnormalities, ophthalmoplegia and early constipation. Myasthenia gravis occasionally presents with primarily proximal weakness in childhood. Repetitive nerve stimulation reveals characteristic abnormalities in both of these disorders.

Poliomyelitis and other enteroviral infections of the anterior horn cell cause acute focal and asymmetric limb weakness, usually in association with fever and pain. While nerve conduction studies reflect acute denervation without demyelination, CSF analysis shows a polymorphonuclear pleocytosis . A definitive diagnosis is achieved by serologic testing.

Management

Children with GBS should be admitted to hospital at beginning of sickness for monitoring. Although weakness and hypotonia may be relatively mild at onset, the potential for sudden, sometimes fatal, respiratory or autonomic compromise should always be anticipated.

Vigilant supportive therapy is vital in GBS and includes monitoring for respiratory and autonomic complications of this disorder in addition to pain management and prevention of complications of immobility (constipation, bed sores, contractures, and renal calculi). The vital signs and respiratory capacity should closely be monitored. Progression to mechanical ventilation is likely to occur in those patients with rapid disease progression, bulbar dysfunction, dysautonomia, inability to lift the elbows or head, vital capacity <60% and markedly attenuated (>80%) CMAP amplitude of the deep peroneal nerve (25,26). As many as 15- 20% of children require ventilatory support for acute GBS.

Blood pressure liability may be prominent, especially in very sick children. Hypertension should be treated only in symptomatic and extreme cases, because there may be marked sensitivity to antihypertensive agents. Pacing devices are rarely required for children with severe bradycardia. Some patients with severe GBS require treatment for gastroparesis, ileus and urinary retention.

Pain is commonly under recognized and undertreated in childhood GBS. Non-steroidal anti-inflammatory medications and neuropathic pain relieving agents (such as

gabapentin, carbamazepin and tricyclic antidepressants) are used. Corticosteroids may be effective in alleviating pain. Opioid analgesics are often required for adequate analgesia. It is not acceptable clinical practice to let a child suffer pain because of concerns for the potential respiratory effects of narcotics.

Physiotherapy should be initiated immediately after control of pain in childhood GBS and continued throughout the recovery period. Careful attention should also be paid to nutritional requirements of the patient because inadequate caloric intake may lead to muscle catabolism.

Treatment

Among available specific therapeutic interventions aimed at mitigating the harmful effects of the disturbed immune reaction, at present plasma exchange and intravenous immunoglobulin (IVIg) represent the mainstay of immunomodulatory treatment of GBS. Both treatments have proven to have beneficial effects in controlled trials, favorably altering the natural course of the disease. In a large group controlled trial, combination treatment with plasma exchange followed by IVIg did not provide additional significant benefit (27).

Intravenous immunoglobulin is generally preferred for treatment of childhood GBS. A total dose of 2 g/kg of IVIg is given over 2-5 days and is generally tolerated well at all ages.

Plasma exchange (PE) can be a safe and effective treatment of GBS for children weighing more than 10 kg. The PE regimens involved exchanging approximately one volume, 35-45 mL/kg, on five separate occasions over 1 to 2 weeks. (28).

Alternative techniques of immunoglobulin ultra filtration, such as CSF filtration and immunoabsorption, have been reported in small adult series, but have not yet been tried in children with GBS.

The role of corticosteroids in the treatment regime of GBS may have some changes in the future. In contrast to other autoimmune disease, steroids have no rational place in the treatment of GBS. However in a Dutch study the combination of IVIg and corticosteroids, compared with IVIg per se had a positive effect on early ambulation (29).

Prognosis

Children with GBS have a shorter clinical course and more complete recovery than adult. Mortality is low, and if occurs due to respiratory complications and fatal cardiac arrhythmias. Relapses are uncommon, and generally responsive to immunomodulatory treatment. A small percentage of children presenting with GBS later develop choronic inflammatory polyneuropathy (30, 31).

Table 1: Definition of Guillian- Barre syndrome (modified from Asbury and Cornblath) 1

I. Features required for diagnosis
- A. Progressive motor weakness of more than one limb
- B. Areflexia or marked hyporeflexia

II. Features strongly supportive of the diagnosis
- A. Clinical features
  1. Progression over days to a few weeks
  2. Relative symmetry
  3. Mild sensory symptoms or signs
  4. Cranial nerve involvement
  5. Recovery, usually begins 2- 4 weeks after progression stops
  6. Autonomic dysfunction
  7. Absence of fever at onset
- B. Laboratory abnormalities
  1. Elevated CFS protein (>45 mg/dl)after the first week of symptoms
  2. Abnormal electrodiagnosis with slowed conduction or prolonged F waves

III. Features casting doubt on the diagnosis
- A. Marked, persistent asymmetry of weakness
- B. Persistent bladder or bowel dysfunction
- C. Bladder or bowel dysfunction at onset
- D. More than 50 mononuclear cells/ µl in CFS (excluding HIV)
- E. Sharp sensory level

IV. Features that rule out the diagnosis
- A. Current history of hexacarbon abuse
- B. Abnormal porphyrin metabolism
- C. Recent diphtheritic infection
- D. Evidence of polio, botulism, toxic neuropathy, organophosphates poisoning, tic paralysis

Table 2: Clinical spectrum of Guillian- Barre syndrome (GBS)

Acute inflammatory demyelinating polyneuropathy (AIDP)
Acute motor axonal neuropathy (AMAN)
Acute motor and sensory axonal neuropathy (AMSAN)
Miller- Fisher syndrome (MFS)
Polyneuritis cranialis
Pharyngeal- cervical- brachial syndrome
Acute sensory neuropathy of childhood
Acute pandysautonomia

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