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Guillian Barre Syndrome

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Abstract

Guillian Barre syndrome is most common cause of rapidly progressing paralysis in children in most countries. It is charachterized by rapidly progressing weakness, often symmetric with relative paucity of sensory symptoms. It often follows upper respiratory tract or gastrointestinal infections and has been associated with a variety of other systemic disorders. Intravenous immunoglobulin therapy and plasma exchange hasten recovery and have greatly reduced the mortality and morbidity. Studies on pathogenesis demonstrate that antibodies against myelin components and macrophages play a major role in causing injury to the myelin or axons.

Keywords: Childhood polyneuropathy; Demyelination; Ganglioside antibodies; Plasmapheresis; Plasma exchange.

Introduction

Guillian Barre Syndrome (GBS) is the most common cause of rapidly progressing paralysis in children and adults. There are few other emergencies that call for rapid and organized approach to diagnosis and management. Mortality from Guillian Barre syndrome was 20 to 30% and much of the reduction in mortality is the result of improvement in management of the critically ill in the Intensive care setting and prompt implementation of supportive and disease modifying therapy. In this paper, we will discuss the clinical features of Guillian Barre syndrome, differential diagnosis and orderly evaluation and management.

Background

Acute paralytic weakness was recognized in 1800's and Landry described 5 patients with the syndrome of acute onset and rapidly progressing weakness, which was referred as Landry's paralysis. Guillian, Barre and Strohl in 1916 described the value of lumbar puncture and cerebrospinal fluid analysis in differentiation from acute poliomyelitis from this disease. Haymaker described the pathology of nerves in these patients and showed it being an acquired inflammatory disorder.[18]

Acute Guillian Barre syndrome affects individuals of all ages, however there are two periods of higher incidence, between 12 and 18 years and another peak in middle aged individuals. The illness occurs sporadically with seasonal increase in number of cases. The incidence of GBS is higher during fall and early winter coinciding with the seasonal increase in viral infections in general. GBS occurs during the early stages of HIV infection and the CSF in these patients can show increase in WBC in CSF.[8] Infections with cytomegalo virus, Ebstein Barr virus and Mycoplasma pneumonia have been associated with sporadic cases of GBS. Sporadic increase has also been seen during immunization campaigns, and with large outbreaks of infectious diseases. GBS also occurs after trauma, surgery and is associated with malignancies and medications.

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Pathogenesis and Pathology

The work of Haymaker and colleagues showed that GBS was an inflammatory disorder. The association of preceding infections in majority of patients and the disease modifying effect of immunosuppressive therapy [9,16,17] suggests an autoimmune etiology for GBS.

In majority of instances GBS follows a prodrome, usually infections of respiratory or gastrointestinal tract. Antibodies to gangliosides GMI, GM2 and asialogangliosides are present in variable number of patients. Pathological studies on peripheral nerves of patients with GBS show focal areas of demyelination. Post mortem examination of patients who died from GBS shows endoneurial and perineural infiltration with mononuclear lymphocytes with severe axon damage and loss. Dorsal root and autonomic ganglia in these patients show dense lymphocytic infiltration. The lymphocytes are CD4 and killer cells with macrophages.[1,2,4, 10,11,28]

Feasby and colleagues brought attention to axonal form of GBS. These patients have axonal injury to sensory and motor axons and often have severe weakness. The clinical course is one of slow and incomplete recovery with significant residual weakness. These patients are often older and have prolonged clinical course in ICU. This form is very infrequent in children.

The Miller Fisher variant is characterized by occurrence of oculomotor weakness, cerebellar ataxia with areflexia. The weakness is relatively minimal in these patients. Antibodies to ganglioside GQ1B is present in majority of these patients. GQIB ganglioside is present in large amounts in neurons of Oculomotor nuclei and cerebellum.

Studies by Griffin and colleagues on patients who developed GBS after Campylobacter jejuni infections have elucidated the pathways of myelin and axon destruction. In patients with acute inflammatory demyelinating polyneuropathy following Campylobacter jejuni infections, antibodies against the lipopolysaccaharide toxin of the Campylobacter jejuni cross-reacts with ganglioside epitopes on myelin sheaths at the nodes of Ranvier. The molecular similarities in the ganglioside moieties between the LPS toxin of Campylobacter jejuni and peripheral myelin is felt to be responsible for the cross reactivity of the antibodies. The antibodies especially IgG moieties bind to myelin epitopes with complement and activate the complement cascade and through the membrane attack complex produce vesicular damage to the myelin folds. The activated complement recruit macrophages, which participate in myelin stripping and digestion of myelin.[14,15]

The demyelinated axon segments have a paucity of sodium channels on the surface of axons and hence are incapable of efficient conduction of the action potential. This results in failure of conduction and causes weakness or numbness in the affected area. In more severe cases there are infiltration of the nerve with mononuclear inflammatory cells and causes axonal damage of sensory and motor axons. These changes occur at multiple sites along the course of the nerve. This results in weakness and sensory loss, often severe and the recovery generally is poor with significant residual weakness. This is more frequent in elderly patients presenting with GBS.

The pathological changes seen in these patients with severe attacks of GBS are very similar to those seen in Lewis rats with allergic experimental encephalitis, triggered by immunization with peripheral myelin and Freund's antigen.

The pure axonal form of GBS is characterized by axon damage with relative sparing of myelin. The prognosis for recovery is good. This form is frequently associated with Campylobacter jejuni infection.[25,26,27] The cross reacting antibodies against gangliosides in response to the Campylobacter jejuni infection bind to the inner layers of myelin, known as adaxonal layer by entering through the incisural lines on myelin sheath. This results in directed injury to the axons and usually occurs at the distal end of motor axons.

The axon at the affected segment undergoes Wallerian degeneration and then followed by regeneration. Since the injury occurs at the distal ends of motor axons, sprouting of axons is usually rapid with rapid recovery. [13,14,15,19]

Clinical Presentation

Weakness, numbness and pain are the principal symptoms in patients with GBS. Weakness is by far the most prominent clinical presentation and often begins distally and progresses upwards. The weakness may start in the feet, however often weakness in proximal muscles of the lower limb leads to seeking medical care. The weakness initially can be mild and difficult to measure objectively and in several instances these patients may be considered as having functional disease. Especially in young children detection of weakness can be a challenge. They may present with chief complaints of refusing to bear weight in their legs. The detection of weakness can be difficult. The causes for toddlers refusing to bear weight is extensive ranging from focal painful lesion in feet to ataxia, to weakness to painful lesions in abdomen, pelvis, spine and cranium.

Weakness usually progresses in a few days to involve the arms, cranial muscle and muscles of respiration. The rate of progression can sometimes be very rapid with the evolution from leg weakness to respiratory failure occuring in hours. The nadir of the illness occurs in a few days and rarely beyond 4 weeks. Weakness infrequently can be most prominent in proximal muscles of upper limbs and patients may present as "man in a barrel".

Sensory complaints are almost always present although less prominent in the face of spreading muscle weakness. Numbness usually begins in the feet and spread proximally. Loss of proprioception can be detected and patients experience loss of balance and this contributes further to gait difficulties. Pain is present almost always and usually vague and widespread. Band like pain across trunk is common and can be confused with myelopathic disorders. Pain in some instances can be severe and need opiod medications to control it.

Changes in tendon reflexes are the most objective and reliable findings on neurological examination. Tendon reflexes are initially hypoactive and then are absent. However, normal tendon reflexes does not exclude the diagnosis of GBS.[3,4,7,33]

Autonomic function is affected in these patients to variable degree. The severity of autonomic disorder is proportional to the severity of weakness. Patients who are intubated for respiratory failure will almost always have autonomic dysfunction. The autonomic dysfunction involves the sympathetic and parasympathetic systems and can be as a result of overactivity or underactivity. Sympathetic overactivity is more common and can result in tachycardia, cardiac tachyarrhythmia and hypertension. Episodes of acute hypertension, profuse sweating and tachyarrhythmia can occur. Similarly episodes of hypotension and bradyarrythmias can occur. Heart block of varying degree including third degree heart blocks can occur. Parasympathetic dysfunction can lead to gastroparesis, ileus, and pseudo obstruction. Bladder dysfunction occurs in greater than 25% in the form of urinary retention and overflow incontinence. Constipation is frequent. Urinary retention and constipation can trigger episodes of acute hypertension, tachycardia and other signs of sympathetic overactivity.

Changes in cerebrospinal fluid are the most prominent changes on laboratory studies. The CSF shows increase in protein with normal glucose and normal cell count. The CSF changes can take up to 2 to 3 weeks to occur. The absence of CSF abnormalities at presentation will not exclude the diagnosis. [3]

Electrodiagnostic studies are abnormal frequently. The changes in electrodiagnostic studies are variable. The earliest changes are prolongation and/or absence of F waves and

prolongation of distal motor latencies. Later the motor compound muscle action potentials are reduced in size. Conduction blocks in motor nerves represents areas of acute demyelination. Slowing of conduction velocity of motor and sensory nerves occurs later in the course. The findings on electrodiagnostic studies are helpful in differentiating the subtypes of Guillian Barre syndrome and are helpful to determine the prognosis. Inexcitable motor nerves and evidence of axonal degeneration is associated with significant motor weakness and sensory deficit.[4,5,33] (Table 1)

Differential Diagnosis

With eradication of poliomyelitis all over the Globe, GBS remains the most common cause of acute paralysis all over the World. Acute myelopathies, exposure to toxins and chemicals, Lyme disease, and metabolic diseases such as porphyria remain the major disorders, which can simulate GBS. Poliomyelitis like syndrome can occur with infections from enteroviruses and West Nile virus and can be difficult to differentiate in the early stages of the illness.

Acute myelopathies presents with weakness and sensory loss with pain. The weakness can progress, especially in myelopathies from mass lesions in the spine, infections in the spinal cord, autoimmune inflammation and vascular disorders. In the acute stages tendon reflexes are absent. Presences of sensory level, early onset of bladder and bowel dysfunction are indicators of myelopathy. The distinction of acute myelopathy form GBS can be difficult in the early stages. Presence of cranial nerve dysfunction favors diagnosis of GBS. When myelopathy cannot be excluded with certainty, magnetic resonance imaging of the spine should be performed before lumbar puncture is done.

Evenomation from toxins of different kinds can produce acute paralysis. Botulinum toxin intoxication occurs form consumption of contaminated food and presents with muscle weakness and areflexia. Bulbar dysfunction is prominent with chlolinergic dysfunction-dilated pupils, dry mouth, constipation and bowel dysfunction. The CSF shows no abnormalities. Electrodiagnostic studies show a reduced motor CMAP and incremental response on tetanic stimulation.

Table 1: Supportive evidence for diagnosis [4,5]

Clinical features	Symptom progression Relative symmetry in paresis Mild to moderate sensory signs Frequent cranial nerve involvement Most common is bilateral 7th; however, others can be involved Autonomic dysfunction Recovery beginning 2-4 weeks after a plateau phase Preceding GI or upper respiratory infection
CSF findings	Elevation of CSF protein CSF cell counts are <10 mononuclear cell/mm3
Electrodiagnostic testing	80% will have evidence of slowing/conduction block Patchy reduction in NC velocity with values less than 60% Distal motor latency increase to as much as 3x normal F-waves indicate proximal velocity slowing 15-20% of patients will have normal nerve conduction studies No abnormalities on the NCS may be seen for several weeks
Findings reducing the possibility of diagnosis	Asymmetric weakness Failure of bowel/bladder symptoms to resolve Severe bowel/bladder symptoms at initiation of disease Sensory level Greater than 50 mononuclear cells/mm3 in CSF Exclusion criteria Diagnosis of other neuromuscular diseases Involvement of nerve root with other pathology

Tick paralysis in children can be difficult to differentiate from GBS. Tick paralysis presents with rapidly progressing muscle weakness beginning in the lower limbs. Reflexes are usually reduced or absent. The weakness can rapidly progress to respiratory failure. CSF findings are normal. Electrodiagnostic studies shows reduced motor CMAP and mild increase in size of CMAP with tetanic stimulation. The diagnosis in the emergency department is made by identifying tick attached to the patient, usually at the nape of neck.[34]

Lyme disease is a rare cause of radiculo polyneuropathy in children. Acute syndrome consists of meningismus and radicular pain and asymmetric weakness with hypo/areflexia. The cerebrospinal fluid shows increase in WBC usually lymphocytes with elevation in CSF protein. The presence of pleocytosis differentiates it from GBS. The diagnosis is made on serological studies.

Bites by snakes producing neurotoxic venom can cause progressive muscle weakness with hypo/areflexia and can lead rapidly to respiratory failure. Presence of ptosis, paralyses of extraocular muscles are prominent with signs of bulbar dysfunction. History of snakebite and presence of bite marks help confirm the diagnosis.

Arsenic toxicity has many similarities with GBS. Nausea and vomiting are common and then develop weakness, which is more prominent in proximal muscles. The reflexes are impaired or lost. However, severe pain especially burning type is common. Evidence of liver dysfunction is common. Examination of nails often reveals Mee's lines-white opaque lines in nails and represents time of exposure to arsenic. Toxicity from lead is considered in patients with GBS who present with predominantly motor weakness. The weakness is usually seen extensor muscles of upper and lower limbs in the form of writs and foot drop. Dark lines may be seen in gums and red blood cells may show basophlic stippling.

Myasthenia gravis in children can result in rapidly progressing muscle weakness. Oculomotor weakness and bulbar muscle weakness is prominent. The rapidly progressing weakness may be the initial presentation or be from acute worsening triggered by infections, medications, and electrolyte disorders hypo/hyperthyroidism or menstruation.

Management

Management of these patients should start concurrently with evaluation. The management will be discussed in steps along with steps in evaluation.

These patients need rapid triaging in the emergency department.

The vital signs need to be evaluated and specifically their airway, breathing and circulatory status need to be evaluated. The patency of airway should be assessed and if there is any obstruction suction needs to be done. If there is any concern about airway patency, intubation must be done to secure the airway. Breathing needs to be assessed and this can be done easily in older children. Forced vital capacity should be measured at bedside and monitored frequently. FVC measures the total amount of air that can be exhaled and is a measure of the lung capacity and strength of expiratory muscles. Normal FVC is 70-ml/kg and cough is ineffective when FVC drops below 20 ml/kg. FVC below 10 ml /kg indicates the need for intubation and mechanical ventilation. (See Table 2) Negative

Table 2: Bedside Pulmonary Mechanics

Vital capacity	Normally over 60 ml/kg
At 30-35 ml/kg cough is compromised	Initiate chest PT
25-30 ml/kg: atelectasis risk	Initiate intermittent positive pressure breathing
15-20 ml/kg: atelectasis and shunting	Intubate electively and initiate mechanical ventilation
10 ml/kg	Hypoventilation and hypercapnea
5-10ml/kg	Hypercapnea and hypoxia

inspiratory force (NIF) is a measure of strength of muscles of inspiration. Normal NIF is greater than 60 cm of water. NIF below 30 cm of water indicated need for imminent intubation. The pulmonary mechanics should be measured with patient sitting if possible and should give maximal effort.

Circulatory system needs to be evaluated by measuring blood pressure and peripheral pulses. Blood pressure needs to be measured in supine and standing position to evaluate for orthostatic intolerance, if possible. Presence of tachycardia and increase in heart rate with standing is often from contraction of blood volume. Management of low blood pressure will need fluid resuscitation.

The evaluation of airway, breathing and circulatory status should be done before neurological and physical examination is done. Laboratory studies are to be done after the vital functions are measured and stabilized.

Patients diagnosed with GBS should be admitted to Intensive care unit and vital signs and pulmonary function should be carefully and frequently measured. Alteration of respiratory function will need intervention as documented in Table 2.

Nursing Management

Good nursing care is paramount. These patients are weak and incapable of activities of daily living. Positioning of limbs is critical especially in patients who are quadriplegic, to prevent occurrence of secondary compressive neuropathies. These usually occur in median, ulnar and peroneal nerves.

Skin care is important and pressure ulcers should be prevented by frequent postural changes and use of air mattresses. Constipation should be prevented and they should be monitored for urinary retention and managed with catheterization. Constipation and urinary retention can trigger tachyarrhythmias and hypertension.

Careful monitoring of vital signs is important and vital signs including blood pressure, heart rate and respiration is to be monitored continuously.

Physical therapy should be started early, initially focusing on maintaining range of movement and preventing contractures.

About the illness, and the possibility of it getting worse and leading to intubation and respiratory assistance should be discussed in age appropriate fashion. Use of communication board should be initiated early and methods of communication established early between the nursing personnel and patients.

Disease Modifying Therapies

The prognosis of patients with GBS has vastly improved with the use of disease modifying therapies.[9,21] Plasmapheresis was started in 1980 and the various trials conducted in Europe and North America in the 1980's proved that plasmapheresis speeds recovery and thereby the attending complications of prolonged critical care. Plasma exchange of 250 ml per kilogram divided over 3 to 5 treatments is effective in shortening the course. Studies show the time to achieve ambulation in non-ambulatory patient is reduced by a significant degree. [12,21,29,30] Plasmapheresis is difficult to perform in young children, due to difficulties in getting vascular access. The complications in children include difficulty in getting vascular access, vascular access line infection and bleeding. Additional problems could arise from depletion of plasma proteins, hypocalcemia, bleeding as a consequence of depletion of coagulation factors.

High dose intravenous immunoglobulin, (HIG) 2000 milligrams per kilogram divided over 4 to 5 treatments is effective.[20,23,31] In trials comparing the effectiveness of plasmapheresis versus HIG, HIG was more effective than plasmapheresis. Variable response to HIG occurs with the dose of the standard dose of 2000 milligrams per kilogram dose and relapses can occur some of them. The study by the Dutch Guillian Barre treatment group shows that the rate of metabolism of immunoglobulin in an individual patient has a significant role in determining response and relapses. The endothelial cells metabolize

immunoglobulin molecules and the rates differ amongst individuals. Patients with rapid clearance of immunoglobulin are more likely to suffer from relapses and impaired responses. These patients would benefit from higher doses and repeated treatments.

HIG is associated with fever, headaches, and flu like symptoms. In rare circumstances, especially in older patients HIG can cause thrombosis in veins, renal arteries, coronaries and cerebral arteries. Aseptic meningitis, pleural and pericardial effusions have been reported with use of HIG. However, in children with GBS and impairment of ambulation HIG is the treatment of choice. Children who are ambulating may not need HIG treatment as long as they are carefully monitored for progression of e disease.[6]

Conclusion

Guillian Barre syndrome is the most common cause of acute and rapidly progressing weakness in childhood. The clinical features of progressing weakness and absent deep tendon reflexes are diagnostic and finding elevated cerebrospinal fluid protein with absence of pleocytosis supports them. The electrodiagnostic studies are useful to make the diagnosis, evaluate prognosis and differentiate the subtypes. Critical care and good nursing care has greatly reduced mortality and improved the prognosis. Disease modifying treatments with HIG or plasmapheresis shortens the disease duration and speeds recovery. Rapid and accurate diagnosis in the emergency department is crucial.

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