Pediatric Guillain-Barré syndrome

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Purpose of review
Guillain–Barré syndrome (GBS) is the most common cause of acute flaccid paralysis in children. This review discusses the heterogeneous presentations of this disorder, the frequency of disease-related complications and the importance of assiduous clinical care in pediatric GBS.

Recent findings
Recent reports have highlighted the variable clinical and neurophysiologic subtypes of pediatric GBS, and emphasized the value of imaging in diagnosis of this disorder.

Summary
Diagnosis of pediatric GBS is often delayed because of its variable presentation. Early recognition and treatment decrease long-term morbidity and mortality. Recent research has cast light on the variable presentations and pathogenesis of the numerous subtypes of this condition, and is now focusing upon a better understanding of the natural history of GBS.

Keywords
axonal, demyelinating, flaccid paralysis, Guillain–Barré syndrome, neuropathy, pediatric

INTRODUCTION

Guillain–Barré syndrome (GBS) is an acute inflammatory polyneuropathy characterized by rapidly progressive, essentially symmetric weakness and areflexia in a previously well child [1▪▪]. Weakness is usually distally predominant, at least at onset. Neuropathic pain is prominent in many affected children. GBS is the most common cause of acute flaccid paralysis in childhood. The variable incidence of GBS in different populations may reflect differential genetic susceptibility or exposure to causative pathogens [2].

CLINICAL FINDINGS

In 50–70% of cases, GBS develops 2–4 weeks after a prodromal gastroenteritic or respiratory illness [1▪▪]. Childhood GBS has never been proven to result from vaccination against poliomyelitis, tetanus or measles [3], but several recent publications have suggested a weak association between GBS and immunization against influenza A (H1N1) [4,5]. On balance, however, the small increase in risk of GBS after such immunizations is far outweighed by the risks associated with these infections [6].

Children with GBS usually complain of weakness and fatigue, paresthesia and pain, and have difficulty walking, arising from the floor or climbing stairs. Weakness is generally symmetrical, starting in the lower extremities then ascending into the upper extremities over days to weeks [7,8,9▪▪]. Neck, back, buttock or leg pain, presumed to result from nerve root and peripheral nerve inflammation, is the first symptom in as many as 50% of children with GBS. This pain is often poorly localized. Recognition of this symptom is especially important in young children in whom irritability and refusal to weight-bear is often initially ascribed to orthopedic or rheumatologic causes [8,10].

Ataxia – resulting from weakness and sensory loss – is very common in children with GBS. There are several recent reports of pediatric GBS presenting as the Miller–Fisher syndrome (MFS) variant, that is, ataxia, ophthalmoplegia and areflexia without peripheral weakness [9▪▪].

Respiratory muscle weakness in GBS is usually slowly progressive and tends to correlate with the degree of limb muscle weakness, but rare cases of pediatric GBS present with acute-onset respiratory failure, which can be life-threatening [11]. Such

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KEY POINTS

- GBS is the most common cause of acute flaccid paralysis in children.
- Recent publications on GBS have highlighted the variable clinical and neurophysiologic subtypes of pediatric GBS.
- MRI is used increasingly in diagnosis of adult and pediatric GBS.
- Current research is focusing on a better understanding of the natural history and treatment-responsiveness of the various subtypes of GBS.

severe cases should prompt consideration of an underlying genetic neuropathy [12].

A number of atypical presentations of pediatric GBS have recently been highlighted in the literature. Very rarely children with severe GBS present with quadriparesis, areflexia and respiratory failure, effectively 'locked-in': neurophysiologic studies show inexcitable peripheral nerves and the prognosis of such cases is poor [11,13].

Physical examination in GBS shows weakness and loss of the muscle stretch reflexes. Weakness usually begins in the legs and progresses rostrally, but can be proximally predominant at onset. The reflexes are usually lost in the first week of the illness, but are occasionally preserved. Interesting recent reports have highlighted rare cases of hyperreflexia in GBS, usually in patients with the acute motor axonal variant of this condition [14▪].

Autonomic involvement – manifesting as blood pressure instability, sinus tachycardia, pupillary abnormalities and abnormal sweating – is common and often underrecognized in pediatric GBS [9▪▪,15,16▪]. Autonomic instability and urinary incontinence are more frequent in atypical or focal forms of pediatric GBS [9▪▪]. Recent reports of headache and severe hypertension as initial manifestations of this disorder demonstrate the importance of considering GBS as part of the differential diagnosis of acute dysautonomia [17,18].

CLINICAL VARIANTS OF GUILLAIN–BARRE SYNDROME

The subtypes of GBS are defined by their variable involvement of peripheral nerve motor and sensory axons (Table 1). Acute inflammatory demyelinating polyneuropathy (AIDP), the classic form of GBS, accounts for about 75% of all cases in Western nations [1▪▪]. The pathologic basis of AIDP is acute injury, mediated by activated T cells and antibody responses, to Schwann cell and myelin epitopes in spinal roots and peripheral nerves. These antibody responses are poorly understood; AIDP is only infrequently linked to specific antibodies against peripheral nerve gangliosides and glycolipids [19].

The acute motor axonal neuropathy (AMAN) form of GBS mimics AIDP, but its fulminant motor deficits are not associated with sensory deficits. AMAN is implicated in epidemics of acute flaccid paralysis following *Campylobacter jejuni* enteritis: *C. jejuni* expresses lipo-oligosaccharides resembling the carbohydrate component of gangliosides [19].

MFS – the clinical triad of ophthalmoparesis, ataxia, and areflexia – can also be associated with bulbar weakness, and such children often have a clinical picture that later evolves to truncal and limb weakness. Recently reported *formes frustes* of MFS include isolated acute ptosis or ophthalmoplegia, with or without ataxia [20,21], while Bickerstaff's brainstem encephalitis may present as MFS with additional long-tract signs and neuroimaging changes attributable to central nervous system involvement [22].

Occasional cases of pediatric GBS are limited to acute pandysautonomia, pure sensory loss, or

Table 1. Clinical variants of Guillain–Barré syndrome in childhood

Clinical syndrome	Relative frequency	IgG antiganglioside antibody association(s)
Acute inflammatory demyelinating polyneuropathy	Common	GM1 (minority)
Acute motor axonal neuropathy	Common	GM1, GD1a
Acute motor and sensory axonal neuropathy	Uncommon	GM1, GD1a
Miller–Fisher syndrome	Uncommon	GQ1b, GT1a
Pharyngeal-cervical-brachial variant	Rare	GT1a, GQ1b, GD1a
Polyneuritis cranialis	Rare	GQ1b, GT1a
Acute (ataxic) sensory neuropathy	Very rare	GQ1b, GT1a
Acute pandysautonomia	Very rare	
Acute ophthalmoparesis	Very rare	GQ1b, GT1a

acute ataxic neuropathy [9▪▪,17,23]. Diagnosis is often delayed in such cases, in which nerve conduction studies often but not invariably show evidence of a more generalized neuropathy, and the lumbar puncture may show a cytalbuminological dissociation.

PATHOPHYSIOLOGY

GBS is likely an autoimmune disorder resulting from B-cell and T-cell activation and production of antibodies directed at antigenic proteins of the peripheral nerves. Infectious agents such as Epstein–Barr virus, cytomegalovirus, *Mycoplasma pneumoniae* and *C. jejuni,* immunization or surgery may trigger antibody production via molecular mimicry. Although most such antibodies are directed at myelin proteins, in some cases axonal moieties may be the primary target of immune-mediated nerve injury [19]. The regional patterns of neurologic deficit in GBS subtypes reflect variable ganglioside expression in different neural tissues. Unsurprisingly, antibody responses against specific gangliosides are most robust in GBS variants targeting peripheral nerve axons (Table 1) [19].

INVESTIGATIONS

The diagnosis of GBS is contingent on supportive evidence from the clinical examination, lumbar puncture, neurophysiologic and radiologic investigations.

Neuroimaging has now become a valuable adjunct to neurophysiologic studies in suspected pediatric GBS. Postgadolinium enhancement of the peripheral nerve roots and cauda equina is seen on spinal MRI in as many as 95% children with GBS and its regional variants, but is not specific to this disorder [24–26]. Similar changes are seen after lumbar puncture and in chronic genetic and inflammatory neuropathies [27].

Antiganglioside antibodies are identifiable in about 50% of children with GBS [19], and can be very useful in confirming diagnosis, particularly in patients with *formes frustes* or atypical presentations of this condition. There is significant overlap between GBS subtypes and the antiganglioside antibodies identifiable in individual subjects (Table 1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of childhood GBS includes disorders involving the central nervous system, peripheral nerves, neuromuscular junction, nerve and muscle. Recent reports have highlighted the overlap between postinfectious inflammatory conditions affecting the central nervous system, such as acute disseminated encephalomyelitis (ADEM) and transverse myelitis, and GBS. Occasional cases of concurrent ADEM and GBS or GBS and transverse myelitis are reported, in which instance there is a case for combined treatment with corticosteroids and intravenous immunoglobulin (IVIG) or plasma exchange [28].

MANAGEMENT

Vigilant supportive therapy in GBS includes monitoring for respiratory and autonomic complications of this disorder, pain management and prevention of complications of immobility. As many as 15–20% of children require mechanical ventilation for life-support during acute GBS [29]. The need for mechanical ventilation relates to the severity of the limb and axial weakness, and is also predicted by severe hypotension [29].

Both plasma exchange and IVIG hasten recovery of independent ambulation in GBS and shorten hospital admissions [15,30,31]. Human IVIG may act by binding pathogenic antibodies, downregulation of B-cell mediated antibody production and accelerated antibody catabolism, and complement inhibition [30]. Plasmapheresis reduces levels of circulating autoantibodies, and may reduce levels of circulating pro-inflammatory cytokines or cell adhesion molecules [31]. Both appear more effective when given within 2 weeks of onset of symptoms. Neither has been proven to improve long-term outcome in this disorder.

IVIG is generally preferred for treatment of childhood GBS because of administrative ease and a preferable side-effect profile. A total dose of 2 g/kg of IVIG over 2–5 days is generally well tolerated at all ages [1▪▪,15]. Comparison of therapeutic regimens has been limited by differences between treatment groups, but a recent meta-analysis of those trials conducted to date suggests that IVIG is as effective as plasma exchange in accelerating recovery from GBS [30].

Plasma exchange or plasmapheresis is a well-tolerated, effective treatment of GBS for children weighing more than 10 kg. Adults with GBS treated by plasma exchange have a slightly higher risk of relapse in the first year after treatment, but 12 months after presentation are more likely to have recovered fully [31]. There are few comparative trials of plasma exchange and IVIG in childhood GBS. A recent Egyptian study reported that plasma exchange might be superior to IVIG in very severe pediatric GBS necessitating ventilatory support, although this benefit was limited to time required

for mechanical ventilation, and not to length of ICU stay or short-term neurological outcome [32].

A current focus of research interest is individual variability in immunoglobulin pharmacokinetics, which may result in very variable IgG levels after immunoglobulin infusions, and hence variable responsiveness to treatment [33]. An ongoing international double-blind randomized trial is examining whether a subpopulation of GBS patients with low IgG increments after infusions will benefit from repeated treatment [34].

OUTCOME

Pediatric GBS is generally associated with a shorter illness and more complete recovery than is typical in adults. As many as 60% of children become nonambulant during their illness, and up to 20% require ventilatory support [9▪▪,15]. Most reach their clinical nadir within 2 weeks, recovery beginning soon after, and few have significant impairment by 4 months from onset [9▪▪,15]. Children with AIDP generally recover more quickly than those with AMAN or acute motor and sensory axonal neuropathy [9▪▪]. Electrodiagnostic markers of severe axonal injury, and development of antibodies to GM1, GD1b, GD1a and GT1a, do not invariably predict poor outcome in pediatric GBS [15].

CONCLUSION

Various aspects of the natural history and response to therapy in GBS are poorly understood.

An international multicentre collaborative study, the IGOS 1000 trial, is currently studying clinical, neurophysiologic, therapeutic, pharmacokinetic, immunological and genetic features in pediatric and adult GBS, with a view to identification of predictors of course, prognosis and response to therapy [7]. Important aspects of such studies are both better definition of the natural history of this clinically heterogeneous condition, and the establishment of outcome measures by which to assess the efficacy of new treatments. Research into pediatric GBS is particularly challenging in that it must address these issues in the context of the maturational and growth-related changes in peripheral nerve function in childhood.

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Conflicts of interest

There are no conflicts of interest.

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