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GUILLAIN-BARRE SYNDROME: A SYSTEMATIC REVIEW

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ABSTRACT Guillain-Barré syndrome (GBS) is an acute immune-mediated polyneuropathy. About two-thirds of GBS patients in their most severe state of disease are incapable to walk. Respiratory insufficiency and autonomic failure are probably the leading causes of death. Optimal general care, physiotherapy and the availability of intensive care facilities are of great significance. Randomized controlled trials show that intravenous immunoglobulins (IVIG) and plasma exchange (PE) are equally beneficial in reducing the time to recovery. The combination of PE ensued by IVIG is not considerably better than IVIG or Plasma exchange alone. Corticosteroids are not recommended in GBS. Approximately 10% of GBS patients deteriorate after initial improvement and often need repeated treatment. Motor GBS is often preceded by a Campylobacter jejuni infection. Progress in the past century includes analyzing the immune-mediated pathophysiology of the disease, understanding the spectrum of presentations, expanding diagnostic modalities, predictive models and executing randomized trials of treatments to improve outcomes. Given the morbidity that can occur without treatment, all physicians should know about the disease.

KEYWORDS : Guillain-Barré syndrome, Brighton criteria, Intravenous immunoglobulins

INTRODUCTION

Guillain-Barre syndrome (GBS) is the most severe acute paralytic(flacid) neuropathy with an incidence of one lakh people developing the disorder every year worldwide. The clinical journey through Guillain-Barré syndrome follows a typical pattern that can be divided into its constituent phases and components.[1,2]

- Preceding infection
- Serum antibodies to gangliosides
- GBS: Progression -- Plateau phase -- Recovery phase -- Disability.

Guillain-Barré syndrome may be preceded by infection or other immune stimulation that produces an aberrant autoimmune response targeting peripheral nerves and their spinal roots.[3,4] The major driving force behind the development of the disorder is molecular mimicry between microbial and nerve antigens at least in the case of Campylobacter jejuni infection. However, the interplay between microbial and host factors causing autoreactivity is not well understood.[5] Most individuals (>99%) exposed to an immune stimulus as a result of Guillain-Barré syndrome-associated infections such as C jejuni do not develop autoimmunity.[6] One to two weeks after immune stimulation, limb weakness, often with sensory and cranial nerve involvement proceeds to its peak clinical deficit in 2–4 weeks.[7] Clinical patterns aid in the diagnosis as biomarkers are not available for most variants of the syndrome. Meticulous monitoring and supportive care are needed for all GBS cases.[8] Recovery ensues as the immune response decays and the peripheral nerve undergoes an endogenous repair explaining the long recovery period which may last from months to years. Early initiation of intravenous immunoglobulins (IVIG) or plasma exchange is crucial and beneficial especially in patients with rapidly progressive weakness.[9]

Pathophysiology

Many infections have been linked with GBS. Most common are gastrointestinal or respiratory illnesses. Up to 70% of patients with Guillain-Barre Syndrome (GBS) report antecedent infections.[10] In our understanding of GBS, molecular mimicry plays a vital role, especially in the axonal variant. There is a similarity between lipo oligosaccharide of Campylobacter jejuni and gangliosides of peripheral nerve membranes.[11] Similar clinical syndromes of flaccid quadriplegia similar are seen following passive immunization of rabbits with these lipopolysaccharides.[12,13] Ganglioside antibodies have different peripheral nerve targets. Anti-GD1a antibodies target paranadol myelin, nodes of Ranvier, and neuromuscular junction.[14,15] Peripheral nerves or neuromuscular junction are usual sites of binding for GM1 and GQ1B antibodies.[16,17] These different peripheral nerve targets result in the heterogeneity of the clinical presentation of GBS.

Certain gangliosides are associated with specific presentations such as Miller-Fisher syndrome which is associated with the anti-GQ1B antibody.[18] Anti-GT1A antibodies may be associated with the pharyngeal-cervical-brachial variant of GBS.[19] The sensitivity and specificity of most antibodies for specific subtypes are low-to-moderate for clinical utility.

Clinical classification and diagnosis

Rapidly progressive bilateral weakness is the key presenting symptom in most patients of GBS.[1,7,20,21] Typically weakness is described as ascending, and usually starts in the distal lower extremities, but can start more proximally in the legs or arms. The latter pattern can be confused with a pyramidal lesion (ie, at the level of the spinal cord or above), but can be explained by focal conduction block at the level of the lumbar and cervical nerve roots rather than along the length of the nerve fibre. Electromyography and nerve conduction studies may help distinguish GBS from its mimics. Paraparesis may be the presentation in a small number of patients which can remain during the disease.[22] Others might involve cranial nerves resulting in facial, Oculomotor or bulbar weakness as in Miller Fisher syndrome. Sometimes patients might have sensory signs, ataxia, and features of autonomic dysfunction in addition to weakness.[23] Reduced tendon reflexes in the affected limbs are seen in most patients. Initially reflexes can be normal especially in pure motor and axonal forms of the disorder or in rare cases even hyper-reflexia.[24] According to various diagnostic criteria for Guillain-Barré syndrome patients can have progression of weakness within 4 weeks. However, most patients reach the nadir within 2 weeks. 20–30% of patients develop respiratory failure in the progressive phase of illness and therefore need ventilation in an intensive care unit (ICU).[7] During or shortly after treatment with IVIG or plasma exchange at least 25% of patients deteriorate clinically which would be worse without therapy rather than an indication of complete treatment resistance.[9] The severity and duration of the disease are highly diverse from mild weakness to ventilator-dependence without signs of recovery for months to years. Eventually patients do recover although some may be left with a disability. Patients might have signs or symptoms of autonomic dysfunction like cardiac arrhythmia, excessive sweating, blood pressure instability or ileus during any phase of the illness.

The commonly used diagnostic criteria for GBS are Brighton and Ninds Criteria (Table 1 and 2).

Table 1: Brighton Criteria

Diagnostic criteria	Level of Diagnostic certainty			
	1	2	3	4
Bilateral and flacid weakness of limbs	+	+	+	+/-

Decreased or absent deep tendon reflexes in weak limbs	+	+	+	+/-
Monophasic course and time between onset-nadir= 12hrs to 28 days	+	+	+	+/-
Absence of alternative diagnosis for weakness	+	+	+	+/-
CSF cell count < 50/ml	+	+/-	-	+/-
CSF Protein concentration >60mg/dl	+	+/-	-	+/-
Nerve conduction study findings consistent with one of the subtypes of GBS	+	+/-	-	+/-

Table 2: Ninds Criteria

Features required for GBS diagnosis	Features supportive of diagnosis	Features casting doubt on diagnosis	Features that rule out diagnosis
Progressive muscle weakness of more than one limb	Progression of weakness for 2-4 weeks	Marked persistent assymetry of weakness	History of hexacarbon abuse
Areflexia or hyporeflexia	Symmetric involvement	Persistent bladder or bowel dysfunction	Acute intermittent porphyria
	Mild sensory symptoms or signs	Severe bladder or bowel dysfunction at onset	Recent diptheria infection
	Cranial nerve involvement	> 50 leucocytes / mm3 in CSF	Poliomyelitis, botulism , toxic neuropathy and functional paralysis
	Recovery begins 2-4 weeks after nadir	Presence of polymorphonuclear leucocytes in CSF	
	Autonomic dysfunction	Sharp sensory level	
	Absence of fever	Central nervous system signs except Miller fisher syndrome	
	Elevated CSF Protein		

Approaches to treatment and clinical trials

Guillain-Barré syndrome is a potentially life-threatening disease. General medical care, as well as immunological treatment is essential. Supportive care is helpful to prevent and manage complications.[4,8] Meticulous attention to respiratory function by frequent measurement of vital capacity and other clinical outcomes and timely transfer to ICU when needed. Erasmus GBS Respiratory Insufficiency Score (EGRIS) can be used on hospital admission to help with decision-making because it determines if artificial ventilation is needed.[25] Supportive care includes cardiac and haemodynamic monitoring, prophylaxis for deep vein thrombosis, management of possible bladder and bowel dysfunction, early initiation of physiotherapy and rehabilitation and psychosocial support.[23]

Several randomized controlled trials (RCTs) studying the effect of immunotherapy in Guillain-Barré syndrome done in the past few decades have proved IVIG and plasma exchange to be effective.[9,26] IVIG or plasma exchange should be started as soon as possible before irreversible nerve damage takes place. Accepted beneficial regimen includes five plasma exchange sessions (each comprising 2-3ltr) over 2 weeks starting within first 4 weeks (preferably 2) from the onset.[26,27] IVIG is proven to be effective in patients who are unable to walk unaided when started within first 2 weeks after the onset of weakness.

Surprisingly, both oral steroids and intravenous methylprednisolone are not beneficial in the disorder.[28] The combination of IVIG and methylprednisolone is not more effective than IVIG alone, although there might be some additional short-term effects after correction for known prognostic factors.[29] A combination of plasma exchange followed by IVIG is not significantly better than plasma exchange or IVIG alone.[30] A completely new approach is being investigated in an RCT for the drug Eculizumab—a humanised monoclonal antibody that binds with high affinity to the complement factor C5 and prevents its cleavage to C5a and the pro inflammatory cytolytic C5b-9 complex.[31,32] Yet at present only IVIG and plasma exchange are proven effective treatments for Guillain-Barré syndrome. Because IVIG is more convenient to give, widely available and generally has only minor side effects, it has replaced plasma exchange as the preferred treatment in many centers. A disadvantage of IVIG is the high cost—a major reason why some centers still use plasma exchange. In low-income countries, both IVIG and standard plasma exchange treatment might be too expensive for a large proportion of patients. New studies to improve the course and outcome of Guillain-Barré syndrome are needed of the hour. IgA deficiency is a contraindication for using IVIG.

Complications

The life-threatening complications are respiratory compromise and bulbar palsies. The multidimensional care of the patient with Guillain-Barre syndrome (GBS) requires coordination of the healthcare team. Nurses should identify and prevent complications including decubitus ulcers and dysautonomia. Pharmacists should recognise the adverse effects that may occur with the administration of treatments for GBS such as IVIG. Respiratory therapists help in preventing atelectasis and aspiration pneumonia. Physical and occupational therapists are crucial as the patient begins to recover.

CONCLUSION

Treatments have been developed and proved effective but these are not sufficient in many patients. Research areas face deep, unsolved issues around the pathogenesis of Guillain-Barré syndrome especially for the acute inflammatory demyelinating polyneuropathy form of the disorder. Newly emerging post-infectious forms of Guillain-Barré syndrome such as those associated with arboviruses including Zika virus need close monitoring as global epidemics spread. Biomarkers, prognostic models and better therapies are essential to address the problem. Many of these issues are being addressed through multicentre collaborative efforts such as International Guillain-Barré syndrome Outcome Study (IGOS). Prevention of severe axonal injury early in the course of the disease remains a major focus because it is an important limiting factor in achieving a good long-term outcome.

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