Factors predicting poor outcome in patients with fulminant Guillaine-Barré syndrome

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Abstract

This paper describes three patients with acute fulminant Guillain-Barré Syndrome (GBS) with electrophysiologically inexcitable peripheral nerves not responding to two courses of intravenous immunoglobulin. Their clinical profile is compared with two other GBS patients having similar severity of disease but with demyelinative features, managed similarly during the same period. Patients who failed to respond were elderly with a mean age of 60 years, had prodromal diarrhea, rapid progression of muscle weakness requiring mechanical ventilation within 24 hours, dense weakness of all four limbs with cardiovascular autonomic symptoms and inexcitable peripheral nerves. The remaining two who recovered well were relatively younger with a mean age of 50 years, had no prodromal diarrhea, required ventilatory support by fourth day of illness, no cardiovascular autonomic symptoms and demyelinative neuropathy.

Key Words

Guillain-Barré Syndrome (GBS), inexcitable nerves, intravenous immunoglobulin (IVIG)

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Introduction

Guillain-Barré Syndrome (GBS) is an acute immune-mediated peripheral neuropathy consisting of demyelinative as well as axonal variants.[1] The axonal variant is more fulminant and has poor prognosis.[2] The pathophysiological mechanism is autoimmune and immnunotherapy with either plasma exchange or intravenous immunoglobulin as the standard treatment.[3] When a given patient fails to respond satisfactorily to one course of intravenous immunoglobulin therapy, repeat course might improve the outcome when given within the first 4 weeks.[4] This paper describes five patients with fulminant GBS who were given repeated courses of intravenous immunoglobulin (IVIg) with varying outcome. The clinical features of those who failed to respond to repeated courses of IVIg are compared with those who recovered well and the factors indicating poor outcome are analyzed.

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Materials and Methods

All patients admitted between January 2007 and March 2012 with acute flaccid hyporeflexic limb weakness were assessed and diagnosed with GBS if they fulfilled the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) criteria.[5] The severity of disability and motor limb weakness was graded by Hughes functional disability scale and Medical Research Scale (MRC) Scale respectively. Cerebrospinal fluid (CSF) analysis was done for cell count, protein, sugar, and bacteriology study. Electrophysiological studies were done including median, ulnar, tibial, and peroneal nerves for motor nerve conduction; median, ulnar, and sural nerves for sensory nerve conduction; F waves in all four limbs and bilateral tibial H reflex using standard conventional protocols.[1] Based on electrodiagnostic studies, the pattern of GBS was classified as demyelinating, axonal, or inexcitable.[6] Other investigations like urine for porphyrin, electrolytes, and thyroid profile were done. Serology for AntiGM_1 and *Campylobacter jejuni* antibody were not done. The patients who developed respiratory failure (based on arterial blood gas analysis) were intubated. After confirming the diagnosis of GBS, all were treated with a standard protocol of high dose IVIg, at a dose of 0.4 g/kg/day for 5 days and were monitored for functional recovery. Those who failed to respond even after 2 weeks were given another course of IVIg. During their intensive care unit (ICU) stay, they received low molecular weight heparin (LMWH) for deep vein thrombosis (DVT) prevention, appropriate antibiotics for nosocomial infections, and neuro-rehabilitative therapy. They were all closely monitored for signs of cardiac dysautonomia

and received appropriate care as and when the complications were detected. Tracheostomy was done on day 12 anticipating prolonged ventilator dependence and weaning was attempted whenever feasible. The clinical profile of these patients including demographic profile, antecedent illnesses, rapidity of progression (assessed by duration from onset to intubation), severity of disease, CSF analysis and electrophysiological studies were analyzed. The duration of ventilator dependence and signs of cardiovascular autonomic disturbances like fluctuations in heart rate and blood pressure (BP) was also noted. Treatment outcome assessed by improvement in Hughes functional disability scale, at the end of 1,3 and 6 months of therapy were noted. Patients who showed functional recovery by at least one grade, were discharged and followed as out-patient.

Results

From a total of 144 patients diagnosed with GBS during this period, 22 were admitted and managed in one neurology unit. Among them, five patients who required ventilatory support for more than 30 days and treated with two courses of IVIg were included in the study. These five patients were divided into two groups based on electrophysiological studies. Three patients in the first group had inexcitable peripheral nerves and two in the second group had features of demyelination. A comparison of the clinical profile of these two groups is shown in Table 1.

All three patients with inexcitable nerves were of older age-group with mean age of 60 years, had prodromal diarrhea, severe motor limb weakness (power 0/5), developed respiratory failure within 24 hours of onset of illness, whereas the other two patients with demyelination were relatively younger with a mean age of 50 years, had no antecedent illness and had motor limb power of 1/5 with progression to respiratory failure over 4 days. Among the three patients with inexcitable nerves, one improved from Hughes scale 5-4 by 164 days of illness and at the end of 1 year could only stand with aid (Hughes scale 3). The other two patients in this group were ventilator dependent (Hughes scale 5) even at the end 6 months. On the contrary, patients with demyelinative features were ventilator dependent for a mean duration of 33 days and had a Hughes scale of 3 at 3 months, with no disability (Hughes scale 0) at the end of 6 months.

Table 1: Clinical profile of fulminant GBS in mechanically ventilated patients

Variables	Inexcitable nerves	Demyelinating neuropathy
Number	3	2
Age (mean years)	60 (52-74)	50 (39-62)
Sex		
Male: Female	2:1	2:0
Severity of limb weakness on admission	0/5	1/5
Prodromal diarrhea	Present	Absent
Rapidity of progression*	1	4
Cardiovascular autonomic dysfunction	Yes	No
Recovery time by 1 grade		
Mean days	164**	33

*Duration (days) from onset of weakness to intubation, **Applicable to one. The other two were ventilator dependent at the end 6 months

Discussion

Acute GBS is a heterogenous disorder consisting electrophysiologically demyelinative and primary axonapathy types; the treatment of which includes either plasma exchange or IVIg.[1] Even though both are equally effective, IVIg is preferred in most of the centers inspite of its high cost as it is simple and convenient to administer.[7] In general the therapeutic response following IVIg is good in those with demyelinative and unsatisfactory with axonopathy features.[1] Few studies have shown that in those who are not responding to the first course of IVIg, a second course may show good response even in those with axonopathy changes.[4] However in spite of the modern immunotherapy as well as good critical care support, the mortality of GBS is still about 4-15% and about 20% of the survivors are disabled.[1] What are the predictors of poor outcome? Can it be identified at the onset itself? The present study has shown that the presence of certain clinical features in the first few days of the disease itself could warn the clinician about the poor outcome. It includes:

a. Mean age above 60 years,
b. Prodormal diarrhoea,
c. Rapid involvement of the respiratory muscles requiring ventilatory support within 24 hours of the illness,
d. Severe muscle weakness with grade 0 power in all four limbs,
e. Presence of cardiovascular autonomic symptoms, and
f. Electrophysiology showing inexcitable peripheral nerves.

An Indian study by Netto *et al*., has shown poor outcome with inexcitable nerves but had not mentioned about using second course of IVIg.[8] Inexcitability of peripheral nerves in GBS can occur due to several reasons. Extensive axonal degeneration due to severe axonal interruption by the polymorphs or by the humoral antibodies, interrupting at a proximal level leaving the axons only to collateral reinnervation rather than to regeneration.[9,10] Sometimes, it occurs secondary to conduction block either in the distal nerve fibres or axonal terminals as seen in Chinese flail paralysis syndrome or at the node of Ranvier by humoral antibodies against the axolemma.[1,9,11] The latter may be reversible by treatment. Thus, the clinical outcome of GBS with inexcitable nerves depends upon the mechanism of axonal damage and the site of axonal interruption. Few earlier studies have observed poor prognosis in those with older age, *antecedent Campylobacter jejuni enteritis*, rapid progression of the disease, axonopathy and presence of anti GM1 antibodies.[2] It is possible that the patients with the above parameters may have severe axonal damage and that there is poor axonal growth and regeneration affecting the recovery in spite of the available treatment.[12]

What is the clinical implication of identifying the predictors of poor outcome? The presence of the above clinical parameters helps the clinician to identify the subgroup of the GBS patients whose prognosis is likely to be poor, in the first few days of the illness itself. It helps to counsel the family regarding the severity and the outcome of the disease as well as to plan

alternative novel therapy. Axonal form of GBS is known to be associated with antibodies to GM1 ganglioside and such patients may respond to a combination of intravenous methyl prednisolone and IVIg.[13] Experimental study involving absorbing the antibodies in a column that has a specific affinity to it, is being tried.[1] Complement mediated mechanism have been implicated in the pathogenesis of this subgroup of patients and drugs inhibiting the complement cascade has been considered in the management of such patients.[1] As the present day immunotherapy is not effective in this subgroup of patients, a better understanding of the pathogenesis of the axonopathy form of GBS is required to plan better treatment.

The major limitations of the study are inclusion of only a small number of patients as well as non availability of certain investigations such as antibodies to GM1 and *Campylobacter* infection. Besides nerve biopsy was not done. However, patients with the above features are likely to be small in number in any single centre and probably a multicentric study may be needed.

In conclusion, acute GBS patients presenting with the following combination of clinical features like:

1. Age above 60 years,
2. Prodromal diarrhoea,
3. Requiring ventilator support within the first 24 hrs of illness,
4. Presence of severe limb weakness,
5. Presence of cardio autonomic dysfunction, and
6. Electrophysiological evidence of inexcitable nerves are less likely to respond to conventional therapy.

Further studies with large number of patients are needed to understand the pathophysiology and plan newer treatment.

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