Intravenous Immunoglobulin for Severe Protracted Pediatric Guillain–Barre Syndrome: Is Single Dose Adequate?

Sir,

Guillain–Barre syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy which may be demyelinating (acute inflammatory demyelinating polyradiculoneuropathy) or axonal (acute motor axonal neuropathy [AMAN]). It is an important cause of acute flaccid paralysis in children globally. It is characterized by acute-onset ascending and symmetric weakness, reaching nadir within 2–4 weeks, with gradual recovery and a mortality of around 5% while 20% of patients are left with disabling motor deficits.[1]

Management of GBS includes supportive therapy and immunotherapy (intravenous immunoglobulin [IVIg] or plasma exchange). In adults, immunotherapy should be offered in severe GBS, impairing independent walking or requiring mechanical ventilation (Class I studies, Level A). IVIg (2 g/kg over 3–5 days) and plasma exchange (200–250 ml/kg over 7–14 days) are equally effective within 2 weeks of onset, while combination of two is not superior to either. In children, low-quality evidence suggests that IVIg hastens recovery in comparison to supportive care.[2] According to a study by Saad *et al*., plasmapheresis (over IVIg) led to a significant reduction in the duration of hospitalization and faster recovery.[3] Further research is needed in milder disease and delayed treatment (>2 weeks after onset). IVIg is preferred than plasma exchange in children, due to ease of administration and avoidance of invasive catheters.

Several factors, for example, age >60 years; severe, rapidly progressive disease; low distal compound muscle action potentials (suggesting axonal loss); delay in therapy; prolonged mechanical ventilation (>1 month); and preexisting pulmonary disease are predictors of poor prognosis.[4] Disease relapse occurs in 5%–10% of patients. It can be early (treatment-related fluctuations; within 3 weeks of immunotherapy) or late (after 4–6 weeks of immunotherapy). Early relapse occurrence is due to disease activity persisting beyond 3 weeks ($t_{1/2}$ of IVIg) and it may respond to repeat dose of IVIg.

Occasionally, severe GBS continues to deteriorate or has a protracted course, despite appropriate immunotherapy (severe protracted GBS/therapeutic resistance). This rare variety has a protracted plateau time with electrical inexcitability and persistent quadriplegia on day 10 of disease. Severe protracted GBS is still a therapeutic enigma; dose of IVIg which can be given in such cases is uncertain.

We hereby present two children with severe protracted GBS who subsequently responded after cumulative IVIg dose of 6 g/kg over a period of 3 months. Case 1: A 5-year-old boy presented, on day 3 of illness, with inability to sit and stand along with respiratory and bulbar weakness within 48 h of onset. He had flaccid quadriplegia, areflexia, autonomic dysfunction, and inexcitable nerves (on electrophysiologic testing), fulfilling Brighton criterion Level 2. The child required mechanical ventilation at admission and received IVIg (2 g/kg over 5 days), initiated within 72 h of onset. In view of no improvement by 2 weeks of IVIg, a second course was administered despite which ventilator dependence persisted. Subsequently, he was started on plasma exchange. Unfortunately, he had severe allergic reaction during plasmapheresis and it could not be continued further. At 7 weeks of illness, a third course of IVIg was instituted in view of (a) severe clinical picture (persistent quadriparesis, autonomic dysfunction, and bulbar and respiratory compromise), (b) poor prognosis (inexcitable nerves), and (c) nonresponsiveness to usual treatment by 6 weeks. Surprisingly, the child recovered over the next 1 week; shoulder power improved and the child could be weaned off ventilator by 2 weeks following the 3rd cycle of IVIg.

Case 2: An 11-year-old boy presented with acute-onset flaccid quadriplegia which rapidly progressed over 48 h to involve facial, respiratory, and bulbar musculature. Electrophysiological testing on admission (day 3 of illness) revealed AMAN variant of GBS. In view of respiratory weakness, mechanical ventilation was initiated and IVIg was given at 2 g/kg over 5 days. After 4 weeks of illness, slight improvement in facial diplegia was noted; however, respiratory and appendicular weakness persisted. Despite a repeat course of IVIg, substantial improvement did not occur. The child continued to have ventilator requirement. Further treatment options were discussed with the parents who refused plasma exchange. In view of the past experience, a third course of IVIg was administered 3 weeks after the second dose. The child showed remarkable improvement within a week of the 3rd dose and could be weaned off the ventilator support and discharged by the 10th week of illness.

GBS has varied clinical presentation, severity, and prognosis. Severe GBS accounts for 25%–30% of all childhood GBSs. The regimen of IVIg administration (2 g/kg over 3–5 days) in severe GBS was determined by extrapolation from studies on hematologic and autoimmune disorders. Brief regimens (<3 days) are associated with early relapses.[2]

Although childhood GBS is expected to have better prognosis than GBS in adults, occasional cases might be refractory to standard treatment. This may be due to marked axonal damage secondary to prolonged and severe autoimmune attack. The consequences of repeat IVIg course in such children are ambiguous. Hence, there is a need to explore alternative dose regimens, especially for protracted GBS with therapeutic resistance.

It has been postulated that specified increase in immunoglobulin G (IgG) level after 2 weeks of IVIg infusion is associated with good recovery. Population with a smaller rise in IgG might benefit from a second course of IVIg. A recently published case series (with three adults) highlighted the role of second course of IVIg (instituted at 5–7 weeks of illness) in protracted GBS.[5] Therefore, such patients might require a higher cumulative dose of IVIg for a satisfactory response. Maximum cumulative dose and time point beyond which permanent damage occurs is unstipulated.

This experience underscores the importance of repeat courses and higher cumulative dose of IVIg (6 g/kg over 8–12 weeks) in protracted pediatric GBS. Improvement in these children might have been due to (a) variable IVIg pharmacokinetics (though we did not measure IgG levels following each dose), (b) severe persistent immune attack requiring a higher cumulative dose of IVIg, and (c) severe axonal damage and natural recovery due to regeneration. Natural recovery seemed unlikely in view of strong temporal relationship to third course of IVIg and rapid recovery (natural recovery is expected to be gradual).

This study highlights the fact that severe protracted GBS is a rare entity with poor prognosis and unclear therapeutic options. A third course of IVIg may be considered; however, studies with large number of patients are required to prove therapeutic benefit of repeat courses and higher cumulative dose of IVIg in severe protracted GBS.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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