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Intravenous Immunoglobulin in the Treatment of Childhood Guillain-Barré Syndrome: A Randomized Trial

ABBREVIATIONS. GBS, Guillain-Barré syndrome; CSF, cerebrospinal fluid; Ig, immunoglobulin; IVIg, intravenous immunoglobulin.

Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating polyradiculoneuropathy manifested by progressive flaccid paralysis.^{1,2} With the eradication of poliomyelitis, GBS has become the most common cause of acute motor paralysis in children. The etiology and pathophysiology of GBS has a postulated immune-mediated mechanism.^{3,4} In classical GBS there is destruction of peripheral nerve myelin sheath, which results in the hallmark symptomatology. There are also less frequently encountered axonal variants, those with and without sensory involvement and an ataxia-ophthalmologic syndrome with no weakness (Miller-Fisher syndrome). These other axonal variants have a more clearly understood immunologic basis that involves antibody attack on a variety of target glycolipid antigens on nerve terminals and axons.⁴ Classic demyelinating GBS syndrome has a less well-defined pathogenesis. The disorder typically begins after recovery from a preceding illness or vaccination. Distal paresthesias evolve into a symmetrically progressive ascending distal and proximal weakness of the limbs. There are diminished or absent tendon stretch reflexes, often in association with facial weakness and limb and back pain.^{1,2} After several days the cerebrospinal fluid (CSF) demonstrates an elevation in protein without significant pleocytosis (albuminocytological dissociation). Weakness may continue to progress rapidly with need of ventilatory support, often with associated autonomic dysfunction. It has generally been perceived that the clinical course in children may be somewhat milder, with greater likelihood of recovery in comparison to adults.¹

Immune-mediated mechanisms involving both cellular and humoral responses in GBS have been postulated. Microscopic studies have demonstrated both lymphocyte and macrophage infiltration into nerve fibers.^{3,4} Experimental allergic neuritis can mimic the symptoms of GBS in rodents and rabbits after immunization with peripheral nerve extracts.^{5,6} Despite failure to exacerbate mild experimental allergic neuritis in rodents with the transfer of sera from patients with GBS, the fact that plasmapheresis has been beneficial as a treatment for GBS suggests

an antibody-mediated mechanism.⁴ A number of cytokines, as well as antibodies directed against specific myelin antigens yet to be defined, are found in the serum of patients with GBS.^{3,7,8} The mechanisms whereby intravenous immunoglobulin (IVIg) may be therapeutic in GBS and other autoimmune neurologic disorders include inhibition of complement binding, neutralization of selected cytokines, down-regulation of antibody production, and modulation of Fc-receptor-mediated phagocytosis, among others.^{3,7,9} IVIg is equally effective as plasmapheresis in speeding up the recovery process.¹⁰ IVIg is a purified product derived from pooled human plasma.⁹ Serum IgG levels increase 5 times after a 2-g intravenous infusion, with decline by 50% in 72 hours and return to baseline levels in 21 to 28 days.⁹ A parallel rise in CSF IgG is noted after 48 hours of infusion.⁹

In this issue of *Pediatrics*, Korinthenberg et al¹¹ report results of a randomized, multicenter treatment trial using IVIg in children with GBS. The results are the culmination of efforts from 63 German, Swiss, and Austrian pediatric hospitals over a recruitment period of 40 months. Children were eligible between the ages of independent walking through 18 years old. Diagnosis rested on accepted published international research criteria including results of CSF examinations. Testing by means of para clinical examination using neurophysiologic measures (nerve-conduction velocity, F-wave response, electromyogram, and spinal MRI) was not mandated. Children with a clinical suspicion for GBS were randomized if inclusion and exclusion criteria were satisfied and informed consent was obtained.

The study was designed to answer 2 clinical questions: (1) Does (early randomization) early treatment with IVIg in children who are still able to walk unaided at the time of diagnosis alter disease severity and long-term outcome? (2) In children who were unable to walk (up to 5 m) unaided at diagnosis, would treatment with a higher daily dose of IVIg over a shorter time frame (2 g/kg IVIg divided every day for 2 days) versus a lower daily dose over a longer time frame (2 g/kg IVIg divided 0.4 g/kg per day over 5 days) affect the time to regain ability to walk unaided? Unfortunately, the estimation of time to recruit sufficient numbers of patients precluded the study from being definitive but rather was planned as an explorative pilot study. Ultimate evaluation was made on an intention-to-treat basis.

From the initial 101 children recruited, 5 were excluded because of incorrect diagnosis, resulting in 95 children fulfilling the diagnostic criteria of GBS. There were 53 boys and 42 girls ranging in ages from 1 to 16.5 years (median age: 6.2 years). At entry into study, 26 of 95 patients were able to walk and were randomized to the early-treatment arm to receive IVIg or no IVIg. After entry, however, 5 children continued to deteriorate and then were randomized a second time into the late-treatment arm. Two children were later excluded, thus leaving 21 children in the early-treatment arm and 51 children in the late-treatment arm. There were 28 additional subjects who could not be randomized because of protocol violations.

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In the early-treatment study comprised of 21 subjects, 7 of whom were randomized to receive no treatment and 14 were randomized to receive IVIg, there were 4 of 7 from the no-treatment arm and 7 of 11 from the early-treatment arm who ultimately lost the ability to walk unaided. The subjects from the no-treatment arm then were randomized a second time on entry into the late-treatment study. One of these subjects ultimately was identified as having relapsing chronic inflammatory demyelinating polyneuropathy. Initial improvement occurred earlier in the 14 subjects randomized for IVIg compared with no treatment (4.5 vs 30 days; $P = .001$). There was also improvement in the main disability score, which maximized at a median of 8 days in the treated group and 32 days in the nontreated group ($P = .046$). The median disability score 4 weeks after randomization was also significantly lower in the IVIg-treated group compared with the nontreatment group. However, the number of subjects was small; thus, overinterpretation of the results must be avoided. Similar findings were concluded in a previously published study of 9 children treated with 1 g/kg IVIg per day for 2 days and compared with untreated patients.¹² These subjects were also shown to recover more rapidly (7.5 vs 11.8 days, respectively).¹² A single dose of IVIg (2 g/kg) was also able to shorten recovery time to independent ambulation in another small study of 9 children.¹³ One could argue that the hastening of earlier maximum disability and shorter duration of maximum disability make early treatment worthwhile. This is especially true when one considers that although these early-treated children were still walking and likely had milder disease, they were still weak, unsteady, and probably uncomfortable. However, from a study-design perspective, treatment failed to alter the severity or long-term outcome, and no data were provided regarding length of hospital stay or differences in rehabilitative services required. Perhaps an equally important question to ask would have been: Did the subjects feel better faster and go home sooner?

In the late-treatment study there were 51 subjects included in the intention-to-treat analysis. Time from first symptoms to randomization, duration from first symptoms to treatment, and duration of disease progression were not significantly different between the 2 treatment arms. There were 25 children assigned to receive IVIg over a 2-day course and 26 subjects assigned to receive IVIg over a 5-day course. There were no significant differences in the disability scores between the groups: at inclusion into study, height of disease 4 weeks after randomization, or median time to improve 1 point in disability score. A higher disability score, however, did correlate to a slower recovery. It is important to note, however, that there were early transient deteriorations seen in the group treated for 2 days versus the group treated over 5 days. Additionally, the duration of the progressive phase was longer in those subjects suffering a secondary deterioration. Analysis determined no influence of treatment schedule on the main outcome criteria on the "days to regain unaided walking."

Side effects were nearly identical in both groups (18% and 20%, 2- vs 5-day treatment course).

In the only other large-scale prospective study in children using IVIg for GBS, Koule et al¹⁴ documented shorter duration of disease, shorter hospital stay, fewer children requiring mechanical ventilation, and no mortality in a cohort of 42 children using 2 g/kg IVIg divided 0.4 g/kg per day over a 5-day interval. They too saw early transient deterioration in 11.9% (5 of 42) of the subjects,¹⁴ compared with the 21% (5 of 23) in the current study by Korinthenberg et al, in which relapses were seen only in those children treated with a 2-day regimen.¹¹ Thus, early transient relapses may occur with either a 5- or 2-day treatment course. It is uncertain if this difference is because of specific individual subject immune-related factors or the mode and timing of IVIg administration.

Korinthenberg and colleagues deserve congratulations in their attempts to clarify the best mode and timing of IVIg in children with GBS.¹¹ Although the severity and long-term outcome were not significantly different between treated and untreated subjects with mild disease, IVIg did hasten the onset of motor recovery sooner. Even this may be worthwhile after weighing the perceived benefits of a faster onset of recovery against the risks of treatment (eg, allergic reactions, hyperviscosity and thromboembolic events, headache, infection, aseptic meningitis, and other effects).^{3,15} A 2-day high-dose IVIg regimen showed no clear benefit over a more protracted 5-day regimen in terms of disease recovery. It is unfortunate that no data were provided regarding length of hospital stay or differences in rehabilitative services required to assess other potential indirect benefits in either group (early- or late-treatment arms). There was an increased likelihood of potential secondary deterioration (21%) with the 2-day high-dose IVIg regimen, which may be unacceptably high. Although the timing to the secondary deterioration was not specifically noted in the current study, it has been reported previously to occur within 3 weeks of treatment completion (median: 11 days).¹⁴ Although not encountered by Korinthenberg et al, higher-dose IVIg infusions may have higher risks for other treatment-related complications.

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Understanding Abnormalities in Vascular Specification and Remodeling

ABBREVIATIONS. MMP, matrix metalloproteinase; bFGF, basic fibroblast growth factor; ECM, extracellular matrix; VEGF, vascular endothelial growth factor; TGF, transforming growth factor; TIMPs, tissue inhibitors of matrix metalloproteinase.

Accurate classification, diagnosis, management, and treatment of vascular lesions in children can be hindered by the wide range of clinical presentations and varying clinical course of these lesions. In this issue of *Pediatrics*, Marler et al¹ report novel findings that elevated levels of angiogenesis-related proteins, specifically high molecular weight matrix metalloproteinases (MMPs) and basic fibroblast growth factor (bFGF), can be detected in the urine of children with vascular anomalies and can mark clinical progression of these lesions. These findings suggest that a noninvasive test can be developed to characterize aggressive vascular malformations and tumors and provide additional evidence that antiangiogenic agents may be useful for the treatment of these lesions.

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To approach diagnosis and management of congenital vascular lesions rationally, an understanding of the basic cellular, molecular, and genetic mechanisms of blood vessel formation is required. Recent advances in the field of vascular biology have contributed to our knowledge of how blood vessels are assembled during early embryonic development. Blood vessel morphogenesis involves discrete steps in continuum that are regulated by specific signaling pathways involving soluble effectors, cytokines and their receptors, proteases, and extracellular matrix (ECM) components. These various pathways control integral events that contribute to the formation of a functional vasculature including endothelial and mural cell (pericyte/smooth muscle cell) differentiation, cell proliferation and migration, and the specification of arterial, venous, and lymphatic fate. Dysregulation of these processes can result in vascular malformations affecting 1 or multiple vascular types including capillary, arterial, venous, lymphatic, or arteriovenous channels.

BLOOD VESSEL FORMATION

During embryonic development, blood vessels form *de novo* from endothelial progenitors by the process of vasculogenesis.² This process has been studied most extensively in the mouse yolk sac, wherein endothelial progenitors are specified in the mesoderm and induced to form an initial capillary plexus by effectors derived from the adjacent visceral endoderm, including vascular endothelial growth factor (VEGF), Indian hedgehog (Ihh), and bFGF. Specification of the early capillary plexus into arterial or venous fate occurs as the plexus goes on to remodel into a circulatory network of branching vessels. Recent studies reviewed by Torres-Vazquez et al³ provide evidence that distinct molecular differences between arterial and venous endothelial cells exist before blood vessel assembly and the onset of blood flow. Early arterial specification is regulated by complex molecular pathways involving VEGF, members of the Notch signaling pathway, and neuropilin-1 (VEGF₁₆₄-specific receptor). Specification of venous fate involves other distinct signaling pathways that include neuropilin-2 and Tie2. Further downstream, demarcation of arterial-venous boundaries is established through the EphrinB/EphB signaling pathway, wherein EphrinB2 is distinctly expressed by arterial endothelial cells, and its receptor EphB4 is expressed in venous endothelium. Although endothelial cells demonstrate early specification to an arterial or venous fate, they can exhibit plasticity, and further patterning of arteries and veins is controlled by other factors such as blood flow. In a recent study using the chicken yolk sac as an experimental model to assess arterial-venous differentiation, purposeful disruption of arterial blood flow on one side of the yolk sac led to venous differentiation of vessels on that side, suggesting that flow is a major factor controlling arterial patterning.⁴ In addition, this study demonstrated that exogenous application of EphrinB2 and EphB4 *in vivo* to the allantois at a later, more mature stage of yolk sac vascular development induced the formation of arterial-venous

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