Child Neurology: Chronic inflammatory demyelinating polyradiculoneuropathy in children

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ABSTRACT

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune disorder characterized by patchy demyelination of nerve roots and distal nerves. The course may be monophasic progressive or relapsing-remitting. CIDP is less common in children than in adults. As in adults, children with CIDP present with proximal and distal weakness and loss of deep tendon reflexes. Children are most often brought to medical attention due to gait disturbance and falling. As in adults, immunomodulatory treatment is the mainstay of therapy. Based on the small number of case series available, children with CIDP seem have a more favorable long-term course than adults. **Neurology® 2008;71:e74-e78**

CLINICAL CASE, PART I A 5-year-old previously healthy boy was brought to the Emergency Department for evaluation of difficulty walking. His mother had first noticed a change in his gait 3 months earlier, when he began to limp intermittently after receiving a set of routine immunizations. Two months later in the setting of an upper respiratory infection she noticed that he had trouble running while playing soccer. Within the next 2 weeks he developed persistent difficulty with walking, climbing stairs, arising from a chair, and putting on his pants. He had no sensory complaints and had no change in bowel or bladder function. Neurologic examination was notable for proximal and distal weakness of the lower extremities, diffusely diminished deep tendon reflexes with flexor plantar responses, and mildly decreased vibration sensation in the feet. He used a Gowers maneuver to rise from the floor, was unable to jump, could not walk on his heels, and had a wide-based gait. There were no cranial nerve abnormalities, no weakness of the upper extremities, and other sensory modalities were intact.

Differential diagnosis. In the evaluation of gait difficulty, as with other neurologic complaints, localization based on history and physical examination is the first step. The decreased tendon reflexes, flexor plantar responses, and Gowers maneuver ("walking" the hands up the thighs to arise from a squat) all suggest a lower motor neuron localization. Within this broad category, diseases of the motor neuron and spinal cord, nerve, neuromuscular junction, and muscle should be considered. Among motor neuron and spinal cord etiologies, tethered spinal cord and spinal muscular atrophy type III can both present with depressed or absent reflexes and should be considered. Intrinsic spinal cord processes such as neoplastic, vascular, and demyelinating lesions are also in the differential, although these are less likely to present with hyporeflexia. Inherited and acquired neuropathies are possibilities, and are discussed in more detail below. The lack of fluctuation in his symptoms makes a neuromuscular junction disorder such as myasthenia gravis less likely, although this does not exclude it completely. Inherited and acquired myopathies are also possible, although the patient does not have some of the classic associated symptoms or signs of these disorders, such as the calf hypertrophy of muscular dystrophy, myalgias of infectious myositis, or heliotrope rash of dermatomyositis.

Among polyneuropathies, two key distinctions that assist with the differential diagnosis are inherited vs acquired etiologies and demyelinating vs axonal physiology. The subacute onset suggests that this is more likely to be acquired. The physiology cannot be determined until electrophysiologic testing is performed. Another important distinction is between large and small fiber neuropathies. In this case, the lack of prominent sensory symptoms makes a small fiber neuropathy less likely.

An important class of acquired neuropathy is the autoimmune neuropathies. Among these, acute inflammatory demyelinating polyradiculoneuropathy (AIDP), or Guillain-Barré syndrome, is less likely due to the

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Disclosure: The authors report no disclosures.

Figure 1 The patient's motor nerve conduction study revealing markedly prolonged latencies and decreased conduction velocities with temporal dispersion, and low amplitudes of bilateral tibial compound motor action potentials

subacute presentation. This patient's clinical course is more consistent with CIDP. CIDP is an autoimmune disorder characterized by proximal and distal weakness that develops over a period of at least 1 month, with a monophasic progressive or relapsing-remitting course. Deep tendon reflexes are diminished or absent. Pathologically, there is patchy demyelination of nerve roots and distal nerves. Although this disease is rare in children, it is important to recognize since children with CIDP often respond favorably to immunomodulatory therapy.^{1,10}

Other acquired neuropathies should also be considered in children who present with a subacute to chronic peripheral neuropathy. These include those resulting from infectious causes such as HIV and Lyme disease; metabolic derangements such as uremia, hypothyroidism, or vitamin B12 deficiency; inflammatory causes such as vasculitis; or exposure to toxins, such as lead or heavy metals.¹

If this patient's course had been more chronic, inherited neuropathies would be more prominent in the differential diagnosis, especially since the onset is typically in childhood. Charcot-Marie-Tooth disease is the most common inherited neuropathy. Other considerations include the neuropathies of more generalized inherited disorders, such as Krabbe disease and metachromatic leukodystrophy. Inherited neuropathies tend to present with uniform rather than patchy involvement of nerves on electrophysiologic testing, with some notable exceptions.¹ Sensory loss may be more prominent than in CIDP. The time course of inherited neuropathies tends to be chronic, rather than subacute or relapsing, so that findings such as pes cavus or contractures are more commonly observed.^{1,2}

CLINICAL CASE, PART II The patient was admitted to the Neurology service, where he underwent a lumbar puncture. This revealed four white blood cells per mm³, 155 red blood cells per mm³, glucose of 67 mg/dL, and protein of 93 mg/dL. He underwent an MRI of the brain, which was normal, and an MRI of the spinal cord, which revealed enhancement of the anterior nerve roots of the cauda equina. EMG/nerve conduction studies (NCS) revealed severely prolonged distal latencies, decreased conduction velocity (right common peroneal 17.3 m/s [normal ≥ 44 m/s], right tibial 28.7 m/s, left tibial 17.9 m/s [normal ≥ 41 m/s]) with temporal dispersion, and low amplitude bilateral tibial and right peroneal compound motor action potentials (figures 1 and 2). Further laboratory workup for infectious, meta-

Figure 2 Normal motor nerve conduction study for comparison

bolic, toxic, and inflammatory causes of neuropathy was normal. Based on the electrophysiologic findings, cytoalbuminologic dissociation, and nerve root enhancement on MRI, he was diagnosed with CIDP.

DISCUSSION Epidemiology. CIDP is much less common in children than in adults. In a large population of adults the prevalence of CIDP has been estimated at 1–1.9 per 100,000. In the same population, the prevalence of patients under age 20 with CIDP was 0.48 per 100,000.⁵ Since the disease occurs so infrequently in children, knowledge of the clinical characteristics, response to treatment, and prognosis are all based on several small case series, making generalizations difficult.

Clinical characteristics. The most common complaint that brings children with CIDP to medical attention is gait disturbance and falling. This results from symmetric, predominantly motor involvement of the proximal and distal lower extremities. Upper extremity weakness, hand tremor, and ataxia are also present in some cases. Deep tendon reflexes are always reduced or absent.^{1,4,9} Some studies indicate that at least one-third of pediatric patients experience sensory symptoms, characterized by paresthesias, dysesthesias, and large fiber sensory loss.^{2,4,7,9} Cranial nerve involvement, respiratory muscle weakness, and autonomic dysfunction are all uncommon in childhood CIDP.⁹

Prodromal events, most often upper respiratory infections, have been described in 33–57% of children with CIDP in various series.^{3,4,6,8,9} In contrast, as many as 60–80% of children with AIDP (or Guillain-Barré syndrome) have a history of a prodromal event.⁹

The onset of this disease may be insidious over a period of months, or there may be a more acute presentation of symptoms with recurrent episodes.² Compared with adults, children present earlier in the course of the disease, exhibit a more rapid progression of neurologic dysfunction, and are more likely to have a relapsing-remitting course.^{4,7,9}

It may sometimes be difficult to distinguish CIDP from AIDP initially, especially since patients with both conditions can reach maximal motor disability within 4 weeks.⁹ A history of antecedent illness, weakness of facial and respiratory muscles, pain, and autonomic dysfunction are all more common in AIDP.^{1,9}

Pathogenesis. CIDP is an autoimmune disorder in which the inflammatory process is mediated by both the cellular and humoral immune systems.^{1,2} Demyelination is segmental and occurs anywhere from the nerve roots to the distal portion of nerves. In addition

to demyelination, sural nerve biopsy reveals inflammatory infiltrates and subperineural edema. Chronic disease may be associated with “onion bulb” formation, due to concentric proliferation of Schwann cells in the course of repeated demyelination and remyelination.^{1,2,6,11} Axonal loss is variably observed, and may correlate with a more severe prognosis.²

Diagnostic studies. There are three basic diagnostic studies that help support the diagnosis of CIDP. NCS/EMG provide the most data, and can also provide information about the severity of the disease. Lumbar puncture and spine MRI can provide supportive evidence. Laboratory studies can help exclude other causes of neuropathy.

NCS/EMG in patients with CIDP show evidence of a predominantly demyelinating polyneuropathy, typically in a segmental, or nonuniform pattern (figure 1). Some axonal loss may be present. Demyelinating features include diminished motor and sensory conduction velocities, prolonged distal latencies, and prolonged or absent F waves. Nonuniform features include abnormal temporal dispersion, conduction block, and disparities in nerve conduction slowing between nerves or within a nerve.^{1,2,6,9}

CSF analysis in children with CIDP commonly reveals albuminocytologic dissociation, defined as a protein greater than 35 mg/dL and white blood cell count less than 10 per mm³, similar to that seen in AIDP.^{1,2} If there is a significant pleocytosis in the CSF, other conditions should be considered. In two recent case series the mean CSF protein ranged from 194–197 mg/dL.^{8,9} However, not all children with CIDP have an elevated CSF protein, and albuminocytologic dissociation is not specific to AIDP or CIDP, although it provides important supportive information.¹

As observed in AIDP, patients with CIDP may demonstrate enhancement of nerve roots on spine MRI. This enhancement likely relates to disruption of the blood–brain barrier due to the inflammatory process.^{1,8}

Adults with CIDP may have identifiable serum autoantibodies (e.g., anti-GM1, anti-MAG, anti-sulfatide), but these have not been observed in children and are thus not commonly tested.² Sural nerve biopsy is also no longer routinely performed for the diagnosis of CIDP in children.¹

CLINICAL CASE, PART III The patient was treated with IV immunoglobulin (IVIg) at a dose of 2 g/kg over 2 days. He was also treated with 5 days of IV methylprednisolone at a dose of 30 mg/kg, then discharged home on a prednisone taper over the next 10

days. His strength and gait returned to normal over the course of the next month.

Four months later he had the first of two relapses of his symptoms. He was again treated with IVIg 2 g/kg over 2 days. He had no improvement in his symptoms, so 1 month later he began oral prednisone 1 mg/kg/day and monthly IVIg infusions of 2 g/kg, with full recovery after 3 weeks. He later relapsed in the setting of adenoviral pneumonia, and this was treated successfully with an increase in his prednisone dose and IVIg. After recovery the prednisone was weaned to an every other day regimen, and he continues on monthly IVIg. He has no residual symptoms and is back to playing soccer.

Treatment. Immunomodulatory therapy is the mainstay of treatment for CIDP. Our approach to therapy is derived from 1) large adult studies, 2) small case series in children, and 3) our own personal experience with a number of such pediatric CIDP patients. One difference in our approach to pediatric CIDP compared to adults is a higher threshold for the use of steroids.

IVIg is more of a first-line therapy for CIDP in children compared to adults. While there have been no randomized controlled trials in children, several case series have indicated that a large proportion of pediatric patients with CIDP show clinical improvement after treatment with IVIg.^{8,10,11} Our personal experience with several patients correlates with these findings. The initial dose is 2 g/kg divided over 2 to 5 days, and most patients require maintenance therapy of 1 g/kg/day for 1 to 2 days every 1 to 6 weeks.¹¹ Drawbacks to the use of IVIg include cost; the need for IV placement; infusion-related side effects such as headache, nausea, rash, fever, chills, and hypotension; risk of infectious exposure; aseptic meningitis; anaphylaxis in IgA deficient individuals when non-IgA depleted IVIg is used; hemolytic anemia; and thromboembolism.

Plasmapheresis is a reasonable alternative in older children, especially those whose peripheral veins are accessible for large-bore IV lines. In adults, plasmapheresis appears to be of equivalent efficacy to IVIg.^{2,6} Plasmapheresis may need to be administered more frequently than IVIg, although this has not been clearly established across series.⁴ Risks of the treatment include coagulopathy, electrolyte abnormalities, hypotension, and anemia in those treated chronically.

Prednisone was the first agent identified as an effective treatment for CIDP in adults.^{1,10} A large proportion of children in several case series responded favorably to prednisone, usually within several weeks.^{2-4,6,8,10} Recent studies in children have recommended initiating treatment with prednisone at a

dose of 1–2 mg/kg daily or on alternate days, followed by a gradual wean as symptoms improve.^{7,10} The side effects of steroids in children must be taken into consideration, such as weight gain, hypertension, hyperglycemia, cataracts, osteopenia, poor wound healing, infection, and growth suppression. The medical and cosmetic complications of steroid therapy have more substantial long-term consequences in children than in adults, thus we prefer not to use them unless the alternatives are not efficacious or tolerated.

There are little data regarding other options for treatment of children with refractory CIDP. Other immunomodulatory agents such as azathioprine, methotrexate, cyclosporine, cyclophosphamide, and interferon have been used, but at present there are no clear data favoring one of these treatments over another.^{4,6,8}

Prognosis. Children with CIDP have a more favorable outcome than adults, with complete remission or minimal residual weakness seen in the majority of patients.^{3,4,7,8,10} In adults, the relapsing form has a better prognosis than the monophasic form of CIDP, and children are more likely to present with the relapsing form of the disease.^{7,10} In children, the number of relapses does not seem to be associated with the severity of prognosis. However, few studies have followed children to adulthood. In one series most children required treatment for at least 1 to 2 years, although in many cases treatment could ultimately be discontinued.¹⁰ Relapses often occur in the setting of intercurrent illness or weaning of immunomodulatory medication.^{4,8,10} Most of these relapses occur within the first 2 years after diagnosis, although patients have relapsed after 7–10 years.^{8,10}

FUTURE PERSPECTIVES CIDP is an uncommon disorder in the pediatric population. It is a disease that can dramatically affect a child's quality of life, and if left untreated may result in permanent disability. However, if diagnosed properly and treated in a timely fashion, most children with CIDP will respond to immunomodulatory therapy. Children with CIDP typically suffer a relapsing-remitting course and require close monitoring by a neurologist. Nevertheless, the prognosis for remission of neurologic deficits is generally good.

Further research is needed to evaluate the efficacy of different therapies in the pediatric CIDP population, including randomized controlled trials with a sufficient number of patients. The formation of a multicenter consortium could help to pool the experience of different hospitals and enable a large group of patients to be followed over time.

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Neurology 2008;71:e74-e78

DOI 10.1212/01.wnl.0000336646.91734.b1

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