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Chronic Inflammatory Demyelinating Polyneuropathy in Children: A Review of Clinical Characteristics and Recommendations for Treatment

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Context: Chronic inflammatory demyelinating polyradiculopathy (CIDP) is an acquired and autoimmune neuropathy, characterized by a chronic, rapidly progressive, symmetric weakness. In children, abnormal gait is as a first symptom of muscle weakness.
Evidence Acquisition: The diagnosis of CIDP is on the basis of clinical characteristics, electrodiagnostic that shows the severity of the disease, lumbar puncture and spine magnetic resonance imaging (MRI).
Results: The first-line treatments in childhood CIDP are intravenous immunoglobulin (IVIG), corticosteroids, and plasmapheresis. Response to first-line therapies is usually satisfactory; nevertheless, recommendations regarding the choice of second-line therapy can only be prepared on the basis of the existing practice described in some of the case reports.
Conclusions: This review demonstrated the clinical presentation, diagnosis, and treatment of childhood CIDP.

Keywords: Childhood; Inflammatory Demyelinating Polyradiculopathy; Chronic; Therapy

1. Context

Chronic inflammatory demyelinating polyradiculopathy (CIDP) is an acquired neuropathy, characterized by a chronic, rapidly progressive, proximal and distal symmetric weakness, accompanying with hyporeflexia and sensory symptoms (1). 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 (2). The two traditional types of acute inflammatory demyelinating neuropathy (AIDP; Guillain-Barre syndrome) and CIDP have similar presentations except that the symptoms peak in less than four weeks in AIDP and are monophasic, and advancement for eight weeks or more in CIDP. For an illness that reaches its hardship between 4 - 8 weeks, the term subacute demyelinating polyneuropathy has been used (3). CIDP is an autoimmune disorder and demyelination is segmental and occurs everywhere from the nerve roots to the distal portion of nerves. In addition to demyelination, biopsy of nerve reveals inflammatory infiltrates and subperineural edema (4, 5). The diagnosis of CIDP is based on electrodiagnosis that shows the severity of the disease, lumbar puncture and spine magnetic resonance imaging (MRI). Laboratory studies can help to exclude other causes of peripheral neuropathy (6, 7). Immunomodulatory therapy is the basis of treatment for CIDP. The standard therapies for CIDP are intravenous immunoglobulins (IVIG), corticosteroids and plasma exchange, but about 15% of cases are treatment refractory (8). Childhood CIDP is rare but potentially treatable and with favorable outcomes. Therefore, early diagnosis and initial treatment decline demyelination and prevent from secondary axonal loss. Hence, we prompted to review most of the literatures about childhood CIDP with respect to clinical presentation, especially the atypical ones, as well as treatment responses.

2. Evidence Acquisition

PubMed and Google Scholar database were searched for original articles and reviews on CIDP using the search terms "CIDP", "chronic inflammatory demyelinating neuropathy", "child or children", "clinical" and "treatment", alone and in combinations. The search was limited to articles published in English-language journals, selecting those published from 1994 to 2015. The abstracts were retrieved and selected by content and full articles were obtained as applicable.

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3. Results

3.1. Epidemiology

CIDP is much less common in children than in adults. The prevalence of CIDP in adults has been estimated at 1 - 1.9 per 100 000. In contrast, the prevalence of patients under 20 years old with CIDP was 0.48 per 100,000 (9, 10). Males are more frequently affected than females with an incidence of 0.58 in males and 0.38 in females per 100,000 (10). Congenital presentation has been described as extremely rare (11, 12). Since the disease occurs so infrequently in children, the knowledge of clinical characteristics, response to treatment and prognosis are all based on several small case series, making generalizations difficult.

3.2. Pathophysiology

Although the cause of CIDP and its variants is unknown, there is evidence to support the suggestions that the disorders are immunologically-based and have multiple causes. Both the cellular and humoral components of the immune system seem to be involved in the pathogenesis of CIDP and its variants (13). The immune development starts with loss of tolerance to self-antigens by mechanisms such as molecular imitation or cytokine stimulation and activating T-cell recognition of autoantigens, which encompass both cellular and humoral responses (14). CIDP appears to be mainly T cell-mediated with no reports of antibodies in childhood and a candidate autoantigen (P0 myelin protein) in only 20% of adults (15-17). In adults with CIDP, both monoclonal and polyclonal autoantibodies (ganglioside and sulfatide autoantibodies, acidic glycolipids , proliferating non-myelinating human, Schwann cells , and b-tubulin autoantibodies) have been revealed in subgroups of patients, but these have not been detected in children and thus have not usually been tested (2, 5, 16, 18). Infiltrates around the epineurial vessels (non-invading walls) are commonly CD4 and CD8 T cells, but are seldom found in childhood compared to adult CIDP (15, 17, 19).

3.3. Clinical Manifestations

CIDP occurs in young children, generally between 5 - 18 years of age, and may cause long-lasting disability if not treated quickly. Several children may have more recurrent relapses than adults, but they mostly respond to treatment and tend to have a more encouraging long-term outcome than adults (20-22). In many patients who develop CIDP during childhood, the disease appears to stop developing after several years. Several children with CIDP can experience complete remission or stable remaining deficits without the need for additional treatments. The most common complaint of a child with CIDP is gait disorder and falling (2). CIDP in children presents with symmetric, mostly motor neuropathy, evolving over several weeks or months, frequently developing to delay or loss of ambulation. Upper extremity weakness, hand tremor (19), and ataxia (23) are also seen in some cases. There is also reduced or absence of deep tendon reflexes (24). Some studies showed that at least one-third of pediatric patients may have sensory symptoms such as paresthesias, dysesthesias and large fiber sensory loss (25). Neuropathic pain is minus. The diagnostic criteria, revised at the childhood CIDP consortium, contain mandatory clinical criteria that reveal the disease presence and a development over at least four weeks (15). According to the Consortium's criteria, the absence of abnormality in the cerebrospinal fluid (CSF) means that this is only a possible case of CIDP. A review of mostly adult experiences biased an approach to the classification of CIDP that uses the pattern of clinical involvement (26). Various patients may show multifocal acquired demyelinating sensory and motor neuropathy (MADSAM). Connolly illustrated two major clinical types of CIDP in children. The first was a monophasic disorder getting maximal weakness over three months and the second was a disorder that progressed even more slowly, but predisposed to have a relapsing and remitting course (5). Monomelic neuropathy is also described as a variation in CIDP. McDonald et al. presented a child of nine years old who showed right upper limb weakness; she was lost to follow-up, but re-presented three years later with extensive progressive weakness in her other limbs. She showed improvement in the right arm after years (27). Jha et al. reported rare features of CIDP with phrenic nerve involvement and respiratory failure that required mechanical ventilation (28). Ryan et al. describe three in a group of 16 children with mild respiratory symptomatology (20). One exceptional case was described, where associated unilateral phrenic nerve palsy in an 11-year-old girl resulted in respiratory failure (23). Cranial neuropathy is unusual (5%) in CIDP (29). Exceptually, facial weakness was found in 20-33% of the children (21). In some studies, cranial nerve dysfunction has been described (20, 25, 30, 31). In these children, diplopia has been a common feature (25, 30-32). Other oculomotor symptoms comprised afferent pupillary defect and partial right VIth nerve palsy, ptosis, abduction deficit and unilateral tonic pupillary dilatation (20, 33). Bulbar disorders resulted in dysphagia, and mastication, hypophonia and lingual fasciculations (31, 34, 35). Generalized facial weakness and dysarthria have also been shown (30-32, 34). Sensorineural deafness was defined in one patient (35).

3.4. Congenital Chronic Inflammatory Demyelinating Polyneuropathy

Demyelinating neuropathies exciting in infancy are unusual. Neuropathy at this early age would frequently suggest a genetic or congenital cause. Sladky et al. reported six patients with CIDP of infancy (36). The onset of the disease was at birth for two patients and after two years of age for three of the residual four. At first, the patient

had normal fetal movements with a sudden lack of movements two weeks before delivery. The presence of calcaneovalgus at birth as well as the early neurophysiological findings of re-innervation advocated that the demyelinating process initiated in the utero. Pearce et al. also, reported a female infant with reduced movements of right wrist and left foot at birth (12).

3.5. Clinical and Paraclinical Diagnosis

The diagnostic criteria for childhood CIDP were last revised during the 88th European neuromuscular center conference (Table 1). Based on these criteria, a diagnosis of "possible" or "confirmed" CIDP can be prepared (15).

Based on the criteria, the electrophysiological finding of CIDP must show the following three of four conditions: (1) reduction in conduction velocity (CV) in two or more nerves; (2) conduction block or abnormal temporal dispersion in one or more motor nerves; (3) prolonged distal latencies in two or more nerves; (4) absent or prolonged minimal F-wave latencies in two or more nerves. Electrophysiological studies in children suspected to CIDP should contain the study of four motor nerves and the results must be compared with well-recognized childhood normal values (15).

Diffuse nerve root thickening and gadolinium enhancement on spine MRI were shown in 60% of adult CIDP patients (37). These thickened nerves displayed increased signal intensity on T2-weighted images, predominantly evident on short Tau inversion recovery (STIR) images. Brain MRI revealed diffuse thickening of bilateral trigeminal nerves (38). Cranial nerve thickening in CIDP has been reported in adult studies, as well as rarely in children (32, 39). These findings have also been detected in childhood CIDP and can support the diagnostic certainty when present, but it should be considered that similar MRI findings may appear in inherited neuropathies such as Charcot-Marie-tooth disease (40-42). MRI finding does not appear to correlate with the disease activity, the disease severity or any clinical or laboratory findings (15). However, Rossi et al. reported a significant difference in nerve root enhancement (NRE) of patients with improving CIDP with respect to those with stable or progressing disease at the time of follow-up MRI (43).

Table 1. The Diagnostic Criteria for Childhood Chronic Inflammatory Demyelinating Polyradiculopathy (CIDP)

Mandatory Clinical Criteria
Progression of muscle weakness in proximal or distal muscles of upper and lower extremities over at least four weeks; alternatively, when rapid progression (Guillain-Barre-like presentation) is followed by a relapsing or protracted course (more than one year) and areflexia or hyporeflexia
Paraclinical Finding
Patients must demonstrate at least three of the following four major electrophysiological abnormalities in motor nerves or two of the major plus two of the supportive criteria
Cerebrospinal Fluid Studies
-CSF protein > 35 mg/d
-Cell count < 10 cells/mm^3
Nerve Biopsy Features
-Nerve biopsy with predominant features of demyelination
Exclusion Criteria
-Clinical features or history of a hereditary neuropathy, other diseases or exposure to drugs or toxins that are known to cause peripheral neuropathy
-Laboratory findings including nerve biopsy or DNA studies that show evidence for a different etiology other than CIDP
A: confirmed CIDP: mandatory clinical features and electrodiagnostic features and cerebrospinal fluid features.
B: possible CIDP: mandatory clinical features and one of the three paraclinical findings (fulfillment of electrodiagnostic, CSF or biopsy criteria)
Major Electrophysiological Criteria
1. Conduction block or abnormal temporal dispersion in one or more motor nerves at sites not prone to compression
2. Reduction in conduction velocity (CV) in two or more nerves: < 75% of the mean minus 2 standard deviations (SD) CV value for age
3. Prolonged distal latency (DL) in two or more nerves: > 130% of the mean 2 SD DL value for age
4. Absent F-waves or prolonged F wave minimal latency (ML) in two or more nerves: > 130% of the mean 2 SD F wave ML for age.
Supportive Electrophysiological Features
When the conduction block is absent, the following abnormal electrophysiological parameters are indicative of non-uniform slowing and thus of an acquired neuropathy-abnormal median sensory nerve action potential (SNAP), while the sural nerve SNAP is normal. - Abnormal minimal latency index (TLI). - Difference of > 10 m/s in motor CVs between nerves of upper or lower limbs (either different nerves from the same limb, for example left median versus left ulnar, or the same nerve from different sides, for example left versus right ulnar nerves).

3.6. Differential Diagnosis of Childhood Chronic Inflammatory Demyelinating Polyradiculopathy (CIDP)

Other acquired neuropathies should also be considered in children who present subacute to chronic peripheral neuropathy. These contain infectious diseases such as HIV and Lyme disease; metabolic disorders such as uremia, hypothyroidism or vitamin B12 deficiency; inflammatory origins such as vasculitis; exposure to toxins such as Glue sniffing, lead or heavy metals and also diphtheria, lymphoma and porphyria (4, 25, 44). In patient with chronic course, inherited neuropathies would be more noticeable in differential diagnosis, particularly since the onset is usually in childhood. These include metachromatic leukodystrophy, Krabbe's disease, hereditary motor sensory neuropathies (HMSN) (Charcot-Marie-tooth disease) with types 1a, 1b, X, and hereditary liability to pressure palsies. Distinguishing between hereditary and acquired neuropathies includes long-standing weakness without relapses, distal weakness more than proximal weakness, typically more severe sensory loss, and uniform rather than patchy involvement of nerves on electrophysiologic testing (4). The sensory loss may be more prominent than CIDP. The course of inherited neuropathies tends to be chronic rather than subacute or relapsing, so that findings such as pes cavus or contractures are more frequently observed (4, 5). Family history and examination of parents and siblings should be considered when a genetic neuropathy is suspected (45).

3.7. Treatment

Treatment in CIDP should be deliberated at controlling the inflammation and preventing from axonal degeneration. The first-line treatments in childhood CIDP are IVIG, corticosteroids, and plasmapheresis. Efficacy appears to be equivalent for the three therapies and the choice for one of them is dependent on each individual's conditions (15, 46, 47). However, a combination is often used (48). The initial response to each of these therapies in adult CIDP is 60% compared to 80% - 100% initial response rates in children (49).

3.8. Intravenous Immunoglobulin

Most children showed a good response to initial IVIG treatment (25, 30, 34, 50). Best response to IVIG occurred in infants and children with generalized and constant demyelination of recent onset. In such situation, this treatment had remission in 90% of cases (51). The value of IVIG therapy would be limited in patients with established axonal loss. The immunomodulatory effects of IVIG occurred by neutralizing the pathogenic cytokines and autoantibodies as well as inhibiting the complement activity (52). Headache, fever, nausea and vomiting are its side effects. Severe side effects can include anaphylaxis, thromboembolism, aseptic meningitis, renal failure and congestive heart failure (53). The most frequently used dosage is a course of 0.4 g/kg/day for five days, either a single treatment or repeated every three to four weeks (19, 20, 22, 54-56). Some groups prefer to administer 2 g/kg over two (25, 57) or three days (58) or 1 g/kg during two days per month (35, 59). Others prefer 0.4 g/kg/alternate day (combined with plasma exchange) or weekly infusions of 0.8 g/kg (60).

3.9. Prednisone

Prednisone is best appropriated for younger patients with CIDP who have few other medical illnesses (61). Corticosteroids apply their benefits through some immunological mechanisms (62). Steroids induced short-term improvement in 71% - 100% of children in small series (63). As a first-line therapy, oral prednisone is usually administered at a dose of 1 - 2 mg/kg/day in the initial four to six weeks, then reduced over the next four to six weeks (45, 64), or even by tapering over 3 - 6 months.6 Interval therapy (2 mg/kg/day for 3 - 8 days, repeated every four weeks) and also alternating therapy (2 mg/kg/alternate day) have been designated (58, 65). In some patients, high-dose 'pulse' methylprednisolone therapy (15 - 20 mg/kg/day for three days) was intravenously administered before the origination of oral prednisone therapy (31, 33, 48). The side effects of long-term use of corticosteroids in children include osteopenia, growth suppression, cataract, immune compromise, hypertension, hyperglycemia, gastrointestinal symptoms and weight gain (45).

3.10. Plasmapheresis

Plasmapheresis is an appropriate alternative in older children, especially those whose peripheral veins are available for large-bore intravenous lines. In adults, plasmapheresis seems to be of equivalent efficacy to IVIG (5, 20), whereas plasma exchange (PE) is superior to placebo for adult CIDP with comparable efficacy to IVIG; this therapy seems to be less beneficial for childhood CIDP (66, 67). Although 60% of patients reply to PE, it is less frequently applied in children because of procedural difficulties with installation of central catheters and it may be the reason of its limited use in young children (25). Only 14% of patients showed a good response to PE as a first-line therapy portentous, which it is less valuable than other standard treatments in childhood CIDP (50). In the reports on childhood CIDP, PE therapy comprised three sessions of six days (15, 54), five exchanges of a plasma volume all over 10 - 14 days (30), repeated processes at two-to-four-week intervals over more than one year (34) or alternate day PE, collective with IVIG (60). Patients intractable to immunosuppressants/IVIG may improve when PE is followed proximately by IVIG (60, 68).

3.11. Immunosuppressive and Cytotoxic Drugs

Immunosuppressants are approved for second-line therapy. These contain azathioprine, cyclosporine A, cy-

clophosphamide, tacrolimus, mycophenolate mofetil, methotrexate, interferon alpha and beta-1a, rituximab, alemtuzumab, and also autologous stem cell transplantation (25, 69). Azathioprine is commonly administered when first-line therapy is unsuccessful or when a dose decline of corticosteroids is predicted. The doses of azathioprine consumption in childhood CIDP were 1 mg/kg/day (in mixture with corticosteroids and IVIG), and 2 - 3 mg/kg/day up to 50 - 150 mg/day (28, 48, 58, 65). Cyclosporine A inhibited the activation and proliferation of T cell. The dose of cyclosporine was 5 mg/kg/ day (70). Its adverse effects included electrolyte disorders, crises of hypertension, vomiting, edema, renal failure, and hirsutism (71). Mycophenolate mofetil was designated to result in a partial response in one patient; in association with corticosteroids, it improved motor power in an eight-year-old girl (25, 35). Methotrexate, a folic acid analogue blocking DNA creation, showed notable response in a one-year-old boy for two years after discontinuing azathioprine due to vomiting and no benefit from cyclosporine (14). The dose of drug with good effect was 10 mg weekly (20). Another drug was Cyclophosphamide with a dose of 4 mg/kg/day. From all of the side effects, this drug only showed minimal bone marrow depression after nine months of consumption (20). Interferon-a-2a or interferon-b were used when the patient was refractory to prednisolone, azathioprine, plasma exchange and IVIG or had a fractional response to IVIG/PE and relapses on prednisone, azathioprine and cyclosporine (65). In some studies, the use of monoclonal antibody such as rituximab (anti-CD20) and alemtuzumab (anti-CD52) was advised when the patient was resistance to IVIG, prednisolone and azathioprine and also patients with refractory childhood CIDP (25, 72-75).

3.12. Prognosis

In comparison with adults, children with CIDP have complete remission in about 70% - 100% of cases or minimal residual weakness appeared in majority of patients (5, 25). Pain at onset and infectious prodromal illness suggest a better outcome while axonal loss on electrodiagnostic studies predicts a poor prognosis (5). Nevo et al. reported that the duration of the initial onset of the weakness was associated inversely with disability (21). Therefore, children who initially progressed to their nadir of weakness over one to three months had a tendency to a monophasic course and were more likely to recover entirely. Children who initially progressed over more than three months had a tendency to a more chronic, relapsing-remitting course (21).

4. Conclusions

CIDP is an important acquired and rare neuromuscular disorder of childhood. In comparison with adults, it may appear more sub-acute and with numerous relapses. The obvious response to initial immunomodulatory therapy remained consistent and rapid, with improvement in all children, and an excellent outcome from the initial episode in most of them. The initial choice of therapy would remain IVIG. The addition of corticosteroids is warranted in patients with either a poor response to IVIG or in those with a relapsing sequence. There is insufficient evidence to agreement on any recommendations about the use of immunosuppressive and cytotoxic agents in childhood CIDP. With respect to well responses to standard therapies, we would like to emphasize the importance of initiating the treatment as early as possible with the purpose of reducing the demyelination and secondary axonal damage.

Conflict of Interest

None declared.

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