Progressive Chronic Inflammatory Demyelinating Polyneuropathy in a Child with Central Nervous System Involvement and Myopathy

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A B S T R A C T

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a chronic disorder, manifesting with monophasic or relapsing course. Progressive course is rare in children. The article presents a boy with progressive generalized muscle weakness and areflexia since the age of two, developed after viral infection. Electromyoneurography showed severe neurogenic lesion, with myopathic pattern in proximal muscles. Increased serum ganglioside antibody titers (anti-GM1 and anti-GD1b) were registered. Sural nerve biopsy revealed demyelination and onion bulbs. Inflammatory perivascular CD3 positive infiltrates were present in muscle and nerve biopsies. Brain magnetic resonance imaging showed cortical atrophy, hyperintensities of the white matter and gray matter hypointensities. Improvement occurred on intravenous immune globulins and methylprednisolone treatment. Demyelination might develop in central and peripheral nervous system associated with inflammatory myopathy in patients with progressive course of CIDP.

Key words: *chronic inflammatory demyelinating polyneuropathy, inflammatory myopathy, central nervous system, child, antiganglioside antibody*

Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) manifests itself with monophasic, relapsing or progressive course. Children with CIDP present with more severe clinical features than adults[1]. It is characterized by multifocal demyelination involving nerve roots, intermediate nerve segments and nerve terminals. Demyelinating changes of the brain have been reported in some adult patients with CIDP[2], and scarcely among pediatric patients, mainly in the white matter[3]. The pathogenesis of CIDP is still unknown, but involvement of the immune system has been firmly established[4]. Different ganglioside autoantibodies have been detected in adults with CIDP[5].

We present a case of a boy with early onset progressive muscle weakness since the age of 2, associated with focal central nervous system (CNS) involvement of white and gray matter, inflammatory myopathy and positive anti-GM1 ganglioside antibodies.

Case Report

A boy of normal psychomotor development, now at the age of 10, was born after normal pregnancy and labor. At the age of two he manifested progressive generalized muscle weakness, hypotonia and small muscles hypotrophy, developed three weeks after viral infection. Electromyoneurography performed after six months showed axonal lesion and mild loss of motoneurons and myopathic pattern in proximal muscles. Muscle biopsy showed muscle fiber regeneration and necrosis, perivascular inflammatory infiltrates, and subsarcolemal accumulation of mitochondria without visible structural abnormalities. Brain magnetic resonance imaging (MRI) showed mild cortical atrophy, hyperintensities of the white matter and the gray matter hypointensities, whereas angiography was normal. He was treated with physiotherapy, without improvement.

At the age of 4.5, examination revealed muscle weakness (grade 4), generalized hypotonia and small muscles

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hypotrophy, peroneal gait, positive Gowers' sign, areflexia, and right abducens palsy. Functional score of motor deficit was estimated according to Hughes grading scale (grade 0 – healthy, grade 1 – minor signs or symptoms not interfering with normal social life, grade 2 – able to walk without support of a stick but incapable for manual work, grade 3 – able to walk 5 meters with assistance, grade 4 – confined to bed or chairbound, grade 5 – requiring assisted ventilation, grade 6 – dead)[6]. Electromyoneurography showed severe neurogenic lesion, spontaneous activity, low compound muscle action potentials (1 mV), decreased motor nerve conduction velocity (7.9–11.3 m/s; normal values 56.14±4.96 m/s)[7,8], prolonged distal latency, and myopathic pattern in proximal muscles. Cerebrospinal fluid examination revealed increased protein content (0.40 g/L). Proton magnetic resonance spectroscopy indicated decreased levels of N-acetyl--aspartat in cerebral cortex and increased lactate. Positive serum anti-GM1 (IgM, 2000 Bühlmann Titer Units-BTU) and anti-GD1b (IgG, 2300 BTU) antibodies were detected. CK was 97–127 U/L (normal values 75–230 U/L at 37 °C). Follow-up brain MRI showed multiple white matter lesions, and repeated muscle biopsy showed neurogenic atrophy. Sural nerve biopsy revealed demyelination and onion bulbs. Inflammatory perivascular CD3-positive infiltrates were present in both biopsies. Visual evoked potentials showed bilaterally prolonged latencies. Metabolic and immunological tests were normal, same as aryl-sulphatase A and galactocerebrosidase activities. Mutations for Charcot-Marie-Tooth disease 1A and hereditary neuropathy with pressure palsies, as well as connexin and spinal muscle atrophy mutations were excluded. Mitochondrial genome analysis showed gene polymorphism in sequence T13933A in ND5 gene, confirmed by mitochondrial genome sequencing. Methylprednisolone treatment (1 mg/kg/day) induced significant improvement after four weeks. Tapering off the steroids, a few months later, caused serious neurological impairment, so steroids were reintroduced at a lower dose.

On examination at the age of 6, peroneal gait, positive Gowers' sign, muscle weakness (grade 2), small muscles hypotrophy, areflexia, distal hypesthesia, left talocrural and interphalangeal 5th finger contractures were present. Follow-up electromyoneurography showed progression of the neural loss, inelicitable compound muscle action potentials on the left peroneal nerve and very low (250 μV) on the right, with prolonged distal latency and completely absent sensory neural potentials. Further clinical improvement occurred after intravenous immune globulins (IVIG) treatment (2 g/kg/5days). The following electromyoneurography showed very low, but elicitable left peroneal (250 μV), and increase of the amplitude of the right peroneal compound muscle action potentials. On examination at the age of 7.5, he manifested slight improvement of muscle strength (grade 1), without additional changes in neurological examination. The recent electromyoneurography, at the age of 9.5, showed inelicitable left peroneal nerve compound muscle action potentials (Table 1 and Figure 1). Azathioprine was introduced (1 mg/kg/day). He was treated with maintenance steroid dose (0.5 mg/kg) on alternate day, azathioprine (1mg/kg/day) and periodic intravenous immune globulins treatment (1 g/kg/3days) every 8–10 weeks. Follow-up brain MRI and proton magnetic resonance spectroscopy at the age of 8 showed improvement with hyperintensities of the white matter mostly in frontal region (Figure 2).

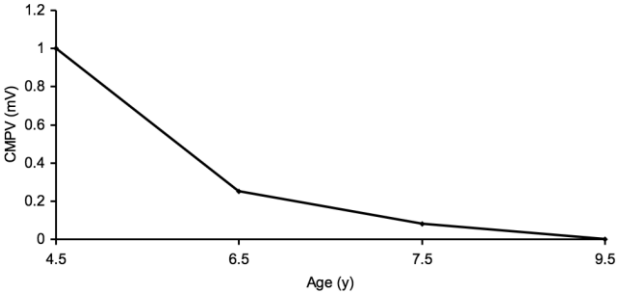

Fig. 1. Decreasing of compound muscle action potential amplitude during long term follow-up recorded in extensor brevis mus-

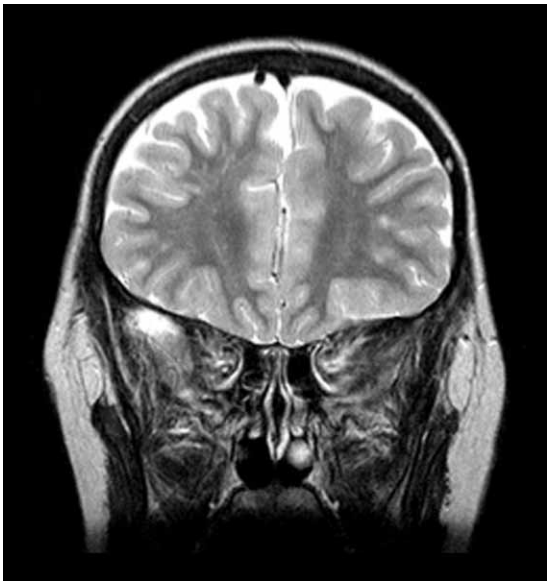

Fig. 2. T2 – weighted brain magnetic resonance imaging (MRI) coronal section (repetition time (TR), 5800.0 / echo time (TE), 90.0 ms). Hyperintensity of the white matter in left frontal region.

Discussion

Our patient manifested limb girdle muscle weakness and progressive small muscles atrophy associated with CNS involvement. Electromyoneurographical findings fulfilled diagnostic criteria for CIDP[9,10], which was confirmed by nerve biopsy, whereas muscle biopsy showed myopathy with perivascular inflammatory infiltrates. CIDP manifests itself with broad heterogeneous clinical

TABLE 1
FOLLOW UP OF NEUROGRAPHIC ABNORMALITIES

Age (yrs.)	MNCV (m/s)		CMAP (mV)		DL (ms)	
	M	P	M	P	M	P
4.5	11.3 56.4±4.22*	7.9 56.14±4.96*	nd	1 7.1±4.76*	0.71 2.27+7/–0.45*	2 3.01±0.43*
6.5#	15.5 59.5 ±5.1*	8.33 57.05±4.54*	S1 – 1 S2 – 0.5 12.37±4.79*	S1 – 0.25 S2 – 0.5 8.15±4.19*	1.17 2.73±0.44*	0.9 3.25±0.51*
6.5##	nd 59.5 ±5.1*	12 57.05±4.54*	nd	S1 – 1 S2 – 1 8.15±4.19*	nd	1.11 3.25±0.51*
7.5	14.2 59.5 ±5.1*	13 57.05±4.54*	0.6 12.37±4.79*	0.08 8.15±4.19*	1.11 2.73±0.44*	0.5 3.25±0.51*
9.5	13.3 59.5 ±5.1*	0 57.05±4.54*	0.8 12.37±4.79*	0 8.15±4.19*	0.93 2.73±0.44*	0 3.25±0.51*

MNCV – motor nerve conduction velocity, CMAP – compound muscle action potential, DL – distal latency, M – median nerve, P – peroneal nerve, S1- distal stimulation point, S2 – intermediate stimulation point, y – years, nd – not done, *normal values, #2 years after steroid treatment introduction, ##4 weeks after intravenous immunoglobulin (IVIG) treatment

and electrophysiological symptoms[2]. Axonal features are observed rarely in children[10]. Children with CIDP manifest more proximal muscle weakness[11]. The diagnosis of CIDP in our patient was established according to proposed electrophysiologic criteria by American Academy of Neurology in 1991[9]. His electromyoneurography showed the conduction abnormalities in both distal and intermediate segments with prolonged distal latencies more than 125% of the upper limit, and pronounced decreasing of motor nerve conduction velocity. Multifocal demyelination is a diagnostic hallmark of CIDP, but the degree and distribution of demyelination is variable[12]. Recently, conduction block/temporal dispersion have been proposed as more sensitive and reliable electromyoneurographical criteria for the diagnosis of CIDP[13]. Other than pronounced demyelinating polyneuropathy, electromyoneurography in our patient showed absent or very low compound muscle action potentials, especially on distal stimulation, suggesting severe and afterwards complete axonal degeneration. Primary demyelination is the main pathological feature in CIDP. However, axonal degeneration in distal parts of the nerves was seen on autopsy in patients with CIDP[14]. Axonal degeneration is often responsible for neurological impairment in autoimmune and inherited disorders of central and peripheral nervous system[15]. Distribution pattern of electrodiagnostic abnormalities in inflammatory demyelinating polyneuropathies correlates with clinical features, response to treatment and outcome[12]. In accordance with observation reported, our patient showed diffuse pattern with slowly progressive and relapsing course.

Onion bulbs and inflammatory perivascular CD3 positive infiltrates were registered in his nerve biopsy. Inflammatory infiltrates are registered often around epineurial blood vessels, consisting of CD4 and CD8 T lymphocytes[10], thus suggesting the important role of the cellular immunity in the pathogenesis of CIDP. Macrophages are involved in striping of the myelin from axons with variable axonal loss.

Proximal muscle weakness, myopathic pattern in electromyoneurography and CD3 positive infiltrates in muscle biopsy of our patient are compatible with the diagnosis of inflammatory myopathy. Normal CK values do not exclude the muscle fibers involvement in our patient. Polimyositis associated with CIDP has never been reported. However, Kimura et al. described a boy with myasthenia gravis and CIDP, suggesting the spreading of immune response from neuromuscular junction to peripheral nerve[16].

Cerebrospinal fluid analysis of our patient revealed slightly increased protein content (0.40 g/L, normal values up to 0.37 g/L) and suspected IgG intrathecal synthesis, suggesting disfunction of the blood – cerebrospinal fluid barrier surrounding the nerve roots.

IgG and IgM anti-GM_1 antibodies were also present in our patient as reported previously in adult patients with CIDP[5]. The role of these antibodies in the pathogenesis of the disease is unknown. Gangliosides may act as target antigens in the immunopathogenesis of neuronal/myelin damage. Our patient manifests both central and peripheral nervous system involvement. None of the reported patients with CIDP and elevated IgM anti-GM1 antibodies manifested definite CNS involvement, but showed spontaneous activity and similar electrophysiological findings as our patient[17]. In patients with amyotrophic lateral sclerosis expression of antiganglioside antibodies varies between 5.5–78%[18,19] also suggesting that increased anti-GM1 IgM titers are closely associated with purely motor or resembled motor neuron disease mostly reversible by treatment.

CNS involvement in CIDP presenting initially with spinal symptoms and MRI intramedullary lesion has been observed in the child. Later on, demyelination developed in the brain and peripheral nerves[3]. Differential diagnosis of CIDP in children includes hereditary sensory and motor neuropathies, leukodystrophies (metachromatic, Krabbe) and other demyelinative disorders of CNS, as well as aryl-sulphatase A pseudodeficiency[20], which were excluded in our patient. Some patients with Charcot-Marie-Tooth disease show worsening and inflammatory infiltrates in their biopsies[21] clinically responding to corticosteroids. It might also be possible that patients with CIDP and mutations found in Charcot-Marie-Tooth disease manifest more pronounced symptoms[22].

Some of the clinical symptoms in our patient resemble mitochondrial encephalomyoneuropathies. CNS involvement included radiological signs of both white and gray matter. Proton magnetic resonance spectroscopy revealed high lactate and decreased levels of N-acetyl--aspartate while the first biopsy performed at the age of 3 showed subsarcolemal accumulation of mitochondria without visible structural abnormalities. Both of these findings are not specific and might be present secondary to different inflammatory conditions[23,24,25]. Visual evoked potentials analysis showed signs of demyelinating optic neuropathy. Optic neuropathy is not an uncommon finding in CIDP. The association of a multiple sclerosis (MS)-like disease and pathogenic Leber's hereditary optic neuropathy (LHON) mutations was reported previously in several publications[26,24,27]. Very recently the pathology of the MS-like lesions on autopsy was investigated in a patient carrying the mitochondrial DNA 14484 pathogenic LHON mutation[28]. Nuclear and mtDNA analysis in our patient revealed only gene polymorphism, confirmed by mitochondrial genome sequencing, thus excluding pathogenetic role of mitochondrial DNA mutation.

Immunomodulating treatment has been shown to be effective in children with CIDP[10,1]. IVIG is effective as the first line therapy in CIDP according to the controlled clinical trials. IVIG action in CIDP includes inhibition of complement and membranolytic attack complex activation beside modulation of autoantibodies as well as of inhibition or activation of receptors[29]. Remissions are usually achieved after IVIG treatment but the vast majority of patients still need additional intermittent IVIG treatment at the dose 0.15–0.4 g/L every 6–8 weeks. The tapering off the steroids in our patient resulted in clinical deterioration and progression of small muscles atrophy. Some authors reported steroid dependant course of relapsing CIDP, which did not respond well to IVIG[30]. Children with rapid progression of CIDP are more responsive to steroids[30,10]. Azathioprine has been shown to be effective in the treatment of CIDP in children after initial remission induction with steroids. None of the serious side effects occurred during 12 years of follow-up[10]. The efficacy of interferon β1 (a or b) still waits for proper investigation of its place in treatment of CIDP.

Follow-up electromyoneurography showed slight improvement of distal compound muscle action potentials in our patient after IVIG treatment, as previously reported in adults[31]. Clinical improvement thus correlated with resolution of conduction block in distal nerve segments. However, inelicitable peroneal nerve and severe axonal loss were observed most recently in our patient. Resistance to the treatment might be induced by the axonal involvement during the long course of the illness[12].

Clinical outcome and response to treatment are excellent in children with CIDP, although electrodiagnostic parameters of pronounced demyelination or axonal damage might remain unchanged during long-term follow--up[20].

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KRONIČNA UPALNA DEMIJELINIZIRAJUĆA POLINEUROPATIJA PROGRESIVNOG TIJEKA U DJEČAKA UDRUŽENA SA ZAHVAĆANJEM SREDIŠNJEG ŽIVČANOG SUSTAVA I MIOPATIJOM

S A Ž E T A K

Kronična upalna demijelinizirajuća polineuropatija se očituje monofazičnim tijekom ili ponavljajućim pogoršanjima bolesti. Progresivan tijek bolesti u djece je rijedak. U članku prikazujemo dječaka sa progresivnom generaliziranom mišićnom slabošću i arefleksijom, koja se razvila u dobi od 2 godine, nakon preboljele virusne infekcije. Elektromioneurografijom je nađeno teško neurogeno oštećenje s miopatskim uzorkom u proksimalnim mišićnim skupinama. U tijeku obrade dokazan je povišeni titar serumskih protutijela na GM1 i GD1b gangliozide a pregledom biopta suralnog živca potvrđena je hipertrofična demijelinizirajuća neuropatija i formacije poput lukovica. Upalni CD3 pozitivni infiltrati nađeni su u bioptatima mišića i živca. Magnetska rezonancija mozga pokazala je kortikalnu atrofiju, hiperintenzitete bijele tvari i hipointenzitete sive tvari. Poboljšanje je uslijedilo nakon intravenske primjene imunoglobulina i terapije metilprednisolonom. Demijelinizacija se može razviti u središnjem i perifernom živčanom sustavu udružena s upalnom miopatijom u bolesnika s progresivnim tijekom kronične upalne demijelinizirajuće polineuropatije