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Tytuł: „Diagnostyka kliniczno-elektrofizjologiczna przewlekłej zapalnej polineuropatii demielinizacyjnej u dzieci.”

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne.

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ABTSRACT

Clinical and electrophysiological characteristics of children with chronic inflammatory demyelinating polyneuropathy.

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare heterogeneous autoimmune acquired polyneuropathy. The typical form of the disease is characterized by progressive for more than 8 weeks weakness and/or sensory symptoms and hypo- or areflexia. To date no specific marker has been found, therefore the diagnosis is made mainly on clinical features and nerve conduction studies results (NCS). It is worth mentioning that so far 15 different criteria for the diagnosis of CIDP have been published, which may indicate diagnostic difficulties and a heterogeneous clinical presentation of this autoimmune polyneuropathy.

The disease occurs mainly in adults, rarely in children. In the youngest group of patients the difficult part of diagnosing of CIDP is the differential diagnosis because most childhood neuropathies are hereditary. Furthermore, the more dynamic course of the disease, occurring more often in this age group than in adults, needs to differentiated from Guillain-Barre syndrome (GBS). Another diagnostic challenge in childhood CIDP is the diagnosis of atypical variants of the disease, which have not been fully understood and described in the youngest group of patients.

The first-line treatment, according to the latest 2021 EFNS/PNS guideline for CIDP, are intravenous immunoglobulin (IVIg) or oral/intravenous corticosteroids therapy. It is worth emphasizing that subcutaneous immunoglobulin (SCIg) has recently been available in Poland as maintenance of the treatment after stabilization with IVIg, which significantly improves the patients' quality of life, as it reduces frequent hospitalizations. If the response to these treatments is insufficient both IVIg and corticosteroids can be given as a combined therapy because an enhanced suppression of proinflammatory effect has been noticed. So far, there has not been a sufficient number of clinical trials with immunosuppressive drugs (most commonly used are: azathioprine, methotrexate). In drug-resistant cases, a trial of treatment with rituximab is recommended. Plasma exchange (PE) is currently rarely performed due to side effects.

The prognosis, especially among pediatric patients, is good, with complete or partial remission in most patients after treatment. However, it is worth emphasizing that, especially in children, the lack of an early and accurate diagnosis may have dramatic consequences with permanent weakness of the upper and lower limbs, causing gait disturbances and hands disability, less often also permanent palsy of the cranial nerves.

A series of publications includes one case report of the patient, the results of one original study and one review.

The aim of the study was:

1. Analysis of the clinical phenotype, including typical and atypical variants of CIDP in children with discussion about their frequency in the group and the dynamics of the disease process.

2. Analysis of electrophysiological results in children with CIDP, with particular emphasis on parameters helpful in differentiating CIDP from hereditary neuropathies according to the Childhood CIDP criteria Nevo et al. published in 2002.

3. Summary and discussion of the most common diseases important in the differential diagnosis of CIDP in children.

4. Evaluation of the treatment options effect in children with CIDP.

Material and method:

The presented case report discusses diagnostic and therapeutic difficulties in a 4-year-old patient with a severe, recurrent course of CIDP requiring many years of combined therapy. The original paper presents a group of 37 children with CIDP. This study presents one of the largest groups of the pediatric population with CIDP among the few previously published. We conducted a retrospective analysis of clinical symptoms, NCS results, including a comparison of the fulfillment of the Childhood CIDP electrophysiological criteria Nevo et al. published in 2002 and 2010 EFNS/PNS criteria for CIDP that were current back then, modes of treatment and their effectiveness. The review concerned mainly on the critical assessment of standard clinical and electrophysiological diagnostics, especially the differential diagnosis of atypical variants, the division of which was in accordance with the then current 2010 EFNS/PNS criteria for CIDP**.**

Results:

On the example of a 4-year-old patient with CIDP, the possibilities of intensifying treatment were discussed. In this case, although the response to IVIg was very good, the effect was initially maintained for less than 3 weeks, even despite the combined therapy with oral immunosuppressive drugs. It has been shown that sometimes long-term polytherapy is necessary, with a higher than standard and gradually reduced maintenance dose of IVIg, which allows for a very good stable neurological status.

The original paper presents a retrospective analysis of 37 children with CIDP aged 3,5–17 years with the final diagnosis of CIDP (18 girls, 19 boys). The group was divided into 3 age subgroups of patients, i.e. 0-4 years of age, 4-13 years of age and 13–18 years of age. The study includes detailed assessment of the disease dynamics, preceding event, time from the first symptoms to the correct diagnosis, the course of the disease, NCS results, treatment options and its effectiveness in each subgroup. The follow-up period ranged from 10 to 222 months. In the typical variant symptoms progress gradually over a period of more than 8 - in the presented group it was found in 30/37 patients (81,1%), while 4/37 patients (10,8%) had an acute onset (<4 weeks), and 2/37 patients (5,4%) had a subacute onset (4-8 weeks). More rapid disease progression was seen more frequently in younger children (<4 years and 4-13 years). The typical presentation of CIDP was observed in 18/37 patients (48,6%), others had atypical variants: distal - 12/37 children (32,4%), pure motor in 5 /37 patients (13,5%) and one patient had a pure sensory variant (1/37, 2,7%).

The NCS was performed in all children. The Childhood CIDP criteria by Nevo et al. 2002 were fulfilled as confirmed in 26/37 patients (70,3%) and 7/37 patients (18,9%) met the criteria of possible CIDP. The 2010 EFNS/PNS electrophysiological criteria for CIDP were fulfilled as definite in 35/37 patients (94,6%).

The clinical course was comparable between the age groups. Most children (26/37 patients, 70,3%) had a maximum modified Rankin Scale (mRS) score of 3 throughout follow-up, but six patients (16,2%) were unable to walk without assistance. None of the patients scored 5 on the mRS scale.

During the entire observation, 23/37 patients (62,2%) received IVIg treatment, while 22/37 patients (59,5%) received monotherapy with corticosteroids and 6/37 patients (16,2%) were treated with both IVIg and corticosteroids. The immunosuppressive drugs, including azathioprine, but also methotrexate and rituximab, were given to 12/37 patients (32,4%). One patient was treated with plasmapheresis. Remission with residual symptoms or minimal deficit was observed in 4/37 patients (10,8%), whereas 14/37 patients (37,8%) remained on treatment with gradual improvement.

The review presents the difficulties of diagnosis CIDP, discusses the multifactorial cause of this phenomenon, including the heterogenous clinical features, especially misleading in atypical variants, electrodiagnostic pitfalls and the objective assessment of response to treatment.

Conclusions:

1. The clinical features and course of childhood CIDP is quite similar to CIDP in adults, but in younger patients the disease is more dynamic. Atypical variants of the disease occur more often in children than in adults, even in about 50%.

2. The Childhood CIDP electrophysiological criteria by Nevo et al. 2002 are helpful in differentiating inflammatory polyneuropathy from hereditary neuropathies, which are more common in younger age.

3. Apart from hereditary neuropathies, the differential diagnosis of CIDP with the acute or subacute onset, which is more frequent in children than in adults, has to be differentiated from GBS.

4. In children with CIDP, IVIg is currently the most common first-line therapy with rapid improvement after each infusion, observed in the majority of patients. Some patients require intensification of treatment with higher and more frequent maintenance doses of IVIg and polytherapy. The prognosis in pediatric CIDP is good, with residual, mostly minor, symptoms or complete remission in most patients, which has also been reported in smaller groups in the literature.

In conclusion, it should be emphasized that early diagnosis and correct treatment is the most important in improving the quality of life of patients.