The Spectrum of Polyneuropathies in Childhood Detected with Electromyography

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Only a few studies have been reported describing polyneuropathies in a series of children. To study the clinical and neurophysiological spectrum of polyneuropathies in a large series of children and obtain an overview of their etiologies, this retrospective study reevaluated all electromyograms and electrophysiologic studies performed between 1995 and 2004 in children under 17 years of age at the Radboud University Nijmegen Medical Center, a tertiary neuromuscular reference center. Electromyograms revealing polyneuropathy were selected for further analysis (n = 118), and the medical records were reviewed to supplement electromyographic findings with the clinical diagnosis. Hereditary polyneuropathies made up 68% of the total, and 54% of these were isolated polyneuropathies; in the remaining 46%, polyneuropathy was part of a more complex disorder. The acquired polyneuropathies were primarily inflammatory. Nerve biopsies had been performed in 22 of the 118 cases (19%) and led to a diagnosis in 4 cases. Despite sophisticated investigation, 11 cases (9%) remained unclassified for underlying cause. Hereditary motor and sensory neuropathies are the most common type of polyneuropathy in childhood, followed by polyneuropathies as part of an inborn error of metabolism and inflammatory polyneuropathies (in patients in whom electromyography was used to diagnose the neuropathy). In the full series of patients, nerve biopsy did not play a prominent role in the diagnostic work-up of childhood polyneuropathies, due to the increasing availability of other laboratory (genetic and metabolic) diagnostic tools. Nerve biopsy nonetheless proved to have an important diagnostic yield in selected, complex cases. © 2007 by Elsevier Inc. All rights reserved.


Introduction

Most polyneuropathies in childhood are genetically determined [1-3]. The largest groups are the hereditary motor and sensory neuropathies (HMSN) and complex hereditary syndromes, especially inborn errors of metabolism and neurodegenerative disorders with polyneuropathy as one of the features. In contrast to the findings in adults, polyneuropathy in childhood is rarely caused by an acquired systemic disorder such as diabetes [4].

In recent decades, only a few large studies describing polyneuropathies in children have been published [1-3,5]. Ouvrier and McLeod [3] included only biopsy-proven cases of peripheral neuropathy. In the other four studies [1,2,4,5], the cases were collected from medical files of patients with peripheral neuropathy, without specifying criteria as ‘biopsy-proven’ or as ‘confirmation by neurophysiological studies.’ A considerable expansion of knowledge regarding the molecular genetic basis of polyneuropathies has provided insights into these disorders. In everyday practice, electromyography remains one of the mainstays of diagnosis, except for patients in whom the presence and nature of the neuropathy are already obvious for other reasons, such as iatrogenic causes (e.g., chemotherapy), during critical illness, or when a complex multisystem disorder involving the peripheral nervous system has already been identified.

The objective of the present project was to study the profile of polyneuropathies as detected by electromyography in childhood over a 9-year period from a tertiary reference center, and thereby to offer clinical practitioners a current insight into the diagnosis and epidemiology of polyneuropathies.

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Table 1. Overview of polyneuropathies in childhood

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary</td>
<td></td>
</tr>
<tr>
<td>Hereditary motor and sensory neuropathy (HMSN)</td>
<td>43 (36)</td>
</tr>
<tr>
<td>Neuropathy as part of a neurodegenerative disorder</td>
<td>22 (19)</td>
</tr>
<tr>
<td>Neuropathy as part of an inborn error of metabolism</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Acquired</td>
<td></td>
</tr>
<tr>
<td>Inflammatory neuropathy</td>
<td>22 (19)</td>
</tr>
<tr>
<td>Drug-induced neuropathy</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Critical illness neuropathy</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Neuropathy due to a systemic disorder (uremia, systemic lupus erythematosus)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>118 (100)</td>
</tr>
</tbody>
</table>

Patients and Methods

We retrospectively studied the results of all electromyograms that had been performed between 1995 and 2004 in children under the age of 17 years at The Radboud University Nijmegen Medical Centre. All electromyographic data were available from a computerized database. The electrophysiological workup consisted of motor and sensory nerve conduction studies, study of the H-reflexes of the soleus muscles, and needle electromyography. Nerve conduction studies were performed in the sural nerve and at least one other nerve. Needle electromyography was performed in at least one muscle. Two trained neurophysiologists independently reevaluated all electromyographic data.

The polyneuropathy was classified as demyelinating when motor nerve conduction velocities were below 70% of the lower limit of normal for age. The presence of prolonged distal motor latencies, prolonged or abnormally dispersed F-waves, and conduction blocks was interpreted as compatible with the diagnosis of an inflammatory demyelinating neuropathy. Polyneuropathy was defined as axonal when there were low distal sensory responses (at least in the sural nerve), possibly with additional low distal motor compound muscle action potentials, absent tibial H-reflexes, neurogenic motor units greater in distal than in proximal muscles, and in the absence of demyelinating features. The criteria described by Johnsen and Fuglsang-Frederiksen [6] were used.

Medical records of all patients in whom the electromyogram revealed a polyneuropathy were reviewed for the diagnosis made, patient history, neurological examination, laboratory tests, molecular genetic tests, neuroimaging, and muscle and nerve biopsies performed. The acquired data were further analyzed by categorizing the patients into groups, primarily based on the final diagnosis, and by studying the details of individual patients in whom no underlying diagnosis had as yet been made. Hereditary polyneuropathies were further categorized as isolated polyneuropathies or as polyneuropathies as part of a complex, multisystem disorder. Acquired polyneuropathies were classified according to the presumed underlying pathophysiological mechanism.

Results

Between 1995 and 2004, based on electromyographic findings, 118 children were diagnosed with polyneuropathy. The electromyogram demonstrated a demyelinating neuropathy in 73 cases and an axonal neuropathy in 45 cases. Table 1 and Figure 1 provide an overview of the results.

Figure 1. Classification of polyneuropathies in childhood. HMSN, hereditary motor and sensory neuropathies.
**Inherited Neuropathies**

Most patients (68%) in this series were diagnosed with a hereditary polyneuropathy, roughly half of them suffering from an isolated polyneuropathy (hereditary motor sensory neuropathy). The genetic defect in the isolated demyelinating polyneuropathies (subtypes HMSN-I, -III, and -IV) could be clarified in 21 of 29 patients (72%) (Fig. 1). In contrast, none of the cases of HMSN-II could be proven genetically.

In nearly half of all patients with an inherited polyneuropathy (37/80), the neuropathy was part of a more complex disorder. Of these 37 patients, 15 suffered from an inborn error of metabolism: mitochondrial encephalomyopathies in 7 cases, porphyria in 3 case, and metachromatic leukodystrophy, Krabbe’s disease congenital disorder of glycosylation 1a, Tay-Sachs disease, and sialidosis in 1 case each. Of the remaining 22 patients in this category (i.e., with inherited neuropathy as part of a complex disorder), 11 were diagnosed with a known multisystem disorder, as follows: spinocerebellar atrophy (n = 2), giant axonal neuropathy (n = 1), spinal muscular atrophy (n = 1), congenital muscular dystrophy (n = 3), congenital cataracts facial dysmorphism neuropathy syndrome (n = 1), infantile axonal polyneuropathy (n = 1), and ataxia telangiectasia (n = 2). The remaining 11 were classified as unknown; in 6 of these 11 cases, the polyneuropathy was accompanied by a nonspecific white matter disorder of the central nervous system.

**Acquired Neuropathies**

The inflammatory polyradiculoneuropathies (Guillain-Barré syndrome) were predominant among the acute, acquired polyneuropathies (18/31; 58%). The remaining acute polyneuropathies could be classified as drug-induced polyneuropathy (n = 5), systemic lupus erythematosus (n = 2), due to uremia (n = 1), and critical illness neuropathy (n = 8). Critical illness neuropathy is an axonal neuropathy associated with systemic inflammatory response syndrome in patients admitted to an intensive care unit. The pathogenesis is still not well understood.

**Nerve Biopsies**

Twenty-two nerve biopsies (19%) had been performed in the study population, always of the sural nerve; only in 4 of these cases did the nerve biopsy show specific findings that were helpful toward making the final diagnosis. The typical focally folded myelin found on nerve biopsy led to the diagnosis Charcot-Marie-Tooth subtype IVb in one patient; subtype IVc (due to mutations in the SH3TC2 gene, alias KIAA1985) was diagnosed in another patient. HMSN-III was considered in one patient in whom the nerve biopsy showed the classical histological picture, which was later confirmed by mutation analysis of the PMP22 gene. The fourth patient, born of consanguineous parents, suffered from a chronic inflammatory demyelinating polyneuropathy that could not be differentiated from HMSN without histological data.

**Discussion**

Most of the polyneuropathies in the present study were hereditary neuropathies. This result is in agreement with the common experience in pediatric neurology and with larger series presented in the literature [1-3].

There is a notable bias in the study population, in that we only included patients in whom the neuropathy was confirmed by electromyography. It is likely, therefore, that the data underestimate the number of patients in whom an electromyogram is not routinely used or is not deemed necessary for establishing the diagnosis. Thus, the number of patients with critical illness or chemotherapy-induced PNP are low in the present study, even though hundreds of these patients were treated at the same university hospital during the study period. The same probably goes for patients suffering from more complex multisystem disorders that are diagnosed under their other, presenting, features.

Nonetheless, patients suffering from an isolated neuromuscular syndrome that is suspected to be a polyneuropathy will generally undergo electromyographic examination. Therefore, the number of study patients with disorders such as hereditary motor and sensory neuropathies, Guillain-Barré syndrome, or chronic inflammatory demyelinating polyneuropathy will reflect the total number of these patients seen in our hospital quite well. The electromyogram of one patient, who suffered from spinal muscular atrophy, showed abnormalities compatible with an additional peripheral neuropathy. The rare association between spinal muscular atrophy and peripheral neuropathy has already been demonstrated in the literature [7].

In the present study, three out of four patients with chronic inflammatory demyelinating polyneuropathy were in their teens (the fourth was 4 years old). Kararizou et al. [8] recently showed that chronic inflammatory demyelinating polyneuropathy appears to be a frequent cause of polyneuropathy in teenagers (up to 20%). This incidence is much higher than that in the present study (3%) or other published series describing polyneuropathies in children of all ages, but it is similar to that seen in adults. This might be explained by the changes of the morphological characteristics of the peripheral nerves in teenagers [9].

A sural nerve biopsy showed specific findings that were helpful toward making the diagnosis in 4 of the 22 cases in the present series. This is in line with the published data about the limited value of nerve biopsy as a routine diagnostic procedure in the general neurological population, and the important role of the nerve biopsy in selected complex cases, in whom the diagnosis is not immediately apparent [10,11].

Finally, almost 10% of the polyneuropathies in the present study population remained unclassified, despite
routine and sophisticated investigations. This involved primarily the patients with hereditary axonal-type polyneuropathies and patients with inherited multisystem disorders in whom no underlying etiology could be established.

The present results offer novel insights into the epidemiology of polyneuropathies in childhood and thereby provide an additional instrumental guide for medical practitioners dealing with children who present symptoms of a polyneuropathy.

References