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Original Article

Pediatric Nerve Biopsy Diagnostic and Treatment Utility in Tertiary Care Referral

Cristiane M. Ida MD [a], Peter J. Dyck MD [b], P. James B. Dyck MD [b], Janean K. Engelstad HT [b], Wei Wang MD [c], Duygu Selcen MD [b,d], John B. Bodensteiner MD [b,d], Michelle L. Mauermann MD [b], Christopher J. Klein MD [a,b,e,*]

[a] *Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota*
[b] *Department of Neurology, Mayo Clinic, Rochester, Minnesota*
[c] *Department of Neurology, China Japan Friendship Hospital, Beijing, China*
[d] *Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota*
[e] *Department of Medical Genetics, Mayo Clinic, Rochester, Minnesota*

ABSTRACT

BACKGROUND: Pediatric neuropathies are both unique and similar to their adult counterparts, with genetic varieties thought to be more common. The objective of this work was to assess the utility of nerve biopsy in children at a tertiary referral center in light of availability of current genetic testing. **METHODS:** We retrospectively reviewed the clinical, nerve biopsy, and genetic testing findings of 316 pediatric (age ≤18 years) patients. **RESULTS:** Median age at diagnosis was 9.8 years (4 days to 18 years). Nerve biopsy was nontargeted in 198 (182 whole sural, seven superficial peroneal, and nine other), targeted in 21 (14 fascicular sciatic and seven brachial plexus), and unknown in 97 cases. Prebiopsy localizations and diagnoses were diverse, most commonly with length-dependent localizations (n = 150). Median follow-up was 6 months (0 to 480 months). A distinctive histopathologic diagnosis was made in 106 cases (33%), including inflammatory or immune (n = 30), neoplastic (n = 19), hereditary (n = 41), vasculitis (n = 10), and other (n = 6). Nerve biopsy confirmed the suspected diagnosis in 91 (29%) individuals and changed or refined the initial diagnosis in 182 (58%). Treatment modifications as a result of biopsy occurred in 80 (25%) cases; 59 (19% of the entire cohort) with clinical improvements noted, most commonly by immunotherapy (n = 30). Low diagnostic yield occurred in "hypotonic infants" without nerve conduction abnormalities. Pain at the biopsy site beyond 1 month was rare (n = 3; 1%). Forty-four patients underwent genetic testing. Among demyelinating varieties, mutations were identified in five of 11 (46%) cases compared with only six of 33 (18%) cases of axonal varieties. **CONCLUSION:** Pediatric nerve biopsy provides diagnostic information that frequently alters treatment recommendations. Furthermore, it leads to clinical improvements, especially in inflammatory immune neuropathies. For suspected inherited varieties, genetic testing has the highest diagnostic yield in demyelinating phenotypes.

Keywords: pediatric, peripheral nerve, biopsy, neuropathy, diagnosis

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Introduction

Pediatric peripheral neuropathies are both unique and similar to their adult counterparts. Among children with peripheral nerve diseases, hereditary forms are believed to be the most common,[1-4] whereas in older adults, many are acquired or polygenic in nature.[5] Clinical presentation, diagnostic evaluation, and treatment of pediatric peripheral neuropathies are nevertheless similar to those of adults with the same diagnosis. Hereditary motor and sensory neuropathy (HMSN) also known as Charcot-Marie-Tooth (CMT) disease and acute inflammatory demyelinating polyneuropathy (a.k.a. Guillain-Barré syndrome) are frequent

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* Communications should be addressed to: Dr. Klein; Department of Neurology; Mayo Clinic; 200 First Street SW; Rochester, MN 55905.
E-mail address: Klein.christopher@mayo.edu

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causes of peripheral neuropathy in children.[6,7] Although nerve biopsy is not typically needed for diagnosis of acute inflammatory demyelinating polyneuropathy, utility of nerve biopsy for inherited neuropathies has not been systematically evaluated in pediatric patients in the modern era with available comprehensive genetic studies.

Earlier studies of nerve biopsy utility predate modern genetic technologies and have been mainly limited to adult patients[8-10] or did not specify whether the study population included pediatric patients.[11,12] In addition, such studies were heterogeneous and variably included teased fiber analysis, histochemical and immunochemical staining, and/or epoxy preparations. One focused pediatric series by Miller et al.[13] retrospectively evaluated the diagnostic yield of combined nerve-muscle-skin biopsy in a series of 98 patients, and found a very high rate of informative biopsies (93.5%) among children with abnormal results in electrodiagnostic studies.

Because the youngest children are less likely to accurately report their temporal course and neurological deficits, diagnostic evaluation is often primarily based on the family's observations. Therefore, the differential diagnosis after the initial interview is often broader in children. Nerve conduction studies and electromyography are useful to both establish and determine the pattern (demyelinating, axonal, or mixed) of a peripheral neuropathy. The interpretation of nerve conductions in infants and children, however, requires knowledge of the variability of normal values.[2,14] In adults, when a neuropathy diagnosis remains uncertain after laboratory, electrodiagnostic, and/or genetic testing, nerve biopsy has been established as a valuable diagnostic tool in specific forms.[8,11,15-18]

Herein, we investigate the usefulness of nerve biopsy in children by review of a large retrospective cohort at our institution. Clinical phenotypes that most likely benefited as determined by change in therapy with clinical improvements, and that had the highest genetic testing diagnostic yield are evaluated. In addition, nerve biopsy complication rates are evaluated in comparison with the literature adult counterpart data.[19]

Materials and Methods

This study was conducted according to Mayo Clinic Institutional Review Board–approved protocols. Using an electronic-medical-record retrieval system, 316 nerve biopsies from pediatric (age ≤18 years) patients from 1950 to 2009 were identified in our archives with available medical records. Data extracted included the presence and details of nerve conductions and electromyography, gender, age at the time of nerve biopsy, temporal course of disease, available genetic testing results, peripheral nerve selected for biopsy, prebiopsy and postbiopsy clinical diagnosis, whether the clinical and histopathologic findings were interpreted to be more consistent with an acquired or inherited etiology, presence of biopsy-related complications, history of prior, concomitant, or subsequent muscle biopsy, length of follow-up, and vital status. Electrodiagnostic and histopathologic reports were collected and reviewed in conjunction with the clinical data. Of the 316 nerve biopsies, 204 (65%) had been performed at our institution and followed a standardized processing of the peripheral nerve specimen.[20] Because our institution is a large tertiary referral center, 112 (35%) nerve biopsies were initially consults and had been performed and processed at the referring institution. However, all 316 pediatric patients were clinically examined at our institution. Based on the clinical, electrodiagnostic, and histopathologic information, we critically evaluated the impact of the nerve biopsy findings in patient care. This was assessed by determining whether the nerve biopsy findings resulted in (1) confirmation, change, or refinement of prebiopsy diagnosis, (2) change in treatment, (3) significant clinical improvement, and (4) additional testing. Even though most patients preceded the availability of genetic testing, 44 patients had undergone either focused candidate gene testing (n = 39) or targeted next-generation sequencing (n = 5) for inherited neuropathy-related genes.

Results

Clinical findings

Clinical data are detailed in Table 1. In summary, the female to male ratio was 165:151 and the median age at the time of nerve biopsy was 9.8 years (4 days to 18 years). Electromyography and nerve conduction studies were performed in 294 of 316 (93%) children as part of their clinical evaluation. The most common prebiopsy diagnosis was length-dependent polyneuropathy with or without concern for central nervous system involvement (n = 184, 58%) followed by asymmetric varieties (n = 68, 22%). Hypotonia was another indication in 15 (5%) cases.

Information about the biopsy site was available in 219 (of 316, 70%) cases, and the sural nerve was the most frequently biopsied nerve. Nerve biopsy was nontargeted in 198 (182 whole sural, seven superficial peroneal, and nine other) and

TABLE 1.
Demographics and Clinical Findings

Total# of cases	316
Gender (girls:boys)	165:151
Median age at diagnosis	9.8 years (4 days to 18 years)
Electrodiagnostic pattern	294
PN, axonal	86 (29%)
PN, demyelinating	79 (27%)
Motor neuropathy	13 (5%)
Sciatic neuropathy	12 (4%)
PRNP, axonal	10 (3%)
Brachial plexopathy	10 (3%)
No significant abnormality	24 (8%)
Other/mixed pattern	60 (21%)
Prebiopsy diagnosis	316
Length dependent PN	150 (47%)
CNS disease with PN	34 (11%)
Mononeuropathy	22 (7%)
PRNP	18 (6%)
Hypotonia	15 (5%)
Plexopathy	15 (5%)
Sciatic neuropathy	13 (4%)
Other	49 (15%)
Biopsy site	219
Sural	182 (83%)
Sciatic nerve fascicle	14 (6%)
Superficial peroneal	7 (3%)
Brachial plexus	7 (3%)
Other	9 (5%)
Muscle biopsy performed	65
Alive	304
Died (died of disease)	12 (10; 3%)
Median follow-up (months)	6 (0-480)

Abbreviations:
CNS = Central nervous system
PN = Peripheral neuropathy
PRNP = Polyradiculoneuropathy
Other = pain disorder or exclude infiltrative peripheral nerve involvement.