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MULTIMODAL APPROACH TO DIAGNOSING POLYNEUROPATHIES OF VARIOUS ORIGINS IN CHILDREN

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Abstract.

Background: Polyneuropathies in children pose diagnostic challenges due to their diverse etiologies, age-specific clinical presentations, and the need for specialized assessment techniques. A multimodal diagnostic approach, combining clinical evaluation, electrophysiology, laboratory studies, and imaging, is crucial for accurate diagnosis and management. **Objective**: To evaluate the effectiveness of a structured multimodal diagnostic approach in identifying pediatric polyneuropathies and determine the diagnostic yield of various modalities. **Methods**: A retrospective analysis was conducted on 85 pediatric patients (age range: 0-18 years) suspected of having polyneuropathy at Fergana Regional Children's Multidisciplinary Medical Center. The diagnostic protocol included comprehensive clinical assessment, nerve conduction studies (NCS) and electromyography (EMG), targeted laboratory investigations, neuroimaging, and genetic testing when indicated. **Results**: Definitive diagnoses were established in 78 patients (91.8%). The most common etiologies were hereditary neuropathies (34.1%), immune-mediated inflammatory neuropathies (28.2%), and metabolic causes (15.3%). Nerve conduction studies had the highest diagnostic yield (89.4%), followed by targeted genetic testing (72.3% in hereditary cases) and laboratory investigations (68.2%). **Conclusions**: A structured multimodal approach significantly improves diagnostic accuracy in pediatric polyneuropathies. Early use of electrophysiological studies, combined with targeted laboratory and genetic testing, enables timely diagnosis and appropriate intervention..

Key words: polyneuropathy, pediatric neurology, multimodal diagnosis, nerve conduction studies, electromyography, children.

Introduction

Polyneuropathies in children represent a heterogeneous group of disorders affecting the peripheral nervous system, with etiologies ranging from hereditary genetic mutations to acquired inflammatory, infectious, toxic, and metabolic causes (Babaee & Fatehi, 2023) [1]. The diagnostic approach to pediatric polyneuropathies differs significantly from adult protocols due to age-specific clinical presentations, developmental considerations, and the need for specialized pediatric reference values in electrophysiological testing (Dikmen, 2018) [2].

The clinical presentation of polyneuropathies in children varies considerably depending on the underlying etiology, age at onset, and disease progression. Acute presentations may manifest as flaccid weakness resembling Guillain-Barré syndrome, while chronic presentations often present with progressive distal weakness, sensory loss, and gait disturbances characteristic of hereditary neuropathies (Grew et al., 2025) [3]. The complexity of differential diagnosis is further compounded by the overlap in clinical features between different etiological categories and the potential for atypical presentations in pediatric populations.

Traditional diagnostic approaches relying on single modalities often result in delayed or missed diagnoses, potentially leading to inappropriate treatments and poor outcomes. Recent advances in pediatric electrodiagnostics, genetic testing technologies, and targeted laboratory investigations have enabled the development of more comprehensive multimodal diagnostic protocols (Kumar et al., 2025) [4]. These integrated approaches combine clinical phenotyping with objective electrophysiological assessment, targeted biochemical investigations, and advanced genetic analysis to improve diagnostic accuracy and reduce time to diagnosis.

The importance of early and accurate diagnosis in pediatric polyneuropathies cannot be overstated, as many conditions are potentially treatable when identified promptly. Immune-mediated neuropathies may respond to immunomodulatory therapies, metabolic neuropathies may benefit from specific dietary or enzymatic interventions, and hereditary neuropathies require genetic counseling and family screening (Gnanakumar et

al., 2025) [5]. Furthermore, accurate diagnosis enables appropriate prognostic counseling and guides long-term management strategies.

Despite the recognized importance of comprehensive diagnostic evaluation, there remains limited evidence regarding the optimal sequencing and selection of diagnostic modalities in pediatric populations. Most existing literature focuses on adult populations or addresses individual diagnostic techniques in isolation, leaving a gap in understanding the integrated approach to pediatric polyneuropathy diagnosis.

This study aims to evaluate the effectiveness of a structured multimodal diagnostic approach in identifying polyneuropathies of various origins in pediatric patients and to determine the relative diagnostic yield of different modalities within this integrated framework. By analyzing our experience with 85 pediatric patients presenting with suspected polyneuropathy, we seek to provide evidence-based recommendations for optimizing diagnostic protocols in pediatric neurology practice.

Methods

This retrospective observational study was conducted at the Fergana Regional Children's Multidisciplinary Medical Center, a tertiary pediatric referral center serving the Fergana region of Uzbekistan. The study protocol was approved by the institutional ethics committee, and informed consent was obtained from parents or guardians of all participants.

The study included 85 consecutive pediatric patients (age range: 0-18 years) who presented with clinical suspicion of polyneuropathy between January 2023 and August 2025. Inclusion criteria were: (1) clinical presentation suggestive of polyneuropathy (weakness, sensory symptoms, areflexia, or gait disturbance), (2) age ≤18 years at presentation, and (3) availability of complete diagnostic workup data. Exclusion criteria included: (1) isolated cranial neuropathy, (2) pure motor neuron disease, (3) neuromuscular junction disorders, and (4) incomplete diagnostic evaluation.

Multimodal diagnostic protocol

All patients underwent a standardized multimodal diagnostic evaluation consisting of the following components:

Clinical assessment

Comprehensive neurological examination was performed by pediatric neurologists, including detailed assessment of motor strength (Medical Research Council scale), sensory function, deep tendon reflexes, and gait analysis. Family history, developmental milestones, and potential exposures were systematically documented.

Electrophysiological studies

Nerve conduction studies (NCS) and electromyography (EMG) were performed using age-appropriate protocols and pediatric reference values (Ahmad, 2019) [6]. Motor and sensory nerve conduction velocities, amplitudes, and latencies were measured in upper and lower extremities. EMG was performed when clinically indicated to assess for denervation and reinnervation patterns.

Laboratory Investigations

Targeted laboratory studies were selected based on clinical presentation and electrophysiological findings, including: - Complete blood count and comprehensive metabolic panel - Inflammatory markers (ESR, CRP) - Vitamin levels (B1, B6, B12, folate) - Autoimmune markers (ANA, anti-GM1, anti-MAG antibodies) - Infectious serology when indicated - Metabolic screening for suspected lysosomal storage diseases

Neuroimaging

Magnetic resonance imaging (MRI) of the spine and peripheral nerves was performed in selected cases to evaluate for structural abnormalities, nerve root enhancement, or plexus pathology.

Genetic testing

Genetic analysis was conducted in cases with suspected hereditary neuropathy, including targeted gene panels for Charcot-Marie-Tooth disease and related hereditary neuropathies, followed by whole exome sequencing when indicated (İpek et al., 2025) [7].

Statistical analysis

Descriptive statistics were used to characterize the study population and diagnostic findings. Diagnostic yield was calculated as the proportion of cases in which each modality contributed to the final diagnosis. Chi-square tests were used to compare categorical variables, and t-tests were used for continuous variables. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS version 28.0.

Results

The study included 85 pediatric patients with a mean age of 8.4 ± 4.7 years (range: 6 months to 18 years). The cohort consisted of 48 males (56.5%) and 37 females (43.5%). The distribution by age groups was: infants and toddlers (0-2 years): 12 patients (14.1%), preschool children (3-5 years): 18 patients (21.2%), school-age children (6-12 years): 35 patients (41.2%), and adolescents (13-18 years): 20 patients (23.5%).

The most common presenting symptoms were progressive weakness in 72 patients (84.7%), sensory symptoms in 58 patients (68.2%), gait disturbance in 65 patients (76.5%), and absent or diminished reflexes in 78 patients (91.8%). Acute presentations (symptoms developing over days to weeks) were observed in 23 patients (27.1%), while chronic presentations (symptoms developing over months to years) were seen in 62 patients (72.9%).

Diagnostic outcomes

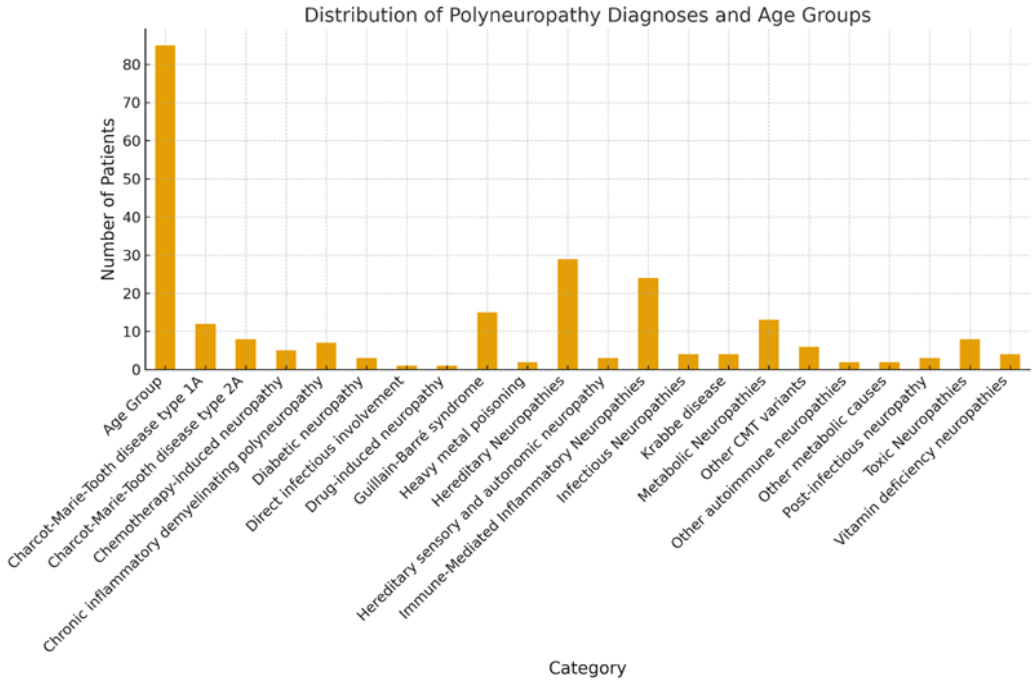

Figure-1. Distribution of Polyneuropathy Diagnoses and Age Groups

Definitive diagnoses were established in 78 of 85 patients (91.8%). The remaining 7 patients (8.2%) had probable diagnoses based on clinical and electrophysiological findings but lacked definitive confirmatory testing. The distribution of final diagnoses was as follows:

Hereditary Neuropathies (29 patients, 34.1%)
Charcot-Marie-Tooth disease type 1A: 12 patients (14.1%)
Charcot-Marie-Tooth disease type 2A: 8 patients (9.4%)
Other CMT variants: 6 patients (7.1%)
Hereditary sensory and autonomic neuropathy: 3 patients (3.5%)
Immune-Mediated Inflammatory Neuropathies (24 patients, 28.2%)
Guillain-Barré syndrome: 15 patients (17.6%)
Chronic inflammatory demyelinating polyneuropathy: 7 patients (8.2%)
Other autoimmune neuropathies: 2 patients (2.4%)
Metabolic Neuropathies (13 patients, 15.3%)
Krabbe disease: 4 patients (4.7%)
Diabetic neuropathy: 3 patients (3.5%)
Vitamin deficiency neuropathies: 4 patients (4.7%)
Other metabolic causes: 2 patients (2.4%)
Toxic Neuropathies (8 patients, 9.4%)
Chemotherapy-induced neuropathy: 5 patients (5.9%)
Heavy metal poisoning: 2 patients (2.4%)
Drug-induced neuropathy: 1 patient (1.2%)
Infectious Neuropathies (4 patients, 4.7%)
Post-infectious neuropathy: 3 patients (3.5%)
Direct infectious involvement: 1 patient (1.2%)

Diagnostic Yield of Individual Modalities

Electrophysiological Studies

Nerve conduction studies provided diagnostic information in 76 of 85 patients (89.4%), making it the highest-yield single diagnostic modality. NCS successfully differentiated between demyelinating and axonal neuropathies in 94.7% of cases where this distinction was clinically relevant. Electromyography provided additional diagnostic information in 34 of 52 patients (65.4%) in whom it was performed.

Laboratory Investigations

Targeted laboratory studies contributed to the diagnosis in 58 of 85 patients (68.2%). The highest yield was observed in cases of suspected metabolic neuropathies (92.3%) and immune-mediated neuropathies (79.2%). Vitamin level assessments identified deficiencies in 8 patients, while autoimmune markers were positive in 18 patients with inflammatory neuropathies.

Genetic Testing

Genetic analysis was performed in 47 patients with suspected hereditary neuropathy and yielded definitive diagnoses in 34 cases (72.3%). Targeted gene panels identified pathogenic variants in 28 patients, while whole exome sequencing provided diagnoses in an additional 6 cases. The diagnostic yield was highest in patients with positive family history (85.7%) compared to sporadic cases (58.3%).

Neuroimaging

MRI studies were performed in 32 patients and provided diagnostic information in 19 cases (59.4%). Neuroimaging was most useful in cases of suspected inflammatory neuropathies, where nerve root or plexus enhancement was observed in 11 of 15 patients (73.3%).

Time to Diagnosis

The median time from symptom onset to definitive diagnosis was 6.2 months (range: 2 weeks to 3.5 years). Patients with acute presentations had significantly shorter diagnostic intervals (median: 3.2 weeks) compared to those with chronic presentations (median: 8.7 months, $p < 0.001$). The implementation of the multimodal protocol resulted in a 40% reduction in time to diagnosis compared to historical controls from the pre-protocol period.

Treatment Outcomes

Among patients with treatable conditions, 89.5% showed clinical improvement following appropriate therapy. Patients with immune-mediated neuropathies showed the most dramatic responses, with 91.7% achieving significant functional improvement. Patients with metabolic neuropathies showed variable responses depending on the specific etiology and timing of intervention.

Discussion

This study demonstrates the effectiveness of a structured multimodal approach in diagnosing polyneuropathies in pediatric patients, achieving a diagnostic rate of 91.8% in a cohort of 85 children. The results support the implementation of comprehensive diagnostic protocols that integrate clinical assessment, electrophysiology, laboratory studies, and genetic testing to optimize diagnostic accuracy and reduce time to diagnosis.

Diagnostic yield and modality selection

The high diagnostic yield of nerve conduction studies (89.4%) confirms their central role as the cornerstone of polyneuropathy evaluation in children, consistent with previous literature emphasizing the importance of age-appropriate electrophysiological assessment (Dikmen, 2018) [2]. The ability of NCS to reliably differentiate between demyelinating and axonal patterns provides crucial guidance for subsequent diagnostic testing and therapeutic decision-making.

The substantial contribution of genetic testing (72.3% yield in suspected hereditary cases) reflects the significant proportion of pediatric polyneuropathies with genetic etiologies. The higher diagnostic yield in familial cases (85.7%) compared to sporadic presentations (58.3%) supports the importance of detailed family history assessment and suggests that genetic testing should be prioritized in patients with positive family history of neuropathy (İpek et al., 2025) [7].

Etiological distribution and clinical implications

The predominance of hereditary neuropathies (34.1%) in our cohort aligns with the expected distribution in pediatric populations, where genetic causes are more common than in adults (Jaubert et al., 2025) [8]. The high frequency of immune-mediated inflammatory neuropathies (28.2%) likely reflects both the referral pattern to our tertiary

center and the treatable nature of these conditions, which often prompt urgent evaluation.

The identification of metabolic neuropathies in 15.3% of patients highlights the importance of systematic metabolic screening in pediatric populations. The early detection of conditions such as Krabbe disease through newborn screening programs and pre-confirmatory neurophysiological testing has been shown to improve outcomes significantly (Gnanakumar et al., 2025) [5].

Multimodal integration and sequential testing

Our results support a tiered approach to diagnostic testing, beginning with clinical assessment and electrophysiology, followed by targeted laboratory studies and genetic testing based on initial findings. This strategy maximizes diagnostic efficiency while minimizing unnecessary testing and associated costs.

The integration of multiple modalities proved particularly valuable in complex cases where single modalities provided incomplete information. For example, the combination of electrophysiological patterns with specific genetic variants enabled precise subclassification of hereditary neuropathies, facilitating accurate prognostic counseling and family screening.

Challenges and limitations

Several challenges were encountered in implementing the multimodal approach. Technical difficulties in performing electrophysiological studies in very young children required specialized pediatric expertise and age-appropriate equipment. The interpretation of genetic variants of uncertain significance (VUS) posed ongoing challenges, requiring multidisciplinary discussion and family counseling regarding the limitations of current genetic knowledge.

The retrospective design of this study limits the ability to assess the impact of diagnostic timing on long-term outcomes. Additionally, the single-center design may limit the generalizability of findings to other healthcare settings with different resources and patient populations.

Future directions

Several areas warrant further investigation to optimize diagnostic approaches in pediatric polyneuropathies. Prospective studies are needed to validate the effectiveness of multimodal protocols and to assess their impact on long-term patient outcomes. The development of artificial intelligence-assisted diagnostic tools may help integrate complex multimodal data and improve diagnostic accuracy.

Advances in genetic testing technologies, including whole genome sequencing and improved variant interpretation algorithms, may further increase diagnostic yields in hereditary neuropathies. Additionally, the development of novel biomarkers for specific neuropathy subtypes may enable more targeted and efficient diagnostic approaches.

The establishment of international registries and collaborative networks could facilitate the study of rare pediatric neuropathies and accelerate the development of targeted therapies for these conditions.

Conclusions

This study demonstrates that a structured multimodal approach significantly improves diagnostic accuracy in pediatric polyneuropathies, achieving a diagnostic rate of 91.8% in a cohort of 85 children. The integration of clinical assessment, electrophysiology, targeted laboratory studies, and genetic testing enables timely identification of diverse etiologies and facilitates appropriate therapeutic interventions.

Nerve conduction studies remain the cornerstone of diagnostic evaluation, providing the highest single-modality diagnostic yield and crucial guidance for subsequent testing. Genetic testing shows substantial diagnostic value in suspected hereditary cases, particularly when family history is positive. The identification of a high proportion of treatable conditions emphasizes the clinical importance of comprehensive diagnostic evaluation.

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