# REVIEW ARTICLE

## What is the Next Step after an Electrodiagnostic Study in Children with Polyneuropathies? Rationale for Laboratory and Other Diagnostic Tests

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## Abstract

The etiology of polyneuropathies varies in the pediatric population, where hereditary or metabolic disorders are far more common than in adults. However, treatable polyneuropathies, also prevalent in these settings, are those to prioritize. Moreover, diagnosing subacute and chronic symptoms in children can be challenging compared to adults. Therefore, selecting the best and most relevant laboratory investigations and paraclinical studies is critical. This taskcan be relatively challenging in countries with limited resources or insurance coverage. This study describe the various types of polyneuropathies found in children and their characteristics and suggest an algorithm for using the best laboratory tests in the context of the Iranian healthcare system.

**Keywords:** Neuropathy, Children, Laboratory tests, Electrodiagnosis, Nerve Conduction Study, Electromyography.
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## Introduction

The prevalence of polyneuropathies has been estimated at 2%-3% in the general population (1, 2). The prevalence of Charcot-Marie-Tooth (CMT) is 17.7 in 100, 000 (3). Ma et al. showed that hereditary neuropathy is less prevalent in patients younger than 16 (3). Acute-acquired inflammatory polyneuropathies (Guillain-Barré syndrome is the most common etiology) affect about 0.4-1.7 in 100, 000 patients annually (4, 5). Differential diagnosis and etiology of polyneuropathies vary substantially in the pediatric population, where hereditary or metabolic disorders are far more common than in adults (6). Detecting new genetic defects causing polyneuropathy has increased significantly in recent years, and over 100 known acquired and inherited disorders are now recognized, making the diagnosis of polyneuropathies in pediatrics even more challenging (6). Diagnosing subacute and chronic symptoms in children can be challenging; however, several studies are available for adults (7–11).

The present study aims to investigate the existing literature on pediatric polyneuropathies. This reserach offers guidance to clinicians about the most appropriate laboratory investigations to select after identifying polyneuropathy in a child by the sole electrodiagnosis.

### Confirmation of Neuropathy

Physical examination and history are always the most valuable tools to explore polyneuropathies, irrespective of the patient's age (12). Signs and symptoms in children include hypotonia, atrophy, gait disturbances, foot drop, limb deformities (pes cavus or planus, claw hands, scoliosis), distal limb weakness, fatigue, frequent falls, and absent or decreased deep tendon reflexes and the like (13). Additionally. positive and negative features exist based on the type of nerve fiber involvement in sensory, motor, or autonomic symptoms; notably, autonomic features are less reported in children (Table 1) (5, 14).

Electrodiagnostic evaluation, including nerve conduction study and needle electromyography (EMG), is a helpful diagnostic tool, specifically when combined with non-neurological signs and symptoms (Table 2), providing essential clues for detecting inherited neuropathies (5, 14). Nerve conduction study (NCS) and EMG, in particular, are crucial tools to address the questions below (1):

-What are the specific nerve fiber types involved (sensory, motor, or sensorimotor)?

-What is the type of nerve involvement (demyelinating, axonal, or combined), and is it uniform or non-uniform?

-What is the severity of the neuropathy?

- Is there any symmetric or asymmetric pattern?

Answering these questions leads to a specific diagnosis in most cases. However, differential diagnosis in the subacute phase of the disease is sometimes confusing. Treatable polyneuropathies, such as inflammatory polyneuropathy, are often misdiagnosed with hereditary neuropathies. Karam et al. introduced three developed and standardized clinical screening criteria that rapidly detect inflammatory neuropathies in adults (15). The three fundamental characteristics of inflammatory neuropathy, including onset, distribution, and associated systemic features (ODS), showed 96%

and 85% sensitivity and specificity, respectively (15). DS+ patients should have one or more of the following: the onset should be acute or subacute (less than eight weeks to reach the plateaus); the distribution should be non-length-dependent, meaning the symptoms could be proximal, distal, multifocal, or asymmetric; or systemic features such as weight loss or skin changes should exist (15). Using these criteria with electrodiagnosis increases the sensitivity of detecting inflammatory polyneuropathy to 100% (15). There appears to be a significant shortage of reports on similar criteria potentially applicable to children. Given the wide range of complex diseases, selecting the next step for paraclinical evaluation can be more challenging in the pediatric group.

Three patterns of nerve involvement are considered to facilitate the subsequent evaluation: sensorimotor, sensory, and motor polyneuropathy. Based on the electrodiagnosis data, the time course and spatial distribution of polyneuropathy, and the topographic distribution of neuropathy, many differential diagnoses must be considered, as shown in Figure 1, Tables 3, 4, and 5.

***Sensorimotor Neuropathy***

This pattern is more common than other polyneuropathies (symmetric demyelinating or axonal polyneuropathy) (Figure 1). Neurophysiological features include axonal versus demyelinating and uniform versus non-uniform (12). The criteria for non-uniform demyelinating polyneuropathy was published by the European Academy of Neurology (EAN; formerly known as European Federation of Neurological Societies, EFNS) and Peripheral Nerve Society (PNS) and has been updated in 2021 with 77%–83% and 94%–98% acceptable sensitivity and specificity respectively (12, 19, 20).

Electrophysiologic features of axonal neuropathy usually include low amplitude or absent sensory and motor nerve action potential amplitudes (12). This feature has shown mild slowing, although it is typically still >75% of the lower normal limit (12). By assessing the type of polyneuropathy and its disease course (acute, sub-acute, and chronic), more relevant laboratory studies (according to Table 3) have to be considered.

**Sensory Neuropathy**

Sensory-predominant polyneuropathies can result from large or small nerve fiber involvement (14, 21). Large sensory afferent fibers, which are myelinated and conduct much more quickly than small fibers, are evaluated by standard neurophysiologic testing. Hereditary sensory and autonomic neuropathies are this category's most known hereditary disorders (13). However, other acquired conditions should be considered (Table 4). Considering the pattern, distribution, age, and history, proposed laboratory studies should be evaluated before genetic studies (Table 4).

**Motor Neuropathy**

Motor-predominant polyneuropathies are less common in children than motor neuron disorders (13, 14)(22). However, some types of hereditary motor neuropathy show genetic and clinical overlap with distal muscular atrophy, i.e., distal hereditary motor polyneuropathies with distal muscular atrophy and CMT type 2 (13, 14). In this category, acute symmetric and asymmetric neuropathy are mostly related to acquired viral infections or toxin exposure (Table 5). Therefore, the laboratory data, patient history, and physical examination should be considered.

**Neuropathy with Normal NCS**

Small-fiber-predominant polyneuropathy (SFPN) can result in normal NCS findings and is a condition in which predominantly thin myelinated Aδ-fibers and unmyelinated C-fibers are affected (23). This develops even in preschool-age children (24). More than half of childhood-onset, unexplained, chronic, widespread pain cases met the diagnostic criteria for SFPN (24). Diagnosing SFPN is difficult because familiar signs of large-fiber neuropathy are absent or minimal. Still, several techniques have been introduced, including skin biopsy, self-reported pediatric pain measures, quantitative sensory testing (QST), corneal confocal microscopy, microneurography, and autonomic testing (24, 25). After diagnosis, detecting the etiology is essential due to treatable causes (23). Small fiber neuropathy (SFN) conditions could be categorized as metabolic, immune-mediated, infectious, toxic, and hereditary (25). This neuropathy could be pure or with mixed fiber neuropathy. The etiology of SFN remains unknown in most of these children despite extensive testing, including whole exome sequencing (WES) (25).

**Complementary Diagnostic Testing**

Selecting the following tests (nerve biopsy, genetic study, and imaging) depends on physical examination, history, and other laboratory data.

**-Nerve biopsy**

In adults, when laboratory findings and electrodiagnostic studies do not assist in diagnosing the cause of polyneuropathy, nerve biopsy is confirmatory in 37%, usually among patients with asymmetric and non-chronic phenotypes (26, 27). Recently, with rapidly expanding diagnostic modalities, the most prominent reason for declining referrals for nerve biopsy is the availability of less invasive diagnostic modalities, mainly driven by advancements in immunology, molecular genetics, and nerve imaging. (26) In the inherited types of the disease, nerve biopsy is less useful due to its potential complications and increasing availability of comprehensive genetic testing at lower costs by next-generation sequencing platforms (27). However, complications following a nerve biopsy are less common in children than in adults (27). Nathani et al. suggested a proposed decision tree to facilitate decision-making for nerve biopsies (26), and they concluded it could play a role in the diagnostic workup of highly selected patients (26). In summary, there is controversy surrounding nerve biopsy, particularly in hypotonic infants, where it may have a much lower diagnostic yield (27).

**-Nerve Imaging**

Recently, significant advances in ultrasound and magnetic resonance imaging (MRI) have revolutionized the evaluation of patients with peripheral neuropathy. Both of these techniques have advantages and limitations in exploring the peripheral nerves. Ultrasound is a non-invasive procedure and is available, specifically in children. Therefore, it is more widely used in this age group than MRI. Nevertheless, operator dependency and low specificity have limited this modality's use as a diagnostic tool. In the consensus of 2021, peripheral nerve imaging is recommended in the cases of local or regional neuropathies without a definitive etiological explanation; imaging methods could reveal possible therapy-relevant lesions (6) .

**-Genetic testing**

A genetic study should be considered when a hereditary type of the disease is suspected,

particularly in the context of a positive family history (6). For instance, over 100 genes have been reported to cause CMT neuropathies. Genetic testing in demyelinating polyneuropathy has more diagnostic value than axonal polyneuropathy (60% versus 20-40%) [26]. About 90% of hereditary neuropathies are caused by PMP22, MFN2, MPZ, or Cx32; however, the range of positive genes varies (30-70%) depending on the type of the disease and family history (28). Therefore, a genetic study is requested based on the most suspicious genes. For example, MLPA for the PMP22 gene's copy number is asked for, specifically in the case of demyelinating polyneuropathy. If the result is inconspicuous, massive parallel sequencing/NGS is usually carried out (6, 28).

## Discussion

One of the most essential questions facing physicians when diagnosing a patient with peripheral neuropathy is what tests to order after the electrodiagnosis study. Several guidelines have been suggested for laboratory tests in adults with polyneuropathy (7, 8, 10, 13, 14), whereas in children, the literature on polyneuropathies is sparse. The American Academy of Neurology (AAN) 2009 published a review to support testing in distal symmetric polyneuropathy in adults (10).

**Table 1**. Positive and negative symptoms of polyneuropathy.

| Nerve | Negative | Positive |
|---|---|---|
| *Motor fibers* | Weakness<br>Fatigue<br>Hyporeflexia or areflexia<br>Hypotonia<br>Orthopedic deformity (pes cavus, hammertoes) | Fasciculation<br>Cramps<br>Myokemia<br>Restless legs<br>Tightness |
| *Sensory* | | |
| Large fibers | Decreased vibration sensation<br>Decreased joint position sensation<br>Hyporeflexia or areflexia<br>Ataxia<br>Hypotonia | Tingling<br>Pins and needles |
| Small fibers | Decreased pain sensation<br>Decreased temperature sensation | Burning<br>Jabbing<br>shooting |
| Autonomic fibers | Hypotension<br>Arhythmia<br>Impotence<br>Urinary retention | Hypertension<br>Arhythmia<br>Increased sweating |

**Table 2**. Non-neurological signs and symptoms in children with polyneuropathies [13, 16–18].

| Signs/symptom | | Possible diagnosis |
|---|---|---|
| Eye | Optic atrophy | CMT2A (MFN2), CMT4A (GDAP1), Mitochondrial disease (OPA1), Friedreich's ataxia |
| | Retinitis Pigmentosa | peroxisomal disease (e.g., infantile Refsum disease), ataxia with vitamin E deficiency (AVED), mitochondrial disease (NARP) |
| | Ophthalmoplegia | Miller-Fisher syndrome, mitochondrial disease (progressive nuclear ophthalmoplegia) |
| | Lich nodules | Neurofibromatosis |
| Ear | Sensorineural hearing loss | CMTX, Cockayne syndrome |
| Skin | Hypopigmentation | Leprosy |
| | Hyperpigmentation | Adrenoleukodystrophy (buccal), Diabetes (acanthosis nigricans), neurofibromatosis (café au lait spots) |
| | Angikeratomas | Fabry disease |
| | Purpura | Systemic vasculitis (Henoch-Schonlein purpura) |
| | Malar or Discoid rash | Systemic lupus erythematosus (SLE) |
| | Photosensitivity | Xeroderma pigmentosa, Cockayne syndrome, SLE |
| | Desquamation | Arsenic exposure |
| | Nail Changes | Arsenic and thallium (Mee's line) |
| Hair | Alopecia | Connective tissue disorders, Thallium poisoning |
| | Tight kinky hair | Giant axonal neuropathy |
| Pharynx | Yellow-orange tonsil | Tangier Disease |
| | Gray pseudomembrane | Diphtheria |
| lymph | Lymphadenopathy | Lymphoma |
| | Splenomegaly | Lymphoma |
| | Hepatomegaly | Mitochondrial disease (PEO), tyrosinemia, hemophagocytosis, toxin (amiodarone) |
| Brain | Developmental regression or seizure | Mitochondrial disorders, Krabbe disease, metachromatic leukodystrophy, lead toxicity, peroxisomal disorders |
| Heart | Cardiomyopathy | Ataxia with vitamin E deficiency (AVED), mitochondrial disease, Friedreich's ataxia |
| | Conduction defect | Mitochondrial disease, glue, and solvent abuse |
| GI | Abdominal pain | Fabry disease, Porphyria disease, mitochondrial disease (MNGIE), arsenic or lead toxicity |
| Extremities | Arthritis | Lyme disease |
| | Tendon Pigmentation | Cerebrotendinous xanthomatosis |

**Table 3**. Sensorimotor polyneuropathy and proposed laboratory studies.

| Neuropathy pattern | Phase | Proposed laboratory studies |
|---|---|---|
| Symmetric sensorimotor axonal polyneuropathy | Acute/ subacute | CSF analysis with cytology, rheumatologic panel, GBS Ab panel (anti-GM1 Ab, Anti-MAG antibody, Anti-GD1a and b, CBC diff, serum ACE, toxin content of urine (Arsenic), vitamin B12 and B1 level |
| | Chronic | ABR, VEP, Brain MRI, FBS, B1 and B2 serum level, Abdominal Sonography,<br>Serum LDH |
| Symmetric sensorimotor Demyelinating polyneuropathy | Acute/ subacute | CSF analysis, blood and CSF Lactate, Viral hepatitis Markers, Rheumatologic panel, |
| | Chronic | ABR, VEP, Brain MRI, heart Echo and ECG., Plasma pyruvate, lactate, alanine, CPK, and muscles biopsy( in mitochondrial disorders) |
| Asymmetric sensorimotor demyelinating polyneuropathy | Acute/ subacute | CSF analysis, Rheumatologic panel, Anti-MAG Ab, |
| | Chronic | CIDP Ab panel (anti-Tubulin Ab, Anti-MAG Ab), ABR, VEP, Brain MRI, |
| Asymmetric sensorimotor axonal polyneuropathy | | CBC diff, ESR, CRP, U/A, ANCA, Cryoglobulin, ANA, RF, ENA, C3 and C4 level<br>Barin and spinal MRI |

Rheumatologic panel: ESR, CRP, anti-CCP, Cryoglobulins, HIV, c-ANCA(PR3), P-ANCA (MPO), urinalysis.

**Table 4**. Sensory polyneuropathy and proposed laboratory tests.

| Neuropathy pattern | Distribution | DDX | Proposed laboratory studies |
|---|---|---|---|
| Acute | Asymmetric | connective tissue disorders | Rheumatologic panel |
| | Symmetric | GBS (Miller-Fisher variant)<br>viral hepatitis* | Anti-GQ1b Ab, Anti-GD1a, Anti-MAG Ab, Anti-Sulfatide Ab |
| Chronic | Asymmetric | connective tissue disorders | Rheumatologic panel |
| | Symmetric | - CIDP variant (ataxia, gait disorder)<br>- Diabetes mellitus, Hypothyroidism*, Acromegaly*<br>- Vit B12, E and folic acid* deficiency, pyridoxine deficiency (vitamin B6)<br><br>- Chronic liver disease, viral hepatitis*<br>- Connective tissue disorders<br><br>- Drug and toxin: platinum anticancer drugs (e.g., cisplatin), thallium, mercury, paclitaxel, metronidazole, metronidazole, antiretroviral medications, phenytoin, colchicine<br>-leprosy<br>Inherited:<br>Friedreich's ataxia,<br>Allgrove syndrome<br>A-betalipoproteinemia,<br>NARP, MERRF<br><br>-Adrenomyeloneuropathy<br>SCA<br>HSANs (to be developed). | - Anti-GD1b, GD3, GT1b or GQ1 if sensory<br>- BS or FBS or Glucose tolerance test, renal function test<br>- B12 and methylmalonic acid if B12 level is between 200–300 mg/dL, Vitamin E and B6 level<br><br>-LFT and Viral hepatitis Markers<br><br>- Rheumatologic panel<br><br>-Thallium and Mercury content of urine or blood,<br>Anti-sulfatide<br><br>-Echo<br>- cholesterolemia and triglyceridemia<br>- Ophthalmologic examination, ABR, serum lactate and pyruvate<br>-Brain MRI, VLCF levels.<br>- Brain MRI |

*Less common in children.

Rheumatologic panel: ESR, CRP, anti-CCP, PR3, MPO, Cryoglobulins, HIV, urinalysis.

**Table 5**. Motor Polyneuropathy and proposed laboratory studies.

| Neuropathy pattern | Distribution | DDX | Proposed laboratory studies |
|---|---|---|---|
| Acute | Asymmetric | Motor neuronopathy, poliomyelitis | CSF analysis with cytology, spinal MRI, and detection of polio from 2 stool specimens |
| | Symmetric | GBS (motor variant), Viral causes of poliomyelitis syndrome (entroviruses, adenoviruse, mumps virus, herpesvirus, togavirus) porphyria, HTLVI, and II, Organophosphates | CSF analysis with cytology, GBS Ab (anti-GM1 Ab, anti-MAG Ab, anti-GD1a, anti-GaNAc-GD1a), spinal MRI, IGM, IgG, and IgA for poliovirus |
| Chronic | Asymmetric | Lead toxicity, ALS overlap disorders | Basophilic stippling of RBC, 24-hr urinary heavy metal testing |
| | Symmetric | N-hexane inhalation, Dapson, Chronic idiopathic intestinal pseudo-obstruction Congenital dSMA, SMA1, 2, 3, X-linked SMA, pontocerebellar hypoplasia type1, SMA with congenital fractures, dHMN I-VI. Juvenile ALS disorders (upper motor neuron predominant, HSP) | Brain MRI |

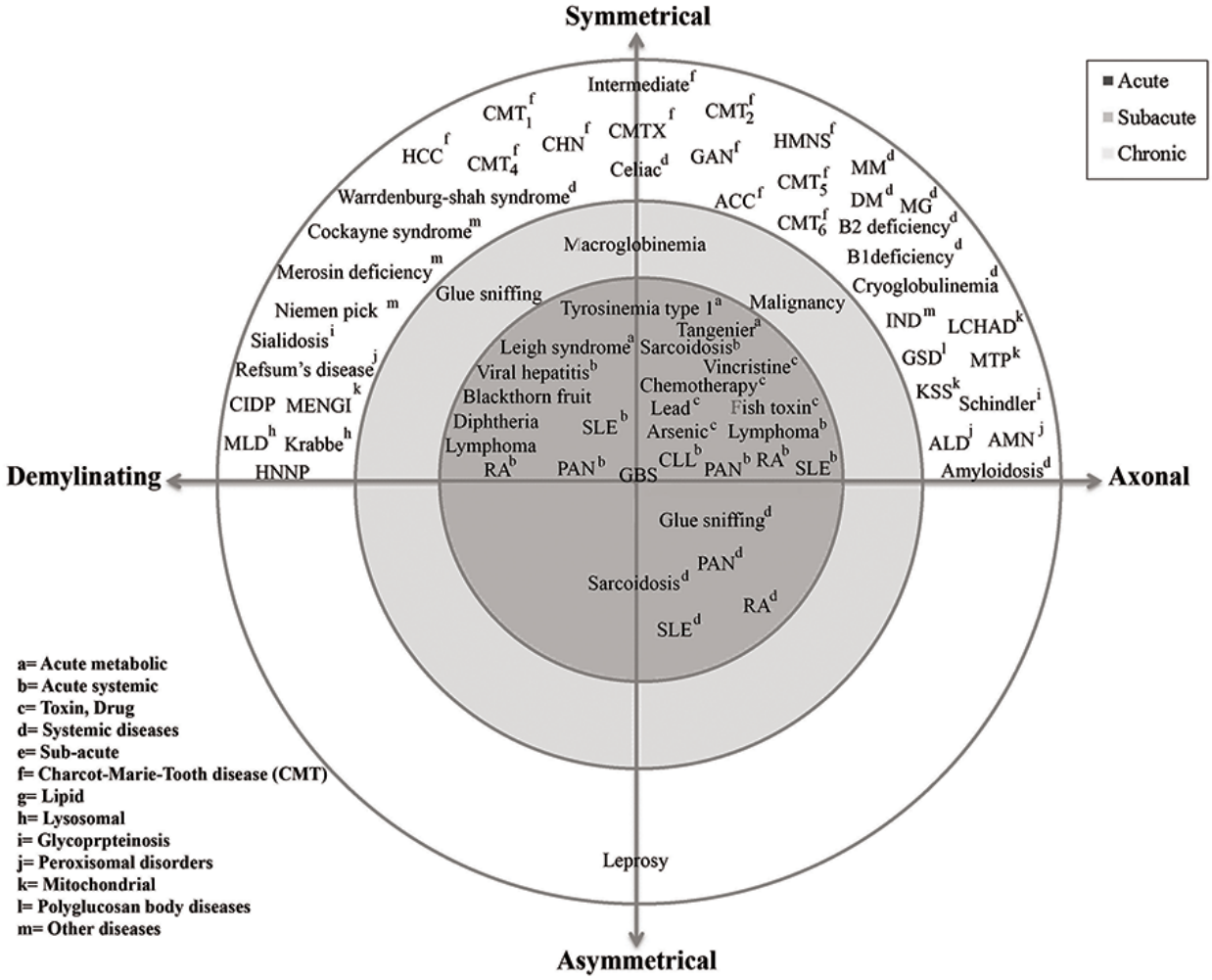


***Figure 1***. *Diagnosis according to the type of polyneuropathy and symmetry. CLL: chronic lymphatic leukemia. IND: Infantile Neuroaxonal dystrophy. GSD: Glycogen storage disease. KSS: Kearn Sayre Syndrome. MM: Multiple myeloma. MG: Monoclonal Gammopathy. GAN: Giant axonal neuropathy.DM: Diabetes mellitus. LCHAD: Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. MTP: mitochondrial trifunctional protein. ALD: adrenoleukodystrophy. AMN: Adrenomyeloneuropathy. CHN: Congenital hypomyelination neuropathy. HNPP: Hereditary neuropathy with pressure palsies. PAN: Polyarteritis nodosa. RA: rheumatoid arthritis. SLE: Systemic Lupus erythematosus. GBS: Guillain-Barré syndrome. CIDP: Chronic inflammatory demyelinating polyneuropathy.*

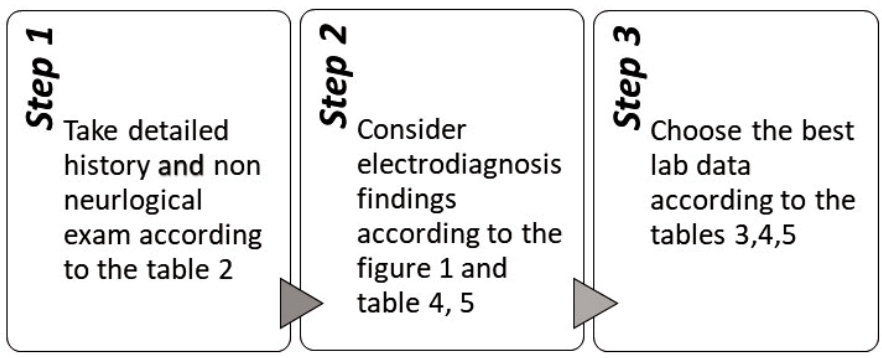


***Figure 2***. *step to step polyneuropathy diagnosis.*

The diagnostic workup in this review supports adults' neuromuscular disorders and provides less information in children due to different differential diagnoses between the two groups.

Generally, history and physical examination (Figure 2) remain the crucial and valuable tools for determining the need for ancillary diagnostic tests (Table 2). Wilmshurst et al. mentioned that the history and the clinical examination are critical clues in resource-poor settings (29). A detailed past medical history may be difficult to obtain due to other differential diagnoses, lack of recall, and the patient's age at communication. Therefore, electrodiagnosis in children is valuable for ruling out other differential diagnoses and defining the polyneuropathy pattern (14). Three types of nerve involvements could be reported in the EDX, including sensorimotor (axonal vs. demyelinating, symmetric vs. asymmetric, and acute vs. chronic), sensory (symmetric vs. asymmetric and acute vs. chronic), and motor (symmetric vs. asymmetric and acute vs. chronic) polyneuropathy. Sensorimotor polyneuropathy is the largest and most challenging group with a constellation of differential diagnoses (14). Although sensory and motor neuropathy is less prevalent, the asymmetric and acute pattern suggests treatable, typically acquired conditions, including neuroinfectious diseases, neuroinflammation, toxins, and vitamin deficiencies (29).

After confirming the polyneuropathy type and characteristics, the third step is to evaluate the polyneuropathy etiology and proposed laboratory tests. Diagnosing and managing children with peripheral neuropathies are approached differently based on the availability of investigations and the extent of insurance coverage, varying wildly from one country to another. In Iran, under Tarh-e Tahavole Salaamat (National Plan for Health Evolution), up to 90% of patients' medical bills at public hospitals are paid for, more than ever before, with extra provision for those with rare diseases or in remote areas [28]. However, some of the new and expensive laboratory testing and genetic studies, e.g., whole exome sequencing (WES), have not been covered by insurance yet, and physicians should consider this situation for the next step of diagnosis, especially in the children population.(30). Wilmshurst et al. considered peripheral neuropathy diagnosis and management in resource-poor settings (29). In their study, basic aids assist the healthcare worker in the early detection and interventions for a child with peripheral neuropathy. However, this study did not precisely suggest necessary laboratory studies after polyneuropathy detection (29). Burns et al. provided a valuable proposed laboratory evaluation for every type of neuropathy, although this study is more related to the adult population (1). Therefore, the present study presented laboratory evaluation and other paraclinical studies tailored to the Iranian population (Table 3, 4, 5). This approach could help choose a focused and efficient strategy with a reasonable price and does not put a patient at an unnecessary risk of a procedure-related complication (e.g. nerve biopsy).

## In Conclusion

This narrative review presents an approach to polyneuropathy in children after an electrodiagnosis study for laboratory and paraclinical test requests. However, this is the first study for reviewing laboratory tests; this field needs more studies to evaluate the most essential and valuable tests in the children's population.

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## Authors' Contribution

MB, JA.U, FF, and MR devised the project, and the main conceptual ideas worked out almost all of the technical details and proof outline.

## Conflict of Interest

The authors declare no conflict of interest.

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