

REVIEW ARTICLE

Peripheral neuropathies across the lifespan: Comparative insights from pediatric and adult populations

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Abstract

Peripheral neuropathies constitute a diverse group of disorders impacting the peripheral nervous system, leading to motor, sensory, and autonomic dysfunction. These conditions stem from a variety of etiologies, including genetic mutations, metabolic disorders, infections, autoimmune diseases, and toxic exposures, with presentations and progression varying significantly between pediatric and adult populations. In children, hereditary peripheral neuropathies such as Charcot–Marie–Tooth (CMT) disease are the most common, presenting with delayed motor milestones, muscle weakness, and foot deformities. Acute acquired neuropathies, including Guillain–Barré Syndrome (GBS), are rarer but often associated with life-threatening complications. Conversely, adults frequently experience peripheral neuropathies due to acquired conditions such as diabetes mellitus, often presenting with chronic, progressive symptoms such as distal sensory loss and weakness at later stages. Specific conditions, including entrapment neuropathies (e.g., carpal tunnel syndrome, ulnar neuropathies, and peroneal neuropathies), acquired conditions (e.g., diabetic neuropathy, GBS, chronic inflammatory demyelinating polyradiculoneuropathy, and chemotherapy-induced neuropathy), hereditary neuropathies (e.g., CMT diseases), and idiopathic form are explored in detail. Understanding age-specific variations in presentation and progression is critical for timely diagnosis and tailored therapeutic interventions. This review emphasizes key differences and similarities in the etiology, clinical presentation, diagnostic approaches, and management of peripheral neuropathies in pediatric and adult populations. A better understanding of age-specific patterns can enhance diagnostic accuracy and guide more appropriate clinical decision-making across the lifespan.

Keywords: Peripheral neuropathy; Adulthood; Childhood

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1. Introduction

Peripheral neuropathy is a prevalent disorder of the nervous system whereby sensory and/or motor axons no longer effectively communicate between the periphery

and the central nervous system. In the United States, studies have shown that nearly 15% of adults over the age of 40 are affected.¹ Peripheral neuropathy is not a single, homogenous disease, but rather, a mix of different clinical presentations, underlying causes, and patterns of progression. Patients may present with motor insufficiency (weakness), sensory abnormalities (numbness, paresthesias, hyperalgesia/allodynia, and apain), autonomic symptoms, or a combination of symptoms, often depending on the particular disease. These various constellations of neurological symptoms suggest motor, sensory, and autonomic axons have differing susceptibilities to various disease processes. In addition, while most neuropathies are chronic, slowly progressive conditions, some neuropathies have a more acute onset and gradual recovery.^{2,3} The heterogeneity of peripheral neuropathies is likely secondary to the initiating event. Few neuropathies are present in isolation, but rather, are often secondary to other systemic illnesses, including diabetes. In addition, peripheral neuropathies may be iatrogenic, arising from the toxicity of drugs given as part of chemotherapy regimens.

Peripheral neuropathies are one of the most common neurological disorders, yet their causes, clinical profiles, and therapeutic approaches vary between pediatric and adult populations. In adults, neuropathies frequently arise from metabolic, toxic, compressive, or immune-mediated mechanisms, and often reflect cumulative exposures or chronic disease states.^{4,5} In contrast, pediatric cases are more often linked to inherited disorders, developmental anomalies, or trauma, and present unique diagnostic and management challenges due to age-related differences in symptom expression and cooperation during clinical evaluation.^{6,7}

Epidemiological data reveal striking age-related differences in the etiological distribution of peripheral neuropathies. In adults, acquired causes predominate, with diabetes mellitus alone accounting for the majority of cases, followed by idiopathic, toxic, inflammatory, and infectious etiologies. Hereditary neuropathies represent only a small minority of adult cases despite advances in genetic diagnostics. In contrast, childhood-onset peripheral neuropathies are predominantly hereditary, with conditions such as Charcot-Marie-Tooth (CMT) disease comprising an estimated 70% of cases. Idiopathic and acquired neuropathies are considerably less frequent in pediatric populations. These divergent patterns reflect differences in underlying pathophysiology, diagnostic priorities, and clinical management across the lifespan. While adult epidemiological data are relatively robust, pediatric data remain limited and are often derived from

specialized referral center cohorts. A visual summary of these trends is provided in [Figure 1](#).^{5,8,9}

In adults ([Figure 1](#), left panel), the majority of peripheral neuropathies are acquired, with diabetic (60%) and toxic (10%) neuropathies as the most common acquired causes. Idiopathic neuropathies (23%) are the second most common form. Hereditary neuropathies are rare in the adult population (0.5%). In contrast, childhood-onset peripheral neuropathies ([Figure 1](#), right panel) are predominantly hereditary (70%), followed by idiopathic (20%) and acquired (10%) etiologies. These estimates highlight distinct age-related patterns in pathogenesis and diagnostic priorities across the lifespan. Compression neuropathies were excluded from the distribution. While comprehensive epidemiological data are available in adults, such data remain scarce for pediatric populations. Pediatric data are adapted from *UpToDate*,⁸ while adult estimates for hereditary and inflammatory causes are approximate and reflect variability across source data and classification methods.

The conventional view of peripheral neuropathies as uniform syndromes across age groups has been challenged by recent advances in molecular genetics, neuroimmunology, and neurophysiology. For example, while carpal tunnel syndrome (CTS) is predominantly an occupational and age-related entrapment neuropathy in adults, its pediatric counterpart is rare and often secondary to mucopolysaccharidoses (MPS).¹⁰ Similarly, the clinical and prognostic profile of Guillain-Barré syndrome (GBS) varies across age groups despite a shared immunopathogenesis.^{11,12}

With improved access to next-generation sequencing (NGS), targeted antibody testing, and refined electrodiagnostic protocols, clinicians are now better equipped to identify neuropathies. However, treatment approaches are largely extrapolated from adult data, particularly in inflammatory and toxic neuropathies, underscoring the need for pediatric-focused guidelines.^{13,14}

This review synthesizes knowledge on peripheral neuropathies across the lifespan, comparing pediatric and adult presentations, etiologies, diagnostic strategies, and management. We aim to provide clinicians and researchers with a resource that integrates emerging insights with clinical pragmatism, advocating for age-sensitive approaches in both diagnostics and therapy.

2. Entrapment neuropathies

2.1. CTS

CTS is the most prevalent entrapment neuropathy in adults, but remains a rare and often secondary condition

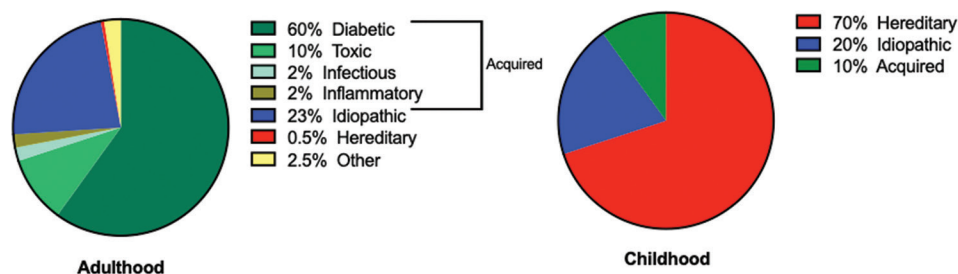


Figure 1. Distribution of peripheral neuropathy etiologies in adults and children

in the pediatric population. This contrast in epidemiology and pathophysiology underlines the need for age-specific diagnostic and therapeutic strategies.

In adults, CTS primarily affects middle-aged individuals, especially women, with population-based data estimating a prevalence of 1.5–3%.^{15,16} Risk factors include repetitive hand movements, obesity, diabetes, arthritis, hormonal changes, and certain occupational exposures.¹⁷ Elderly adults may exhibit more severe CTS on electrodiagnostic studies, often presenting with thenar atrophy despite fewer subjective complaints, complicating the overall clinical diagnosis.¹⁸

Clinically, adult patients typically report nocturnal paresthesia, hand weakness, and pain, radiating proximally, especially in the median nerve distribution involving the radial 3.5 digits (thumb, index, middle, and half of the ring finger). Tinel's sign and Phalen's maneuver are standard provocative tests, though weak thumb abduction is more predictive of nerve conduction abnormalities.¹⁶ Treatment is initially conservative, such as splinting, corticosteroid injections, but escalates to surgical decompression in refractory or severe cases, with both open and endoscopic techniques offering good outcomes.^{19,20}

In contrast, CTS in children is uncommon and typically secondary to genetic, metabolic, or structural disorders. MPS are the most frequently reported etiologies, followed by congenital malformations, trauma, endocrinopathies, and familial predispositions.^{10,21,22} Idiopathic CTS in children is exceedingly rare, with only a few well-documented cases.²³

Pediatric patients often present with atypical symptoms such as hand clumsiness or thenar hypoplasia rather than classic paresthesia. Due to poor cooperation and limited sensitivity of standard electrodiagnostic tests in children, clinical diagnosis requires a high index of suspicion and may necessitate the use of imaging modalities such as ultrasound or MRI.^{6,24} Once a diagnosis is established, management generally follows adult protocols, with

individualized adjustments based on the underlying etiology. For example, children with MPS may experience recurrent symptoms years after surgical decompression, often necessitating revision procedures.²⁵

2.2. Ulnar neuropathy

Ulnar neuropathy, the second most common compressive neuropathy after CTS, exhibits different etiological patterns in adults and children. In adults, it frequently arises due to chronic compression at the cubital tunnel, post-operative complications, or perioperative positioning during surgery.^{26,27} Degenerative changes, such as heterotopic ossification in spastic limbs after brain injury, are also adult-specific risk factors.²⁸ On the other hand, pediatric cases are rare and are often attributed to different etiologies, such as supracondylar or lateral condyle humerus fractures, tardy ulnar nerve palsy, or perioperative positioning errors.^{29,30} In both populations, symptoms typically include paresthesia in ulnar nerve distribution—the fourth and fifth digits—hand weakness, and intrinsic muscle atrophy. Diagnosis in both adults and children relies on clinical examination, electrodiagnostic studies, and imaging. In adults, nerve conduction studies alongside MRI or ultrasonography have enhanced the ability to localize compression sites and guide intervention.³¹

Adult management strategies range from conservative measures to surgical decompression or anterior transposition. Meta-analyses show no significant difference in outcomes between simple decompression and transposition.³² Nerve transfer techniques have emerged as promising adjuncts in selected adult patients with severe motor involvement.³³ In contrast, pediatric ulnar neuropathies respond less favorably to conservative treatment. Outcomes are often poorer in traumatic cases compared to non-traumatic ones,³⁴ and surgical decompression has been reported to be less successful in children than adults.³⁵ Moreover, tardy ulnar nerve palsy from elbow deformities due to poorly healed fractures underlines the importance of long-term surveillance in pediatric patients.³⁶

2.3. Peroneal neuropathy

Peroneal neuropathy, the most common mononeuropathy of the lower limb, presents variably across age groups, with different etiological and clinical patterns in adults versus pediatric populations. In adults, the condition is predominantly compressive in origin, often related to external pressure at the fibular neck, leading to weakness of dorsiflexion and sensory loss over the dorsum of the foot and lateral leg.³⁷ Subclinical peroneal neuropathy, which lacks overt foot drop, affects up to 3.3% of ambulatory adults and is associated with increased fall risk, emphasizing the need for early detection even in asymptomatic individuals.³⁸

Electrophysiologically, adult peroneal neuropathy often shows greater involvement of the deep peroneal nerve, with denervation changes more prominent in its distribution compared to the superficial branch.³⁹ Various iatrogenic and positional factors, including squatting during childbirth,⁴⁰ bariatric surgery with rapid weight loss,⁴¹ and prolonged immobilization, are recognized contributors in adults. Vascular factors such as anterior tibial artery occlusion have also been implicated in rare cases.⁴² Diagnosis relies heavily on clinical examination and electrodiagnostics, with treatment ranging from conservative management and physiotherapy to surgical decompression in refractory cases.^{37,43}

In contrast, pediatric peroneal neuropathies are rare and often underrecognized. The majority are due to compression or trauma, but a considerable proportion arises from potentially correctable causes such as bone tumors⁴⁴ or orthopedic devices like ankle-foot orthoses.⁴⁵ A large pediatric EMG cohort identified compression and entrapment as leading causes, often localized to the fibular head.⁴⁶ Children may also present with peroneal neuropathy who have secondary to rare mechanisms such as ankle sprains⁴⁷ or habitual leg crossing during chemotherapy.⁴⁸ Surgical intervention is rarely required, and the prognosis is generally favorable with appropriate rehabilitation.⁴⁶

3. Acquired neuropathies

3.1. Metabolic neuropathies

3.1.1. Diabetic peripheral neuropathy (DPN)

DPN is one of the most common chronic complications of diabetes mellitus, affecting up to 50% of adults with long-standing disease and leading to substantial morbidity, including pain, foot ulcers, and amputation.^{4,49} In contrast, clinical DPN is rare in pediatric populations, but subclinical neuropathy is increasingly recognized, especially among adolescents with type 1 diabetes.^{50,51} Both age groups share core risk factors: poor glycemic control, disease duration,

and metabolic comorbidities.^{4,52} Adult DPN, particularly in older patients, often presents with painful distal symmetric polyneuropathy and carries greater risks for falls, disability, and mortality.^{4,51} Emerging evidence highlights a striking socioeconomic gradient, with DPN disproportionately affecting individuals in socioeconomically challenged communities.⁵³

Diagnosis remains a major challenge across the lifespan. While monofilament and vibration testing remain standard in adults, their sensitivity level is low in pediatric patients, in whom quantitative sensory testing or pediatric-adapted nerve conduction protocols are more informative.^{51,54} Although uncommon, early-onset symptomatic DPN in youth may occur as a result of poor glycemic control or even rapid correction of hyperglycemia, as seen in treatment-induced neuropathy of diabetes.^{55,56} Prevention in both age groups centers around optimal glycemic control, yet the evidence for reversibility is stronger in type 1 diabetes compared to type 2.⁴ Despite clinical differences, DPN across the age spectrum reflects a convergence of metabolic, vascular, and genetic insults, underscoring the need for early screening, personalized management, and further longitudinal pediatric studies to guide intervention.

3.2. Inflammatory neuropathies

3.2.1. GBS

GBS is an acute immune-mediated polyradiculoneuropathy with a variable but potentially life-threatening course across the age spectrum. Although the pathophysiology rooted in molecular mimicry and antibody-mediated attack on peripheral nerves is similar in children and adults, the clinical trajectory, epidemiology, and long-term outcomes diverge between age groups.^{11,57} The annual incidence of GBS is generally lower in children (0.34–1.34/100,000) than in adults, where it rises with age and can exceed 3.3/100,000 in those over 50 years old. GBS incidence increases by 20% for every 10-year increase in age.^{58,59} While the majority of pediatric cases occur in previously healthy children, adult patients often have multiple comorbidities, which may complicate both diagnosis and recovery.⁶⁰

Clinically, children typically reach nadir faster and exhibit a higher prevalence of pain and bulbar dysfunction, while autonomic dysfunction is particularly predictive of the need for mechanical ventilation in pediatric cohorts.¹² In contrast, adults are more commonly present with severe motor deficits and sensory involvement, and their prognosis is often shaped by age, early disease severity, and electrophysiological subtype.^{57,60} Diagnosis in both populations is based on clinical features, cerebrospinal fluid analysis, and nerve conduction studies, but children may

present atypically, and diagnostic delays are common.^{61,62} While the Brighton criteria have shown high sensitivity in both adult and pediatric cohorts, their diagnostic utility is slightly lower in children due to variability in early presentation.^{61,63}

Despite advances in diagnostic criteria, distinguishing GBS from its mimics remains clinically challenging, particularly when relying on early electrophysiological data. The electrodiagnostic features of GBS, especially in axonal or equivocal variants, can overlap with other peripheral or central nervous system disorders, leading to potential misdiagnosis. Sciacca *et al.*⁶⁴ reported three cases of acute neuromuscular presentations initially mistaken for GBS, later identified as Wernicke encephalopathy, Vitamin B12 deficiency-related neuropathy, and diabetic-associated demyelination. These examples underscore the importance of considering alternative diagnoses, especially when clinical or laboratory features are atypical. Diagnostic uncertainty is further amplified in pediatric populations due to variable presentation and limited cooperation. Thus, a comprehensive evaluation including CSF, neuroimaging, metabolic studies, and careful interpretation of neurophysiological data is essential to ensure accurate diagnosis and timely management.

Treatment protocols, largely originated from adult data, support the use of intravenous immunoglobulin (IVIg) as first-line therapy across age groups, with plasma exchange reserved for IVIg non-responders or severe cases.^{65,66} Despite similar treatment approaches, long-term outcomes differ; while many adults experience residual deficits, the majority of children exhibit excellent neurological and functional recovery, although some may have persistent behavioral or academic difficulties.^{67,68}

3.2.2. Chronic inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIPD) is an acquired immune-mediated neuropathy with a relapsing or progressive course, affecting both adults and children. While the core pathophysiological mechanisms are shared across age groups, there are differences in clinical presentation, diagnosis, and management. Epidemiologically, CIPD incidence increases with age, ranging from 0.06/100,000 in children to 0.73/100,000 in elderly adults, with a male predominance in adult cohorts.⁶⁹

In adults, CIPD typically manifests with symmetrical sensorimotor deficits and reduced reflexes, with most patients requiring long-term immunotherapy. An international CIPD outcome study found that 78% of treatment-naïve adults responded to first-line therapy

within the 1st year, with IVIg associated with the highest rate of clinical improvement (94%) and combination IVIg-corticosteroid therapy yielding the most remissions (44%).¹³ Despite treatment, residual deficits remain common, particularly sensory abnormalities and neuropathic pain. Furthermore, CIPD in adults carries a significant healthcare burden, with patients incurring more than six-fold higher medical costs than controls, largely driven by outpatient therapy and hospitalization.⁷⁰ Diagnostic uncertainty remains a challenge, with studies reporting misdiagnosis rates exceeding 50%, often due to the overlap with mimicking conditions.⁷¹

In contrast, pediatric CIPD is rare and diagnostically more complex due to frequent atypical presentations. A large single-center cohort showed that over half of pediatric cases presented with non-classical variants such as distal, pure motor, or pure sensory phenotypes.⁷ Differentiating pediatric CIPD from hereditary neuropathies like CMT disease is a key challenge, as both can show similar electrophysiological profiles. Specific nerve conduction features, such as prolonged distal compound muscle action potentials, have been proposed as discriminative markers.⁷² Despite these complexities, outcomes in pediatric CIPD are often favorable. Over 50% of children achieve complete remission, and most show meaningful functional improvement.⁷ IVIg remains the frontline treatment, but pulse corticosteroids have shown promise as effective and well-tolerated alternatives, particularly in IVIg-refractory cases.^{73,74} Immunosuppressive agents like rituximab have been used successfully in seropositive and treatment-resistant cases.⁷⁵

3.3. Toxic neuropathies

3.3.1. Chemotherapy-induced peripheral neuropathy (CIPN)

CIPN is a frequent and often debilitating complication of cancer treatment in both adults and children, with overlapping yet distinct mechanisms. Platinum-based compounds (e.g., cisplatin and oxaliplatin) induce DNA damage in dorsal root ganglion neurons. In contrast, taxanes (e.g., paclitaxel and docetaxel) and vinca alkaloids (e.g., vincristine) impair microtubule function, disrupting axonal transport, and promoting axonal degeneration. Proteasome inhibitors like bortezomib cause oxidative stress and mitochondrial dysfunction, while immunomodulatory drugs such as thalidomide exert neurotoxic effects through anti-angiogenic and pro-inflammatory pathways (Table 1). Collectively, these mechanisms lead to sensory symptoms, typically tingling, numbness, or burning pain that begin in the distal extremities and ascend in a characteristic “stocking-glove” distribution.^{76,77} Yet, its clinical profile,

Table 1. Mechanisms of chemotherapy-induced peripheral neuropathy by drug class

Drug class	Example	Mechanism
Platinum compounds	Cisplatin, oxaliplatin	DNA damage, mitochondrial dysfunction
Taxanes	Paclitaxel, docetaxel	Microtubule stabilization, axonal transport disruption
Vinca alkaloids	Vincristine	Microtubule destabilization
Proteasome inhibitors	Bortezomib	Endoplasmic reticulum stress, mitochondrial damage

assessment, and long-term impact vary markedly between age groups.

In pediatric populations, CIPN is often underdiagnosed due to non-specific symptoms and a lack of validated, age-appropriate assessment tools.^{78,79} Sensory and motor deficits, pain, and gait abnormalities are commonly reported in children and may persist for years post-treatment, affecting functional outcomes and quality of life.^{14,80} The incidence in children ranges widely, from 2.8% to nearly 100%, reflecting heterogeneity in risk factors and assessment methods.⁸¹ In contrast, adult studies consistently report a prevalence of 30–90%, often with a more stereotyped “glove and stocking” distribution of symptoms and greater reliance on patient-reported outcomes.^{10,82,83}

The most neurotoxic agents implicated in both populations include platinum compounds, vinca alkaloids, taxanes, and proteasome inhibitors; however, cisplatin appears to cause more severe and lasting effects in children than vincristine.¹² Genetic variations have been linked to increased risk in both populations, but pediatric pharmacogenomics remains underexplored.⁸⁶

Chemotherapy-induced peripheral neuropathy is a frequent and often long-lasting complication among children undergoing cancer treatment, especially with agents such as vincristine and platinum compounds.^{81,84} The incidence of CIPN varies widely (2.8–100%) due to heterogeneity in diagnostic criteria and assessment tools, with motor symptoms occurring in up to 72% and pain in up to 44% of pediatric patients.⁸¹ Pediatric-specific risk factors include younger age, cumulative chemotherapy exposure, genetic predispositions, and race, with Caucasian children appearing more vulnerable.⁷⁸ Although many symptoms resolve, some persist into adulthood, leading to functional limitations and reduced quality of life.⁸⁴ A substantial gap remains in standardized pediatric assessment tools; while tools such as the ped-mTNS and TNS-PV are recommended for children over 6 years of age, no validated patient-reported outcome measure exists

for younger children.^{85,86} Management strategies diverge across age groups: pediatric oncologists are more likely to refer for physical therapy, whereas adult providers tend to reduce or omit neurotoxic agents.⁸⁷ Ultimately, these findings underscore the importance of individualized, developmentally appropriate assessment, and intervention strategies for pediatric peripheral neuropathy.

4. Hereditary neuropathies

With a prevalence of approximately 1 in 2,500 individuals, CMT disease is the most common hereditary neuromuscular disorder. Among hereditary neuropathies, deletions and duplications in the *PMP22* gene are the most frequent causes. Four genes—*PMP22*, *GJB1*, *MPZ*, and *MFN2*—account for up to 90% of genetically identifiable CMT cases. Based on neurophysiological characteristics, CMT is classified into demyelinating (CMT1, CMT3, and CMT4) and axonal (CMT2) forms.⁸⁸

Hereditary neuropathies encompass a broader spectrum of inherited peripheral nerve disorders, each with distinct clinical features. In addition to CMT, hereditary motor neuropathy involves isolated motor neuron degeneration, causing muscle wasting and weakness, especially in the lower extremities. Hereditary sensory and autonomic neuropathy (HSAN) impacts both sensory and autonomic nerves, manifesting as sensory loss along with autonomic dysfunction such as impaired sweating or blood pressure instability. Despite their phenotypic diversity, these hereditary neuropathies are usually slowly progressive, often beginning in childhood or early adulthood, and are diagnosed through clinical evaluation, electrophysiological testing, and genetic analysis.^{89,90}

However, in this review, we will focus more specifically on CMT and its classification into demyelinating and axonal forms, as these subtypes are the most prevalent and clinically relevant hereditary peripheral neuropathies.

4.1. Demyelinating form (CMT1)

CMT disease type 1 (CMT1) is the most common demyelinating hereditary peripheral neuropathy and presents with variable age of onset, clinical severity, and genetic background between pediatric and adult populations. While the majority of adult cases are associated with *PMP22* duplications (CMT1A) and follow a slowly progressive course with distal weakness and sensory loss, pediatric presentations are often more heterogeneous and severe, particularly in autosomal recessive forms.^{91,92}

In children, CMT1A typically presents with delayed motor milestones, frequent falls, foot deformities, and areflexia. Early onset often correlates with greater disease severity and functional impairment.⁹³ Due to prominent

scoliosis and difficulty with running or climbing stairs, certain pediatric patients may require early physical therapy and orthopedic support.⁹⁴

In adults, CMT1 may present more subtly, with slowly progressive distal weakness, sensory loss, and gait imbalance. In addition, adults with CMT1A typically exhibit milder phenotypes and preserved ambulation.^{93,94} Diagnosis is often delayed in adults due to mild early symptoms or misattribution to other causes of neuropathy. The diagnostic approach to CMT1 integrates clinical evaluation, electrodiagnostic testing, imaging, and genetic analysis. Among these, motor nerve conduction velocity (MNCV) is central to neurophysiological classification. Severely slowed MNCVs (<15 m/s) are characteristic of demyelinating forms such as CMT1A or early-onset CMT1B. These findings, combined with the age of onset and inheritance pattern, inform targeted genetic testing. Autosomal recessive inheritance is more frequent in pediatric cases, particularly in consanguineous populations.⁹⁵

Genetic diagnosis in children is often more complex due to broader phenotypic variability and a higher likelihood of *de novo* or compound heterozygous mutations. Nevertheless, the diagnostic yield has improved significantly with NGS panels, particularly for demyelinating forms, where molecular confirmation can exceed 85%.⁹⁶

Several experimental therapeutic strategies are under investigation, including gene expression modulators and agents that alleviate endoplasmic reticulum stress.⁸⁸ Notably, gene therapy studies targeting *PMP22* and *GJB1* have shown promise in preclinical models.⁹⁷ Despite these advances, effective treatments remain limited for both pediatric and adult patients.^{95,98} Given the earlier onset and greater disability in children, early diagnosis and comprehensive supportive care are essential to improving long-term outcomes.

4.2. Axonal form (CMT2)

CMT disease type 2 (CMT2) is a genetically and clinically heterogeneous group of axonal neuropathies, characterized by progressive distal weakness and relatively preserved nerve conduction velocities. Its pathogenesis involves several molecular pathways, including mitochondrial dynamics (*MFN2* and *GDAP1*), axonal transport and endosomal trafficking (*NEFL*, *RAB7*, and *DNM2*), and RNA processing (*GARS*).⁹⁹

The most frequently mutated gene in CMT2, *MFN2*, is associated with motor-predominant phenotypes but may also cause multisystem features such as optic atrophy and hearing loss. Other notable subtypes include

CMT2B (*RAB7* mutations), which presents with sensory-predominant deficits, and CMT2D (*GARS* mutations), typically associated with early hand weakness. Despite their genetic distinctiveness, overlapping clinical features and variable phenotypes even among mutations in the same gene can complicate diagnosis.¹⁰⁰

In adults, CMT2 tends to present with insidious distal weakness, sensory loss, and foot drop. Progression is typically slow, though phenotype varies widely depending on the underlying mutation. Children and adults may demonstrate pes cavus and areflexia.⁸⁸ Compared to demyelinating forms, axonal CMT subtypes may be more challenging to diagnose early in children due to subtler electrophysiological findings and greater genetic diversity.⁹⁴

In children, CMT2 may present with similar clinical signs as CMT1 but sometimes with earlier onset and more severe motor involvement, particularly in *GDAP1*-related cases.⁹³ Although historically considered an adult-onset disorder, early-onset forms are increasingly recognized. Importantly, diagnostic yield improved significantly in cases referred to specialized pediatric neuromuscular centers, underscoring the value of early recognition and tailored genetic workup.¹⁰¹

Although NGS has improved diagnostic capabilities, CMT2 remains more genetically elusive, with an approximate yield of 36%, compared to 87% in demyelinating forms.⁹⁶ This suggests that unidentified genes or complex genetic modifiers may play a larger role in axonal forms, particularly in sporadic or adult-onset cases. Several targeted and disease-modifying therapies are in development: serine supplementation for HSAN1, aldose reductase inhibitors (ARIs) for sorbitol dehydrogenase (*SORD*)-related neuropathy, and mitofusin agonists for CMT2A. Broader interventions such as *HDAC6* inhibition and gene therapy are also being explored in preclinical and early clinical studies.¹⁰⁰

In conclusion, while CMT2 was once considered a predominantly adult-onset disorder, pediatric cases are increasingly recognized. Continued progress in molecular diagnostics and functional modeling will be key to enabling early diagnosis and developing precision therapies across the lifespan.

5. Idiopathic neuropathies

Conventionally, chronic idiopathic axonal polyneuropathy (CIAP) has been considered a diagnosis of exclusion, based on clinical criteria and the absence of identifiable metabolic, toxic, infectious, or immune-mediated etiologies. In adults, particularly those over the age of 60, CIAP is a common clinical entity, often presenting as a

slowly progressive, symmetrical sensorimotor neuropathy with predominant sensory involvement. CIAP accounts for a significant proportion of peripheral neuropathies, 25% of chronic cases in adults.^{5,102,103}

However, recent advances have begun to unravel the “idiopathic” label, identifying genetic, immune, and metabolic contributors in many adult cases. Biallelic mutations in the *SORD* gene have emerged as a frequent cause of recessive axonal neuropathy, associated with intracellular sorbitol accumulation and neuronal toxicity. These findings not only provide a mechanistic explanation for some CIAP cases but also offer therapeutic potential, as ARIs are currently under investigation.¹⁰⁴ Another major breakthrough is the identification of intronic *RFC1* repeat expansions, which are now recognized as a leading cause of cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS) and isolated sensory neuropathies in adults. This discovery has significantly expanded the clinical spectrum of *RFC1*-related disease and has refined diagnostic algorithms for late-onset sensory neuropathies.¹⁰⁵ In addition, a subset of adults with idiopathic small fiber neuropathy has been found to harbor autoantibodies such as TS-HDS, FGFR3, and Plexin D1, suggesting an immune-mediated pathology. Although some patients demonstrate clinical improvement with immunotherapy, including IVIg, a recent negative randomized trial has cast doubt on the pathogenic relevance of these antibodies, warranting further investigation through larger, biomarker-stratified clinical trials.^{106,107}

Collectively, these discoveries underline a paradigm shift in adult idiopathic neuropathies from exclusion-based diagnoses to mechanism-driven classification. As molecular diagnostics and biomarker panels become more accessible, a growing proportion of CIAP cases are likely to be reclassified, enabling personalized therapeutic strategies and targeted clinical trials.

The notable absence of idiopathic peripheral neuropathy in the pediatric population highlights the need for further research to better understand this condition.

6. Overall differences in pediatric versus adult neuropathies: Diagnostic and management implications

Although sometimes peripheral neuropathies in children and adults may present with overlapping symptoms, their management diverges due to developmental, diagnostic, and therapeutic differences. Pediatric care requires age-appropriate approaches and greater clinician adaptability. Diagnosing neuropathy in children is particularly challenging, as limited communication skills, reduced

cooperation, and developmental variability make clinical evaluations and electrodiagnostic testing more difficult. Techniques such as distraction or, when necessary, sedation may be required. In contrast, adults typically provide reliable histories and tolerate standard examinations and nerve conduction studies well.^{85,86,109}

Assessment tools also differ between age groups. Adults benefit from multiple validated patient-reported outcome measures, whereas such tools are lacking for children. Instead, clinicians often rely on objective or modified scales such as the pediatric-modified Total Neuropathy Score (ped-mTNS) or the Total Neuropathy Score-Pediatric Version (TNS-PV), which may not fully capture a child's experience.⁸⁴⁻⁸⁶ These diagnostic limitations influence treatment decisions. Pediatric clinicians frequently prioritize non-pharmacologic interventions, such as physical and occupational therapy, and use pharmacologic agents more cautiously. Adult treatment, on the other hand, more often involves medication-based strategies guided by established protocols.^{84,85,87}

Chemotherapy-induced peripheral neuropathy exemplifies the unique challenges in pediatric populations. Its incidence and severity vary widely based on age, genetics, and drug type. Symptoms may persist long after treatment, leading to functional impairment and neurocognitive consequences. Adults with CIPN are generally managed using standardized, evidence-based guidelines.^{81,84,87,110}

Beyond these practical differences, pediatric and adult neuropathies differ in their underlying causes and clinical contexts. Children are not simply “small adults;” age-specific anatomy, physiology, and disease mechanisms require diagnostic and therapeutic approaches. Pediatric neuropathies often necessitate age-adjusted imaging techniques, electrophysiologic studies, and laboratory reference values. Moreover, the presence of neuropathy in a child, especially entrapment neuropathies, should prompt evaluation for genetic or syndromic conditions, which are less commonly considered in adults.^{35,108} In addition, children may respond differently to medications or surgical interventions, making adult treatment protocols inappropriate in many pediatric cases.³⁵

7. Conclusion

Peripheral neuropathies represent a heterogeneous group of disorders that demand age-tailored evaluation and management strategies. As this review illustrates, the etiological landscape shifts from predominantly inherited and developmental causes in children to acquired, metabolic, and idiopathic mechanisms in adults. Clinical presentations also differ, with pediatric patients often exhibiting subtle or atypical signs that may

delay diagnosis, while adults more frequently present with classic sensorimotor symptoms and characteristic electrodiagnostic profiles.

Although advances in genetic testing, electrophysiology, and neuroimaging have improved diagnostic precision across the lifespan, practical challenges persist. In children, limited availability of validated diagnostic criteria, under-recognition of certain conditions (e.g., chemotherapy-induced peripheral neuropathy), and the lack of pediatric-specific management guidelines remain significant barriers. In adults, comorbidities, diagnostic overlap with mimicking disorders, and persistent treatment gaps in idiopathic or immune-mediated neuropathies complicate care.

To translate these findings into clinical practice, clinicians should adopt a lifespan-informed approach that includes: age-appropriate screening tools and electrophysiological protocols, as well as early referral for genetic testing in pediatric-onset or atypical neuropathies. Ultimately, integrating age-specific insights into routine practice can support earlier recognition, guide more targeted interventions, and improve long-term functional outcomes for individuals with peripheral neuropathies.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Ahmet Hoke

Visualization: All authors

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Ethics approval and consent to participate

Not applicable.

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