Diagnosis and management of pediatric peripheral neuropathies in resource-poor settings

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The diagnosis of a peripheral neuropathy in a child who resides in the majority of resource-poor settings is based on the history taken and the clinical examination. The majority of children, unless they demonstrate additional clinical markers, will lack a more definitive diagnosis beyond the label 'peripheral neuropathy'. The treatable, typically acquired conditions, which are prevalent in these settings, are the priority to identify. This would include neuroinfections, neuroinflammation, toxins and vitamin deficiencies. The management of children with peripheral neuropathies in resource-poor settings must be approached in a different manner to that of more 'resource-equipped' settings. Secondary or tertiary centers are scarce, often significant distances away from the patient, and this leads to long delays before access is possible. Most children present to primary healthcare settings and are seen by practitioners with little training in the features suggestive of a peripheral neuropathy. As such, basic aids to assist the healthcare worker in the early recognition and interventions of a child with a peripheral neuropathy are important. In addition, there must be recognition of the child with a rapidly progressive neuropathy where a life-threatening condition is present, and urgent referral to a tertiary setting made wherever possible.

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Learning objectives

Upon completion of this activity, participants should be able to:

- Report the more prevalent causes of pediatric peripheral neuropathy in resource-poor countries (RPCs)
- Discuss the clinical manifestations of pediatric peripheral neuropathy in RPCs
- Provide the methods of diagnosing pediatric peripheral neuropathy in RPCs
- Review the treatment options available for pediatric peripheral neuropathy in RPCs

Keywords

■ child ■ molecular genetics ■ neurophysiology ■ pediatric ■ peripheral neuropathy ■ resource-poor setting

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The prevalence of peripheral neuropathies in children from resource-poor countries (RPCs) is not known. A study of adult and pediatric patients with neuromuscular disorders in Libya identified that the largest group had forms of Charcot–Marie–Tooth (CMT) disease followed by acute inflammatory demyelinating polyradiculoneuropathy (AIDP) [1]. In Senegal, adults between 20 and 40 years of age were reported to have undefined degenerative neuropathies, labeled 'tropical neuropathies', which were responsible for half of their cases, followed by toxic neuropathies (ethanol and isoniazid), then CMT disease and finally diabetes [2]. The authors highlighted the challenges of gaining diagnostic closure in RPCs such that many of the progressive cases were placed under this generic label of 'tropical neuropathies'. Another study from the same group quoted that 8.16% of their neurology referrals aged 3–80 years were related to peripheral neuropathies [3]. Children with peripheral neuropathies represented one-third of the patients seen in the out-patient neuromuscular service at the Red Cross War Memorial Children's Hospital in Cape Town, South Africa and 3% of the total group attending the service with neurological conditions.

In comparison with more 'developed settings', the disease spectra and the prevalences of pediatric peripheral neuropathies are different in RPCs. There are greater numbers of infections that lead to direct and indirect development of peripheral neuropathy, such as from tuberculosis, HIV type 1 (HIV-1), leprosy and diphtheria [4]. Neurotoxins are seen more often, especially where access to optimal therapy may be limited; for example, some antiretroviral therapy regimens for HIV infection still included 2′-3′-didehydro-2′-3′-dideoxythymidine (stavudine), which is associated with an increased risk of peripheral neuropathy [5]. Nutritional deficiencies, such as vitamin $B_1$and E deficiencies, remain an important aspect of RPCs [6,7]. Unrecognized results of trauma will also be more evident with badly set fractures causing irreversible damage to nerves [8]. This reflects the poor socioeconomic settings where many children have limited access to health facilities, poor nutrition and frequent infections [4]. The hereditary disorders – both those of 'pure peripheral neuropathies' and those related to neurodegenerative and systemic diseases – are also considered to be greatly underestimated in RPCs. The capacity to screen these patients is almost nonexistent, with a lack of access to basic blood analysis, neurophysiology and neuroimaging in most centers in Africa [9]; this is also the case for more complex neurometabolic and molecular genetic screens. Nerve biopsy should only be undertaken in centers with the capacity to perform the sample collection and to analyze the data accurately – this is often lacking, even in a developed world setting [10]. Supportive management of any child with peripheral neuropathy is fairly standard, regardless of the underlying etiology [11]. Limited access to ancillary services, orthopedic care and orthotic devices challenges this. Teaching parents an effective home program is often more practical [12,13]. Exclusion of reversible causes is essential, though challenging in many cases.

Clinical manifestations & diagnostic clues in peripheral neuropathy

The following signs may be seen in isolation or in combination depending on the type and severity of the neuropathy; hypotonia, muscle weakness more marked distally, areflexia, distal contractures and reduced response to pain and other sensations [14,15]. The sensory aspects are often undetected clinically especially in young children. A positive family history should be sought, all available family members examined and a detailed family tree documented, as neuropathies may have been misdiagnosed as other conditions. The issue of stigma is common in RPCs and misinterpretation of symptoms by carers, community members, traditional healers and healthcare workers is common [16]. Clinical markers can be used to identify recognized hereditary peripheral neuropathy subtypes, such as those of onset in early childhood,

some of which have severe evolution. There is heterogeneity in the presentations of many of the hereditary neuropathies, as demonstrated by the patients with CMT1 who can become symptomatic in infancy [17]. Other important broad clinical features to note are neuropathies with predominantly motor signs, those with predominantly sensory involvement, painful neuropathies and recurrent neuropathies (Table 1). Additional features of conditions particularly associated with scoliosis, respiratory involvement with diaphragmatic and/or vocal cord impairment are predominantly upper limb involvement, additional proximal weakness, glaucoma, optic atrophy, deafness, pyramidal tract involvement, central involvement and intellectual disability [18]. Nerve hypertrophy is described in hypertrophic forms of CMT, as well as leprosy and chronic inflammatory demyelinating polyradiculoneuroapathy. These markers are important in supporting a definitive diagnosis and also in identifying complications that would require a different management approach.

Evolution of symptoms typically indicates the difference between acquired (typically monophasic disease) and hereditary (chronic and progressive) disorders. At the onset of the neuropathy this may be challenging, and exclusion of any treatable factor should be considered, namely neuroinfections, toxins and vitamin deficiencies.

Recognition of etiologies

Children who have an acute presentation with peripheral neuropathy should be assessed for AIDP, critical illness polyneuropathy, toxin exposure, diphtheria, postvaccination neuropathy, acute porphyria and tyrosinemia type 1. In resource-poor settings where the lack of access to the essential screens limits the ideal mechanisms to assess these differentials, the clinician must depend on specific aspects of the history and clinical examination to guide them. For example, a child with diphtheria would be notable for their respiratory signs and the characteristic gray pharyngeal membrane; a child with AIDP typically has an ascending evolution of paralysis compared with the patient with diphtheria in whom it is descending; a history of toxin exposure would support a toxic neuropathy; and urine darkening on exposure to daylight would suggest some forms of porphyria. Similarly, episodic neurological crises should draw attention to underlying metabolic derangements such as porphyria or tyrosinemia type 1 [19]. Mononeuritis multiplex can be divided into vascular causes (including diabetes, rheumatoid arthritis and systemic lupus erythematosus), inflammatory (e.g., leprosy, sarcoidosis and Lyme disease), infiltrations (e.g., leukemia and malignancy), immune reactions (e.g., immunization, foreign sera and proteins) and trauma (e.g., multiple nerve injuries). Asymmetry in signs is more likely with vasculitic disorders. Presentation in childhood is very rare. The most important disorders to consider in children from RPCs with mononeuritis multiplex would be leprosy in endemic regions, and malignancies. Table 1 summarizes the conditions associated with key clinical forms of neuropathy and where a diagnosis should be possible in resource-limited settings.

In RPCs, there is a disparity with a greater proportion of patients with acquired causes for their peripheral neuropathies compared with children with hereditary disorders. To an extent, the true proportion of genetic causes is unknown due to limited screening tools. In Oman, 45 out of 82 children with peripheral neuropathies had acquired causes, mostly AIDP, compared with 37 related to hereditary causes, of which 17 (20%) had forms of CMT [20]. In another study of 74 children from Turkey, 73% had acquired pathologies and 27% were considered hereditary [21]. A study of 82 children with chronic peripheral neuropathies from The Netherlands showed the reverse, with 68% of their cohort related to hereditary neuropathies and the remaining 32% being acquired [22]. This study illustrated the differences apparent when children are based in a resource-equipped country without the same levels of socioeconomic challenges.

In the African context, children with HIV infection are often affected by peripheral neuropathy [23]. Types of neuropathy include distal symmetrical polyneuropathy, mononeuritis multiplex, inflammatory demyelinating polyneuropathy and progressive polyneuropathy [24]. Most of these conditions, especially distal symmetrical polyneuropathy, are more recognized in adult patients with HIV-1 infection. Peripheral neuropathy in children with HIV has not been extensively studied, but is also described in the form of AIDP at the time of seroconversion as an immune reconstitution phenomenon, and in relation to secondary infection with *Cytomegalovirus* [25–29]. In differentiating between AIDP in children who are not infected with HIV and those undergoing seroconversion, the former

Table 1. Conditions that are associated with specific clinical types of peripheral neuropathy.

Type of neuropathy	Associated conditions	Capacity to diagnose in resource-poor countries
Predominantly motor	AIDP	Common: highly suggestive clinical findings and history
	Diphtheria	Occurs in areas with limited vaccination programs Clinical features of high fever and respiratory compromise 'laryngeal web'
	Porphyria	Rare: may be limited to darkening of urine on exposure to daylight History of recurrent episodes of systemic collapse with hypotension and abdominal pains
	Lead toxicity	Occurs in areas where products still have high lead content, such as in paints in many resource-poor countries and potentially in cooking devices
	CMT disease	Prevalence unknown, often a diagnosis of exclusion Some canters able to screen for CMT1A Clinical markers may aid the subtype diagnosis
Predominantly sensory	Leprosy	Common in endemic regions, nerve thickening and unhealed ulcerations
	Diabetes	There should be a prior history of diabetes with older children
	Vitamin B_1 (thiamine) deficiency	Rare: may be related to malnutrition, poor absorption or cultural dietary preferences
	Malignany	Unknown frequency: clinically signs of organomegaly and weight loss
	Uremia	Rare: this is usually associated with patients in chronic renal failure, often on dialysis The neuropathy may be painful Those associated with diabetes may be asymptomatic in the early stages and only present in adolescence
	Pyridoxine intoxication	Possible in coadministration with therapy for tuberculosis
	Hereditary sensory and autonomic neuropathy	Rare: several different types including impaired pain awareness, unnoticed injuries and even fractures Autonomic impairment: impaired sweating and blood pressure control Relative sparing of tactile sensation
Painful neuropathies	Nutritional deficiencies	Rare: history should assist Nutritional signs of poor hair and skin condition, weight loss and marasmic state
	Arsenic intoxication	Rare: psychiatric changes and skin changes (pallor)
	Krabbe disease	Rare: neuroregression, onset usually in infancy and a positive family history Without further tools it may be limited to a more definitive diagnosis
	Lyme disease	Occurs in endemic areas: ask for history of tick bite Rare cases are reported from north Africa and Kenya [106,107] Patients can suffer painful radiculoneuropathy [108]
	Vasculitis neuropathies	Rare: asymmetrical presentation
	Fabry disease	Rare: severe painful distal extremities with flushing, anhidrosis and skin peeling
Recurrent neuropathy	Chronic relapsing inflammatory neuropathy	Rare: clinical features of a symmetrical neuropathy, occasional nerve hypertrophy and the history of recurrent relapses
	Refsum disease	Rare: deafness and retinitis pigmentosa Autosomal recessive
	Tangier disease	Rare autosomal recessive mutation of *ABCA1* gene leading to reduced levels of plasma high-density lipoprotein: children tend to present with large yellow–orange tonsils [109] Adults are more likely to have neuropathy that can be remitting/relapsing mono-/poly-neuropathy or a syringomyelia-like neuropathy [110]
	Acute intermittent porphyria	Rare, especially prepuberty: may be limited to darkening of urine on exposure to daylight History of recurrent episodes of systemic collapse with hypotension and abdominal pains

AIDP: Acute inflammatory demyelinating polyradiculoneuropathy; CMT: Charcot–Marie–Tooth; NCS: Nerve conduction studies.

Table 1. Conditions that are associated with specific clinical types of peripheral neuropathy (cont.).

Type of neuropathy	Associated conditions	Capacity to diagnose in resource-poor countries
Recurrent neuropathy (cont.)	Tyrosinemia type 1	Rare: inborn error of metabolism due to fumarylacetoacetate hydrolase deficiency Acute presentations with liver failure, hypophosphatemic rickets and peripheral neuropathy
	Pyruvate dehydrogenase complex deficiency/ Leigh disease	Rare: progressive relapsing mitochondrial disorder, may be brainstem dysfunction, respiratory signs, cognitive delay or hypotonia There may be a positive family history including prior early infantile deaths in siblings related to 'nonspecific' and 'vague' causes
	Hereditary neuropathy with liability to pressure palsies	Rare: older children with striking onset of monoparesis lower motor neuron following compression injury, which recovers with time If NCS are available, generalized demyelinating neuropathy is detected

AIDP: Acute inflammatory demyelinating polyradiculoneuropathy; CMT: Charcot–Marie–Tooth; NCS: Nerve conduction studies.

will have albumin–cytologic dissociation in contrast to acute HIV seroconversion, which will have pleiocytosis. The neuropathy that arises has a similar clinical phenotype to distal symmetrical polyneuropathy [24]. Affected children may have severe sensory features of intense distal burning affecting the hands and the feet, as well as distal weakness [24]. Peripheral neuropathy can occur as an adverse side effect of therapy with the nucleoside reverse transcriptase inhibitors, stavudine and, to a lesser extent, didanosine [23]. The incidence of peripheral neuropathy in children with HIV-1 infection is likely to be underestimated. From the cohort of HIV-infected patients attending the infectious diseases service (n = 80) prospectively reviewed at the Red Cross War Memorial Children's Hospital, 6% had peripheral neuropathies [30]. Another study identified abnormal nerve conduction studies in 12 out of 50 children clinically suspected to have neuropathies [31,32]. A study from Rio de Janeiro (Brazil) quoted a 34% prevalence of peripheral neuropathy in their pediatric patients with HIV-1 infection [32]. The signs of peripheral neuropathy in a chronically sick and malnourished child can be subtle, and may not be detected unless specifically looked out for. The 'layering' effect of HIV-1 infection results in multiple potential causes for a clinical phenotype. Children infected with HIV-1 are at increased risk of malnutrition, poor mobility, drug toxicity and additional infections. Increased incidence of peripheral neuropathy is described with coinfection by HIV-1 and tuberculosis [33]. Clues to support an acquired condition would include an acute onset, a monophasic illness in a previously well child, often with a prior history of infection or initiation of a potentially neurotoxic therapy (i.e., antiretroviral therapy and isoniazid); also, the child with a chronic but relapsing course [5,34]. The most prevalent peripheral neuropathy, also reported internationally, remains to be AIDP. It may not be possible to perform nerve conduction studies, but access to analysis of cerebrospinal fluid, demonstrating a cellular response and a raised protein in the second week of illness, should be available in most centers; also analysis of potential trigger factors – especially prior *Campylobacter* infection. In South Africa, patients with AIDP often have a prior history of *Campylobacter* infection, which results in a more severe course [35,36]. Poliomyelitis, which is still prevalent in parts of Africa, remains a notifiable condition. Screening for enteroviruses and arboviruses in any child with flaccid paralysis is essential.

Acquired conditions seen in other parts of Africa include sickle cell-related sensory neuropathy [37], leprosy-related neuropathy [38], the paralytic form of rabies [39], diphtheria and an ataxic polyneuropathy from Nigeria [40]. Sickle cell disease is prevalent throughout Africa. Previously, an association with peripheral neuropathy affecting children with sickle cell disease who were intoxicated with lead was reported [41]. These children were considered vulnerable to this complication. Lead intoxication remains a hazard in many RPCs and should be considered in children with sickle cell disease presenting with neuropathies. More recent reports describe localized sensory neuropathies occurring in adolescents and adults with sickle cell disease, but not children as such [37]. Leprosy is considered the commonest treatable peripheral neuropathy in the world; there are an estimated 3 million adults and children with leprosy-related neuropathy [16]. A cure is possible where effective antimicrobial treatment against *Mycobacterium leprae* is available. The lack of access to this resource leaves many patients

scarred and suffering stigma as a result. Patients with the neuropathy develop anesthetic skin lesions, although the neuropathy can occur in isolation [42]. Leprosy should be included as a differential diagnosis for children who present with unexplained foot ulceration in endemic areas [43]. The leprosy-related nerve damage is immune-mediated and may start at any point in the disease process (before, during or after treatment).

Rabies remains prevalent in many RPCs; this is exacerbated by packs of dogs roaming townships in many areas [44]. Up to 20% of affected patients develop a 'paralytic' form, which can mimic Guillain–Barré syndrome with axonal degeneration of the peripheral nerves [39,45]. In areas where there is limited access to rabies screening and the virus is prevalent, this differential must be considered for such patients. There may be a long incubation period and history of a dog bite many not be clear [46]. Diphtheritic polyneuropathy is reported as a complication of diphtheria and it can result in bulbar, respiratory and circulatory impairment [47]. Symptoms usually present 3–5 weeks after the onset of the infection. Sensory (proprioceptive) and autonomic dysfunction are typical. Access to nerve conduction studies reveals demyelinating changes [48]. Vitamin deficiencies remain a major challenge in many RPCs [6]. Children suffering from protein–energy malnutrition are at risk of vitamin E deficiency [7]. Affected patients may develop nystagmus, gaze paresis, retinitis pigmentosa, an ataxic gait, areflexia and have impaired position and vibration awareness. Infantile encephalitic beriberi is a rare form of thiamine deficiency (vitamin B_1), which is reported in India [49]. Leigh syndrome can have a similar phenotypic appearance, with life-threatening respiratory and CNS symptoms. Dramatic response to thiamine occurs. Epidemic spastic paraparesis (konzo) is a neurological condition associated with the consumption of cassava roots and minimal protein consumption [50]. The condition is prevalent in Nigeria, Tanzania, Sierra Leone, Mozambique, Central African Republic and the Democratic Republic of the Congo. It occurs in children aged 4–12 years and in young women. Affected children have a clinical phenotype of symmetrical spastic parapesis disease with marked sensory polyneuropathy and ataxia. There is an overlap with the features of dry beriberi. There is a strong case that the condition, at least in part, is the result of thiamine deficiency resulting from the overconsumption of cassava roots. Pyridoxine (Vitamin B_6) supplementation is recommended for patients treated with isoniazid to avoid development of a painful sensory neuropathy [51]. However, there are a few reports whereby pyridoxine therapy resulted in the development of a dorsal root ganglionopathy in adults, but not children [52].

Neuropathies associated with CNS disorders

Patients should be divided into those with and without central involvement [6]. Children with central involvement should be further subdivided into those with predominantly white and those with gray matter disease. White matter disorders will be dominated by the leukodystrophies, especially metachromatic leukodystrophy and Krabbe disease (globoid cell leukodystophy). Lysosomal enzyme studies generally confirm the diagnosis, but are rarely available in RPCs. In the absence of access to lysosomal enzyme analysis, the suspected diagnosis would be supported by raised cerebrospinal fluid protein. Other disorders affecting the white matter would include giant axonal neuropathy (GAN) and Cockayne syndrome. Gray matter diseases include mitochondrial disorders (Leigh disease) and neuroaxonal dystrophy. Friedreich's ataxia has a typical phenotypic presentation with a sensory ataxia, related to loss of large myelinated sensory fibers resulting in impairment to light touch, vibration and position sense with sparing of pain and temperature awareness. There is a loss of the deep tendon reflexes but extensor plantar responses. Optic atrophy is seen later in the course. Echocardiography may support the diagnosis. The clinical phenotypes of a number of these conditions may permit some diagnostic closure. For example, the clinical evolution of metachromatic leukodystrophy is striking with lower-limb long tract signs, despite the presence of a peripheral neuropathy. Patients with Cockayne syndrome have accelerated aging and growth failure. Woolly or 'kinky' hair and learning difficulties are found in patients with GAN.

Where neurophysiology is available

Neurophysiology studies are useful to differentiate between types of demyelinating disease, as well as between axonal and demyelinating disease. The presence of conduction block can support an early diagnosis of AIDP [53]. These results are unlikely to alter management, but may assist with counseling for prognosis [54]. This is most relevant to the hereditary group [55]. Useful neurophysiological markers, other than the typical demyelinating and axonal ranges described in CMT1 and CMT2,

are the extreme slowing evident in CMT3 (usually <10 m/s motor conduction velocity) and most forms of CMT4, as well as the intermediate values seen in patients with distal–intermediate CMT disease and X-linked CMT (CMTX) disease [56,57]. The patients with early-onset neuronal hereditary motor sensory neurology can have values in the borderline axonal/demyelinating range [58]. These patients present before 5 years of age with distal weakness, wheelchair dependency (occuring by the second decade in most) and markedly affected distal upper limb function [58]. At presentation, these children appear to have a waddling gait with proximal weakness and foot drop [58–60]. *MFN2* mutations are reported in 50% of this group, placing them under the subcategory of CMT2A2 [61]. Patients with spinal muscular atrophy with respiratory distress typically have absent sensory responses and compound muscle action potentials are absent or markedly reduced. Electromyography detects denervation [17,62,63]. The patients often present with intrauterine growth retardation, diaphragmatic dysfunction (becoming evident between 1 and 6 months of age), a weak cry, inspiratory stridor and earlier noted foot deformities. Sensory and autonomic nerve involvement can occur, leading to reduced pain perception, excessive sweating, constipation, cardiac arrhythmias and constipation. Fatty pads over the phalanges are an additional clinical marker [62,64]. Peripheral electrophysiology must be performed in a center skilled in performing such studies. The interpretation must be made with caution, as the normal ranges vary significantly until 5 years of age, when the nerve conduction velocity approaches adult levels [65]. In some infants with axonal degeneration and a paucity of large diameter fibers, nerve conduction velocity may be in the so-called 'demyelinating range'. Furthermore, axonal pathology does not always result in measurable abnormality in nerve conduction. In patients with axonal degeneration, undamaged fibers will conduct with normal conduction velocities and the degenerating fibers do not conduct at all. This results in surface electrode measurements potentially in the normal range or only mildly slowed. However, the amplitude of the compound muscle action potential will be reduced due to the smaller number of conducting fibers and motor units activated by the stimulus. In patients with small fiber neuropathy, such as hereditary sensory and autonomic neuropathy types 4 and Fabry's disease, nerve conduction studies will also be normal due to the absence of involvement of large myelinated fibers [66].

Molecular genetic analyses

Molecular genetic analyses for peripheral neuropathies are limited in South Africa to screening for CMT1A. This form is described as the commonest subtype to affect children and adults, estimated at 50% in the former and 70% in the latter [67–72]. However, this figure has not been assessed for RPCs. There are little data describing the incidence of CMT1A in indigenous African populations. A study from Brazil reported that 13% of their cohort with CMT1A were of African descent (n = 6) [73]. In comparison with CMT1A, CMTX typically presents in the second decade. Although it is more symptomatic in males affected, female carriers can manifest with signs of neuropathy potentially leading to diagnostic confusion with CMT1. Neurophysiology studies are typically in the intermediate range and the majority of patients have a mutation in *CMTX1* [74]. If there is access to brainstem auditory responses, these are often abnormal in patients with CMTX. CMT2B1, an axonal subtype of CMT with onset in the second decade of life, is prevalent in northwestern Africa (northwest Algeria and east of Morocco); a founder effect is suggested [75]. In the neuromuscular clinic at the Red Cross War Memorial Children's Hospital in South Africa, children with hereditary neuropathies in the indigenous African population are dominated by axonal forms of CMT. Genetic analysis of this axonal group remains a challenge, even for international centers, and the group has previously had the lowest molecular genetic mutation detection rate [76–80]. With the expanding identification of mutations associated with axonal forms of CMT, namely *MFN2*, *TRPV4*, *GDAP1* and *NEFL*, the molecular genetic diagnostic closure is improving [18]. Such screening is only available in equipped international centers. Storing DNA should be considered, as genetic screening is becoming more cost effective and available and preparing for this may enable families to gain diagnostic closure. Several publications expand on the many identified subtypes of CMT and the specific phenotypes related to them [18,64,74,81]. It is beyond the scope of this article to cover descriptions of all subtypes; only those most relevant are addressed here. For most forms of CMT, the acute and chronic care is the same, and predominantly symptomatic.

Peripheral nerve biopsy

Most guidelines that discuss investigations of peripheral neuropathies recommend

consideration of peripheral nerve biopsy if other routes have failed to confirm an underlying diagnosis [21,82–85]. Peripheral nerve biopsy is a safe investigation, which, if performed and analyzed in an appropriate setting, can enhance the diagnostic yield of complex patients [86]. However, most guidelines, are adult based and few exist with pediatric emphasis [17,21]. Specific features on histology would include the giant axons [64] of GAN, CMT2E/CMT1F, CMT4C and 'glue sniffing' neuropathy related to exposure to N-hexane [87,88], the myelin outfolding of CMT4B [74], the unusual Schwann cell cytoplasmic chains of CMT4C, the extreme paucity of fibers in some cases of *LMNA* mutations and the mixed ultrastructural demyelinating/axonal degenerative picture of *MFN2* mutations (CMT2A2) associated with abnormal mitochondria [76]. In RPCs it may be more cost effective if, while the child undergoes a procedure (usually orthopedic), an 'opportunistic biopsy' is taken. This may enable diagnosis of suspected conditions, such as metachomatic leucodystrophy, GAN, CMT3, among others, to be confirmed. The biochemical and molecular genetic analyses for these conditions are costly and not readily available to RPCs. Prior to such screens being available overseas, histopathological analysis was a useful diagnostic tool. With regard to RPCs there is a case to maintain access to these screens.

Neuroimaging

Other tools yet to be explored include the role of neuroimaging – MRI has identified specific muscle groups affected in particular subgroups of CMT [89,90]. Additional studies have looked at the role of lumbosacral root and sciatic nerve imaging to assess disease severity and progression, as well as to support a diagnosis of a postinfectious radiculoneuropathy found in patients with AIDP and chronic inflammatory demyelinating radicluoneuropathy [91–95]. Though a limited resource, neuroimaging is becoming more available in many parts of Africa and may become a more viable resource for the future.

In settings where access to molecular genetics is limited, screening using all possible tools is essential to attain a diagnostic label. Even when molecular genetic studies are available, the genetic confirmation alone may not correlate with a clinical diagnosis without supporting information from the combined findings of the clinical phenotype, neurophysiology and histopathology.

Management of children with peripheral neuropathies

Acute care

Few centers in South Africa, or other parts of Africa, have access to intensive care support and, thus, the management of the child with progressive weakness and airway compromise is challenging. Recommendations are that centers with access to intravenous immunoglobulin administer the agent to any child suspected of having AIDP who has respiratory compromise or loss of ambulation [96].

Chronic care

In the relatively resource-limited setting that the author works in, the management priorities are addressed and summarized in Figure 1. Once clinical confirmation of a peripheral neuropathy is established, basic interventions can be implemented, commencing with whether the condition is acquired or hereditary.

Toxic peripheral neuropathies are described in patients with HIV infection as an adverse side effect of therapy with the nucleoside reverse transcriptase inhibitors, stavudine and, to a lesser extent, didanosine. Stavudine remains part of the first-line recommended regimen from the WHO guidelines. If peripheral neuropathy occurs, conversion to zidovudine or abacavir is recommended [23,97]. Symptomatic relief is described with gabapentin, if it is available, otherwise amitriptyline can be used [24]. Adult-based trials have assessed the role of acetyl-L-carnitine, which may benefit some patients [98]. The approach used specifically for patients with HIV-1 and peripheral neuropathy in the Red Cross War Memorial Children's Hospital is summarized in Figure 2.

The other toxic neuropathy seen infrequently is related to isoniazid therapy, although with increased frequency when there is coinfection with HIV [23]. Prophylaxis with pyridoxine can reverse this [99]. Seen less frequently are the nutritional deficiency neuropathies, especially vitamin B_{12} deficiency, either in isolation or associated with the HIV-infected patient [100,101]. These seem to be rare in South Africa but are described elsewhere in the continent [102]. For patients with leprosy, multidrug therapy with rifampicin, clofazimine and dapsone is effective in targeting the *M. leprae* but not at stopping the inflammatory impairment of nerve function. Neither steroids nor decompressive surgery have been shown to be effective in Cochrane reviews [103,104]. Treatment with thalidomide is also often used – this in itself is associated with a sensory neuropathy and patients must be monitored for

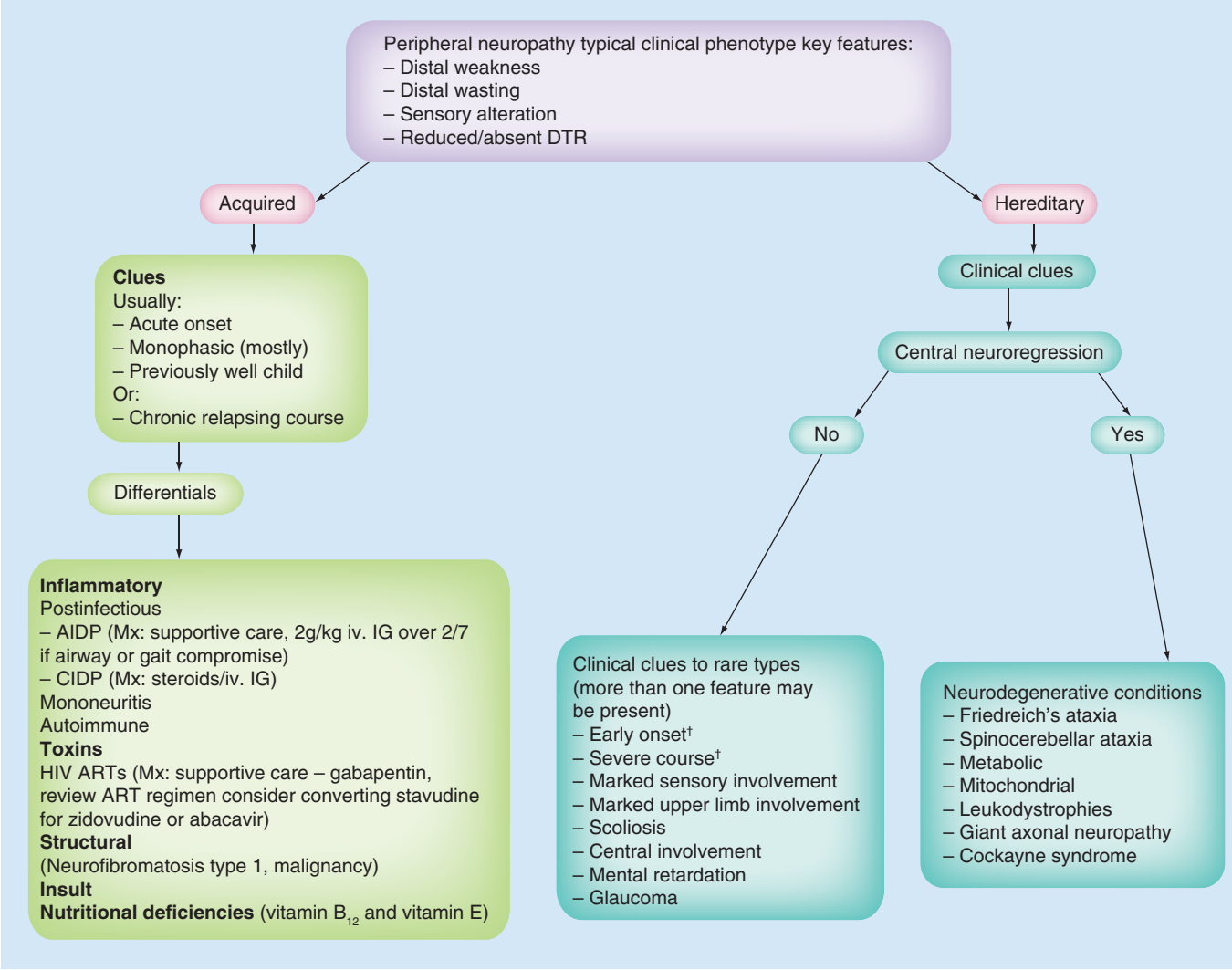

Figure 1. Approach to the child with suspected peripheral neuropathy in a resource-limited setting.
†May also occur with acquired etiologies.
AIDP: Acute inflammatory demyelinating polyradiculoneuropathy; AMC: Arthrogryposis multiplex congenita; ART: Antiretroviral therapy; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; DTR: Deep tendon reflex; IG: Immunoglobulin; iv.: Intravenous; Mx: Management.

this complication clinically if neurophysiological testing is not available [42]. In resource-equipped settings, nerve biopsy would be used to establish the nature and extent of the disease.

A positive family history and a chronic progressive clinical course would support a hereditary nature in a child with peripheral neuropathy. Establishing if there is evidence of neuroregression would further direct elucidation. Neuroregressive disorders with distinct clinical appearances include Friedreich's ataxia, rare childhood forms of spinocerebellar ataxia, various metabolic disorders, mitochondrial disorders, leukodystrophies, GAN and Cockayne syndrome. Centers with the capacity should perform diagnostic neuroimaging and biochemical screens (e.g., cerebrospinal fluid lactate, urinary organic and amino acids, and mitochondrial screens). Frustratingly, most suspected diagnoses require additional support from neurophysiology, molecular genetics and/or histopathology.

The management of both acquired and hereditary peripheral neuropathies should concentrate on the optimal outcome for the child. This requires supportive care, such as pain relief (e.g., carbamazepine or gabapentin), therapeutic interventions where indicated (e.g., immunoglobulins) and ancillary input. Most children present to a primary healthcare center and are managed by a primary healthcare worker who may be a nurse practioner or a medical officer. Limited training in the recognition of the clinical signs of peripheral neuropathy may result in some of these children being misdiagnosed.

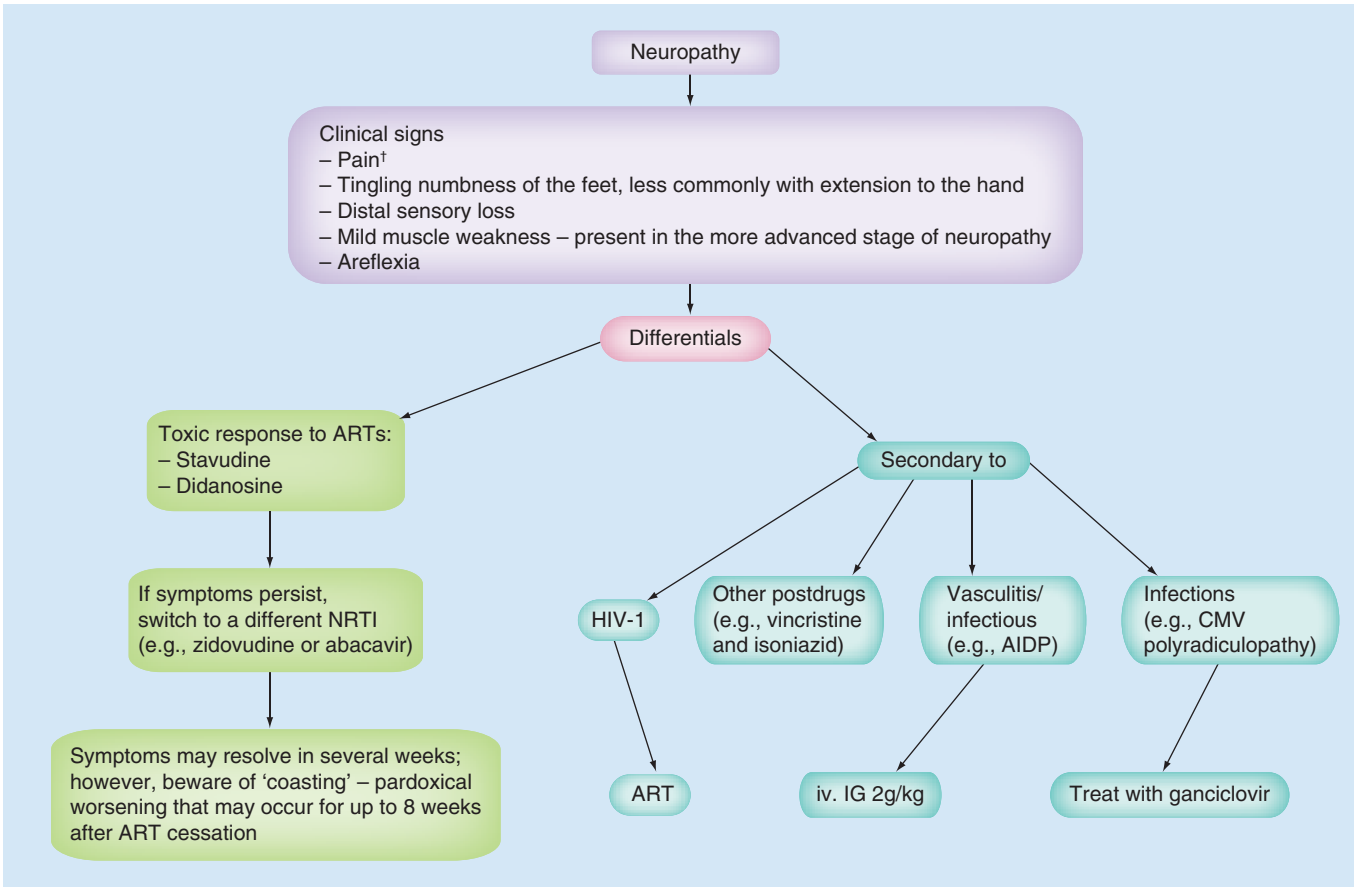

Figure 2. Approach to the HIV-infected child with distal weakness/sensory disturbances.
†Consider using analgesics, amytriptyline and gabapentin; avoid carbamazepine.
AIDP: Acute inflammatory demyelinating polyradiculoneuropathy; ART: Antiretroviral therapy; CMV: *Cytomegalovirus*; IG: Immunoglobulin; iv.: Intravenous; NRTI: Nucleotide analog reverse transcriptase inhibitor.

Commencing regular physiotherapy and occupational therapy early in the child's illness is essential and should be available at most secondary and tertiary centers. The benefits of specific forms of rehabilitation for different types of neuropathy are not established [105].

Across Africa there is a significant limitation in pediatric specialist services and pediatric neurologists are scarce in countries between South Africa and the northern African countries [9]. As a result, the burden of care falls on the primary healthcare workers. Carers can be taught a home program for avoidance of contracture formation. The child and carer should be educated about the increased need to avoid damage to the joints and distal regions caused by sensory proprioceptive impairment. Many children in South Africa live in households where paraffin fires are the main heating and cooking devices. These are rarely protected and burns are frequent complications, which are more likely to occur in children with altered sensory awareness. Orthotic devices are important and should also be available in most referral centers. Access to speech therapy and dieticians is also important. Support from other specialists, such as orthopedic surgeons to undertake surgical interventions to promote mobility is ideal, but often lacking. Regular assessments are necessary to avoid secondary complications such as contractures, scoliosis and respiratory tract infections from occurring. Where available, prophylactic intervention with influenza and pneumococcal vaccinations should be given to those children who are considered to be at risk of chest infections.

The Red Cross War Memorial Children's Hospital has access to neurophysiology, histopathology and limited molecular genetics. Most other centers only have clinical assessment for diagnosis, with the ancillary input often consisting of a community ancillary therapist.

Conclusion

In summary, the basic aims of care for a child with a peripheral neuropathy include: the accurate diagnosis of a peripheral neuropathy,

typically via clinical assessment; wherever possible, to treat and manage any reversible causes of the neuropathy; where available, the child should be referred to a specialist center (there may be only one per country, or none, requiring referral to another country); the carers should be educated in the safety and preventative aspects required when a child has a peripheral neuropathy; counseling on the potential genetic implications (based on suspected etiology) should be addressed; there should be involvement of any available ancillary services and access to orthotic and orthopaedic facilities. These points would address the minimum standards of care when based in a resource-limited setting.

Future perspective

There is a great need for better training at a primary healthcare level to support early recognition of children with peripheral neuropathies, and to raise awareness of treatable or reversible neuropathies such as leprosy, vitamin deficiencies, lead intoxication and adverse drug reactions. The eradication of these conditions through better healthcare also falls into some of the long-term goals set by various working groups such as the WHO.

Access to simple and cheap methods of electrophysiological and quantitative sensory testing would improve surveillance systems.

Though a limited resource, neuroimaging is becoming more available in many parts of Africa and may become a more viable resource for the future.

Current technological advances will promote more comprehensive and cost-effective biochemical and molecular genetic screens. These will form part of the gateway to better counseling, interventions and even cures in the future.

There is a need to train these service providers in the key clinical diagnostic features of peripheral neuropathy subtypes and to establish viable management guidelines for affected children.

Executive summary

Background

- The diagnosis of peripheral neuropathy in most resource-poor countries (RPCs) is based on history and clinical examination due to the lack of basic screening tools.

Etiologies

- Children from RPCs are more likely to have acquired, rather than hereditary, causes of their neuropathy.

Management

- Presentation and care for most children from RPCs with peripheral neuropathies will be to the primary healthcare centers. Practitioners at these centers typically lack the skills and resources to diagnose and manage such patients.
- The capacity to manage children with peripheral neuropathies must be supported by effective home-care programs, as most children live long distances from secondary and tertiary centers and have limited access to transport.
- Acute care for airway compromisation or loss of ambulation is challenging in resource-poor settings, where there is no capacity to offer intensive care or high-care management.

Conclusion

- Little data exist of the prevalence of the subtypes of hereditary forms of peripheral neuropathies in children from RPCs.

References

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1. Radhakrishnan K, el-Mangoush MA, Gerryo SE. Descriptive epidemiology of selected neuromuscular disorders in Benghazi, Libya. *Acta Neurol. Scand.* 75(2), 95–100 (1987).
2. Ndiaye IP, Ndiaye MM, Mauferon JB, Diagne M, Diop AG. Etiological aspects of polyneuritis in Senegal. *Dakar Med.* 34(1–4), 68–71 (1989).
3. Thiam A, Sene-Diouf F, Diallo AK *et al.* Aetiological aspects of neurological diseases in Dakar: follow-up after 10 years (1986–1995). *Dakar Med.* 45(2), 167–172 (2000).
4. You D, Wardlaw T, Salama P, Jones G. Levels and trends in under-5 mortality, 1990–2008. *Lancet* 375(9709), 100–103 (2010).
5. van der Watt JJ, Harrison TB, Benatar M, Heckmann JM. Polyneuropathy, anti-tuberculosis treatment and the role of pyridoxine in the HIV/AIDS era: a systematic review. *Int. J. Tuberc. Lung Dis.* 15(6), 722–728 (2011).
   - ▪ **Adult-based study that illustrates the layering effect of HIV, where neuropathy can develop through a number of direct and indirect mechanisms.**
6. Lanska DJ. Chapter 30: historical aspects of the major neurological vitamin deficiency disorders: the water-soluble B vitamins. *Handb. Clin. Neurol.* 95, 445–476 (2010).
7. Kalra V, Grover JK, Ahuja GK, Rathi S, Gulati S, Kalra N. Vitamin E administration and reversal of neurological deficits in protein-energy malnutrition. *J. Trop. Pediatr.* 47(1), 39–45 (2001).
8. Babar SM. Peripheral nerve injuries in a third world country. *Cent. Afr. J. Med.* 39(6), 120–125 (1993).
9. Wilmshurst JM, Badoe E, Wammanda RD *et al.* Child neurology services in Africa. *J. Child Neurol.* 26(12), 1555–1563 (2011).
10. Wilmshurst JM, Ouvrier RA. Nerve Biopsy. In: *Neuromuscular Disorders of Infancy, Childhood, and Adolescence. A Clinician's Approach*. Royden Jones H, De Vivo DC, Darras BT (Eds). Butterworth Heinemann, PA, USA, 91–109 (2003).

11. Schenone A, Nobbio L, Monti Bragadin M, Ursino G, Grandis M. Inherited neuropathies. *Curr. Treat. Options Neurol.* 13(2), 160–179 (2011).

▪▪ **Provides a comphrehensive update on the various therapies for the Charcot–Marie–Tooth diseases, addressing basic care through to state-of-the-art hypothesized future treatments.**

12. Gona JK, Mung'ala-Odera V, Newton CR, Hartley S. Caring for children with disabilities in Kilifi, Kenya: what is the carer's experience? *Child Care Health Dev.* 37(2), 175–183 (2011).

13. Wallander JL, McClure E, Biasini F *et al.* Brain research to ameliorate impaired neurodevelopment – home-based intervention trial (BRAIN-HIT). *BMC Pediatr.* 10, 27 (2010).

▪▪ **Describes a home-based program that could be extrapolated to other neurodisability conditions in resource-poor countries.**

14. Dyck PJ, Lambert EH. Lower motor and primary sensory neuron diseases with peroneal muscular atrophy. I. Neurologic, genetic, and electrophysiologic findings in hereditary polyneuropathies. *Arch. Neurol.* 18(6), 603–618 (1968).

15. Ouvrier RA, McLeod JG. Chronic peripheral neuropathy in childhood: an overview. *Aust. Paediatr. J.* 24(Suppl. 1), 80–82 (1988).

16. Lancet Neurology. Leprosy as a neurological disease. *Lancet Neurol.* 8(3), 217 (2009).

▪▪ **Summarizes the key issues challenging leprosy worldwide – especially focusing on early recognition (the need to involve and train primary healthcare workers), the need to reduce stigma and the challenges of the treatment of leprosy-related neuropathy itself.**

17. Wilmshurst JM, Pollard JD, Nicholson G, Antony J, Ouvrier R. Peripheral neuropathies of infancy. *Dev. Med. Child Neurol.* 45(6), 408–414 (2003).

18. Wilmshurst JM, Ouvrier R. Hereditary peripheral neuropathies of childhood: an overview for clinicians. *Neuromuscul. Disord.* 21(11), 763–775 (2011).

▪ **Summarizes the known forms of Charcot–Marie–Tooth diseases in children at the time of publication, providing an overview of the key clinical, neurophysiological, histopathological and molecular genetic markers.**

19. Gibbs TC, Payan J, Brett EM, Lindstedt S, Holme E, Clayton PT. Peripheral neuropathy as the presenting feature of tyrosinaemia type I and effectively treated with an inhibitor of 4-hydroxyphenylpyruvate dioxygenase. *J. Neurol. Neurosurg. Psychiatry.* 56(10), 1129–1132 (1993).

20. Koul R, Chacko A, Javed H *et al.* A profile of childhood neuropathies at a university hospital in Oman. *Saudi Med. J.* 23(4), 450–456 (2002).

21. Polat M, Tekgul H, Kilincer A *et al.* Electrodiagnostic pattern approach for childhood polyneuropathies. *Pediatr. Neurol.* 35(1), 11–17 (2006).

22. Shabo G, Pasman JW, van Alfen N, Willemsen MA. The spectrum of polyneuropathies in childhood detected with electromyography. *Pediatr. Neurol.* 36(6), 393–396 (2007).

23. Van Dyke RB, Wang L, Williams PL, Pediatric AIDS Clinical Trials Group 219C Team. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J. Infect. Dis.* 198(11), 1599–1608 (2008).

24. Verma S, Simpson D. Peripheral neuropathy in HIV infection. In: *HIV/AIDS and the Nervous System (Volume 85)*. Portegies P, Berger J (Eds). Elsevier, Edinburgh, UK, 129–137 (2007).

25. Brannagan TH 3rd, Zhou Y. HIV-associated Guillain–Barre syndrome. *J. Neurol. Sci.* 208(1–2), 39–42 (2003).

26. Wilmshurst JM, Burgess J, Hartley P, Eley B. Specific neurologic complications of human immunodeficiency virus type 1 (HIV-1) infection in children. *J. Child Neurol.* 21(9), 788–794 (2006).

27. Puthanakit T, Oberdorfer P, Akarathum N, Wannarit P, Sirisanthana T, Sirisanthana V. Immune reconstitution syndrome after highly active antiretroviral therapy in human immunodeficiency virus-infected Thai children. *Pediatr. Infect. Dis. J.* 25(1), 53–58 (2006).

28. Sohal A, Riordan A, Mallewa M, Solomon T, Kneen R. Successful treatment of cytomegalovirus polyradiculopathy in a 9-year-old child with congenital human immunodeficiency virus infection. *J. Child Neurol.* 24(2), 215–218 (2009).

29. Wilmshurst JM, Burgess J, Hartley P, Eley B. Specific neurologic complications of human immunodeficiency virus type 1 (HIV-1) infection in children. *J. Child Neurol.* 21(9), 788–794 (2006).

30. Govender R, Eley B, Walker K, Petersen R, Wilmshurst JM. Neurologic and neurobehavioral sequelae in children with human immunodeficiency virus (HIV-1) infection. *J. Child Neurol.* 26(11), 1355–1364 (2011).

31. Floeter MK, Civitello LA, Everett CR, Dambrosia J, Luciano CA. Peripheral neuropathy in children with HIV infection. *Neurology* 49(1), 207–212 (1997).

32. Araujo AP, Nascimento OJ, Garcia OS. Distal sensory polyneuropathy in a cohort of HIV-infected children over five years of age. *Pediatrics* 106(3), E35 (2000).

33. Marks DJ, Dheda K, Dawson R, Ainslie G, Miller RF. Adverse events to antituberculosis therapy: influence of HIV and antiretroviral drugs. *Int. J. STD AIDS* 20(5), 339–345 (2009).

34. Koski CL, Baumgarten M, Magder LS *et al.* Derivation and validation of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy. *J. Neurol. Sci.* 277(1–2), 1–8 (2009).

35. Lastovica AJ, Goddard EA, Argent AC. Guillain–Barre syndrome in South Africa associated with Campylobacter jejuni O:41 strains. *J. Infect. Dis.* 176(Suppl. 2), S139–S143 (1997).

36. London L, Bourne D, Sayed R, Eastman R. Guillain–Barre syndrome in a rural farming district in South Africa: a possible relationship to environmental organophosphate exposure. *Arch. Environ. Health* 59(11), 575–580 (2004).

37. Kehinde MO, Temiye EO, Danesi MA. Neurological complications of sickle cell anemia in Nigerian Africans – a case–control study. *J. Natl Med. Assoc.* 100(4), 394–399 (2008).

38. Saunderson P, Gebre S, Desta K, Byass P, Lockwood DN. The pattern of leprosy-related neuropathy in the AMFES patients in Ethiopia: definitions, incidence, risk factors and outcome. *Lepr. Rev.* 71(3), 285–308 (2000).

39. Mallewa M, Fooks AR, Banda D *et al.* Rabies encephalitis in malaria-endemic area, Malawi, Africa. *Emerg. Infect. Dis.* 13(1), 136–139 (2007).

40. Oluwole OS, Onabolu AO. High mortality of subjects with endemic ataxic polyneuropathy in Nigeria. *Acta Neurol. Scand.* 110(2), 94–99 (2004).

41. Imbus CE, Warner J, Smith E, Pegelow CH, Allen JP, Powars DR. Peripheral neuropathy in lead-intoxicated sickle cell patients. *Muscle Nerve* 1(2), 168–171 (1978).

42. Ooi WW, Srinivasan J. Leprosy and the peripheral nervous system: basic and clinical aspects. *Muscle Nerve* 30(4), 393–409 (2004).

43. Rao R, Balachandran C. Multiple grade II deformities in a child: tragic effect of leprosy. *J. Trop. Pediatr.* 56(5), 363–365 (2010).

44. Edelsten RM. Epidemiology and control of rabies in Malawi. *Trop. Anim. Health Prod.* 27(3), 155–163 (1995).

45. Sheikh KA, Ramos-Alvarez M, Jackson AC, Li CY, Asbury AK, Griffin JW. Overlap of pathology in paralytic rabies and axonal Guillain–Barre syndrome. *Ann. Neurol.* 57(5), 768–772 (2005).

46. Grattan-Smith PJ, O'Regan WJ, Ellis PS, O'Flaherty SJ, McIntyre PB, Barnes CJ. Rabies. A second Australian case, with a long incubation period. *Med. J. Aust.* 156(9), 651–654 (1992).

47. Piradov MA, Pirogov VN, Popova LM, Avdunina IA. Diphtheritic polyneuropathy: clinical analysis of severe forms. *Arch. Neurol.* 58(9), 1438–1442 (2001).

48. Kurdi A, Abdul-Kader M. Clinical and electrophysiological studies of diphtheritic neuritis in Jordan. *J. Neurol. Sci.* 42(2), 243–250 (1979).

49. Rao SN, Mani S, Madap K, Kumar MV, Singh L, Chandak GR. High prevalence of infantile encephalitic beriberi with overlapping features of Leigh's disease. *J. Trop. Pediatr.* 54(5), 328–332 (2008).

50. Adamolekun B. Neurological disorders associated with cassava diet: a review of putative etiological mechanisms. *Metab. Brain Dis.* 26(1), 79–85 (2011).

▪▪ **Eloquently assesses the evidence for the hypothesized causes of the ataxic polyneuropathy widely described in resource-poor countries.**

51. Snider DE Jr. Pyridoxine supplementation during isoniazid therapy. *Tubercle* 61(4), 191–196 (1980).

52. Baxter P. Pyridoxine-dependent and pyridoxine-responsive seizures. *Dev. Med. Child Neurol.* 43(6), 416–420 (2001).

53. Atanasova D, Ishpekova B, Muradyan N, Novachkova S, Daskalov M. Conduction block – the diagnostic value in the early stage of Guillain–Barre syndrome. *Electromyogr. Clin. Neurophysiol.* 44(6), 361–364 (2004).

54. Uncini A, Kuwabara S. Electrodiagnostic criteria for Guillain–Barre syndrome: a critical revision and the need for an update. *Clin. Neurophysiol.* 123(8), 1487–1495 (2012).

55. Saporta AS, Sottile SL, Miller LJ, Feely SM, Siskind CE, Shy ME. Charcot–Marie–Tooth disease subtypes and genetic testing strategies. *Ann. Neurol.* 69(1), 22–33 (2011).

▪ **Provides a neurophysiological guide to support the most probable subtype of Charcot–Marie–Tooth disease based on the nerve conduction study findings from a large population of genetically confirmed individuals.**

56. Nicholson G, Myers S. Intermediate forms of Charcot–Marie–Tooth neuropathy: a review. *Neuromolecular Med.* 8(1–2), 123–130 (2006).

57. Pareyson D, Scaioli V, Laura M. Clinical and electrophysiological aspects of Charcot–Marie–Tooth disease. *Neuromolecular Med.* 8(1–2), 3–22 (2006).

58. Ouvrier RA, McLeod JG, Morgan GJ, Wise GA, Conchin TE. Hereditary motor and sensory neuropathy of neuronal type with onset in early childhood. *J. Neurol. Sci.* 51(2), 181–197 (1981).

59. Chung KW, Kim SB, Park KD *et al.* Early onset severe and late-onset mild Charcot–Marie–Tooth disease with mitofusin 2 (*MFN2*) mutations. *Brain* 129(Pt 8), 2103–2118 (2006).

60. Feely SM, Laura M, Siskind CE *et al.* *MFN2* mutations cause severe phenotypes in most patients with CMT2A. *Neurology* 76(20), 1690–1696 (2011).

61. Nicholson GA, Magdelaine C, Zhu D *et al.* Severe early-onset axonal neuropathy with homozygous and compound heterozygous *MFN2* mutations. *Neurology* 70(19), 1678–1681 (2008).

62. Wilmshurst JM, Bye A, Rittey C *et al.* Severe infantile axonal neuropathy with respiratory failure. *Muscle Nerve* 24(6), 760–768 (2001).

63. Pitt M, Houlden H, Jacobs J *et al.* Severe infantile neuropathy with diaphragmatic weakness and its relationship to SMARD1. *Brain* 126(Pt 12), 2682–2692 (2003).

64. Yiu EM, Ryan MM. Genetic axonal neuropathies and neuronopathies of pre-natal and infantile onset. *J. Peripher. Nerv. Syst.* 17(3), 285–300 (2012).

65. Miller RG, Kuntz NL. Nerve conduction studies in infants and children. *J. Child Neurol.* 1(1), 19–26 (1986).

66. Lauria G, Merkies IS, Faber CG. Small fibre neuropathy. *Curr. Opin. Neurol.* 25(5), 542–549 (2012).

67. Skre H. Genetic and clinical aspects of Charcot–Marie–Tooth's disease. *Clin. Genet.* 6(2), 98–118 (1974).

68. Nelis E, Van Broeckhoven C, De Jonghe P *et al.* Estimation of the mutation frequencies in Charcot–Marie–Tooth disease type 1 and hereditary neuropathy with liability to pressure palsies: a European collaborative study. *Eur. J. Hum. Genet.* 4(1), 25–33 (1996).

69. Holmberg BH, Holmgren G, Nelis E, van Broeckhoven C, Westerberg B. Charcot–Marie–Tooth disease in northern Sweden: pedigree analysis and the presence of the duplication in chromosome 17p11.2. *J. Med. Genet.* 31(6), 435–441 (1994).

70. Hagberg B, Lyon G. Pooled European series of hereditary peripheral neuropathies in infancy and childhood. A 'correspondence work shop' report of the European Federation of Child Neurology Societies (EFCNS). *Neuropediatrics* 12(1), 9–17 (1981).

71. Hagberg B, Westerberg B. The nosology of genetic peripheral neuropathies in Swedish children. *Dev. Med. Child Neurol.* 25(1), 3–18 (1983).

72. Emery AE. Population frequencies of inherited neuromuscular diseases – a world survey. *Neuromuscul. Disord.* 1(1), 19–29 (1991).

73. Marques W Jr, Freitas MR, Nascimento OJ *et al.* 17p duplicated Charcot–Marie–Tooth 1A: characteristics of a new population. *J. Neurol.* 252(8), 972–979 (2005).

74. Ouvrier R, Geevasingha N, Ryan MM. Autosomal-recessive and X-linked forms of hereditary motor and sensory neuropathy in childhood. *Muscle Nerve* 36(2), 131–143 (2007).

75. Hamadouche T, Poitelon Y, Genin E *et al.* Founder effect and estimation of the age of the c.892C>T (p.Arg298Cys) mutation in *LMNA* associated to Charcot–Marie–Tooth subtype CMT2B1 in families from north western Africa. *Ann. Hum. Genet.* 72(Pt 5), 590–597 (2008).

76. Vallat JM, Ouvrier RA, Pollard JD *et al.* Histopathological findings in hereditary motor and sensory neuropathy of axonal type with onset in early childhood associated with mitofusin 2 mutations. *J. Neuropathol. Exp. Neurol.* 67(11), 1097–1102 (2008).

77. Zhu D, Kennerson ML, Walizada G, Zuchner S, Vance JM, Nicholson GA. Charcot–Marie–Tooth with pyramidal signs is genetically heterogeneous: families with and without *MFN2* mutations. *Neurology* 65(3), 496–497 (2005).

78. Zuchner S, De Jonghe P, Jordanova A *et al.* Axonal neuropathy with optic atrophy is caused by mutations in mitofusin 2. *Ann. Neurol.* 59(2), 276–281 (2006).

79. Zuchner S, Mersiyanova IV, Muglia M *et al.* Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot–Marie–Tooth neuropathy type 2A. *Nat. Genet.* 36(5), 449–451 (2004).

80. Brockmann K, Dreha-Kulaczewski S, Dechent P *et al.* Cerebral involvement in axonal Charcot–Marie–Tooth neuropathy caused by mitofusin2 mutations. *J. Neurol.* 255(7), 1049–1058 (2008).

81. Yiu EM, Ryan MM. Demyelinating prenatal and infantile developmental neuropathies. *J. Peripher. Nerv. Syst.* 17(1), 32–52 (2012).

82. Chang XZ, Zhou JY, Yuan Y *et al.* Diagnostic value of muscle, sural nerve and skin biopsies in childhood neuromuscular disorders.

Zhonghua Er Ke Za Zhi 44(12), 909–912 (2006).

83. McLeod JG. Investigation of peripheral neuropathy. *J. Neurol. Neurosurg. Psychiatry* 58(3), 274–283 (1995).
84. Vrancken AF, Kalmijn S, Buskens E *et al.* Feasibility and cost efficiency of a diagnostic guideline for chronic polyneuropathy: a prospective implementation study. *J. Neurol. Neurosurg. Psychiatry* 77(3), 397–401 (2006).
85. Willison HJ, Winer JB. Clinical evaluation and investigation of neuropathy. *J. Neurol. Neurosurg. Psychiatry* 74(Suppl. 2), ii3–ii8 (2003).
86. Hilton DA, Jacob J, Househam L, Tengah C. Complications following sural and peroneal nerve biopsies. *J. Neurol. Neurosurg. Psychiatry* 78(11), 1271–1272 (2007).
87. Fabrizi GM, Cavallaro T, Angiari C *et al.* Giant axon and neurofilament accumulation in Charcot–Marie–Tooth disease type 2E. *Neurology* 62(8), 1429–1431 (2004).
88. Chang CM, Yu CW, Fong KY *et al.* N-hexane neuropathy in offset printers. *J. Neurol. Neurosurg. Psychiatry.* 56(5), 538–542 (1993).
89. Chung KW, Kim SB, Cho SY *et al.* Distal hereditary motor neuropathy in Korean patients with a small heat shock protein 27 mutation. *Exp. Mol. Med.* 40(3), 304–312 (2008).
90. Chung KW, Suh BC, Shy ME *et al.* Different clinical and magnetic resonance imaging features between Charcot–Marie–Tooth disease type 1A and 2A. *Neuromuscul. Disord.* 18(8), 610–618 (2008).
91. Cellerini M, Salti S, Desideri V, Marconi G. MR imaging of the cauda equina in hereditary motor sensory neuropathies: correlations with sural nerve biopsy. *AJNR Am. J. Neuroradiol.* 21(10), 1793–1798 (2000).
92. Ellegala DB, Monteith SJ, Haynor D, Bird TD, Goodkin R, Kliot M. Characterization of genetically defined types of Charcot–Marie–Tooth neuropathies by using magnetic resonance neurography. *J. Neurosurg.* 102(2), 242–245 (2005).
93. Liao JP, Waclawik AJ. Nerve root hypertrophy in CMT type 1A. *Neurology* 62(5), 783 (2004).
94. Shah S, Chandrashekar H, Manji H, Davagnanam I. Cranial nerve, spinal root and plexus hypertrophy in chronic inflammatory demyelinating polyneuropathy. *Pract. Neurol.* 12(1), 68–69 (2012).
95. Wilmshurst JM, Thomas NH, Robinson RO, Bingham JB, Pohl KR. Lower limb and back pain in Guillain–Barre syndrome and associated contrast enhancement in MRI of the cauda equina. *Acta Paediatr.* 90(6), 691–694 (2001).
96. Hughes RA, Raphael JC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain–Barre syndrome. *Cochrane Database Syst. Rev.* (1), CD002063 (2006).
97. Beadles WI, Jahn A, Weigel R, Clutterbuck D. Peripheral neuropathy in HIV-positive patients at an antiretroviral clinic in Lilongwe, Malawi. *Trop. Doct.* 39(2), 78–80 (2009).
98. Youle M. Acetyl-L-carnitine in HIV-associated antiretroviral toxic neuropathy. *CNS Drugs* 21(Suppl. 1), 25–30; discussion 45–46 (2007).
99. Steichen O, Martinez-Almoyna L, De Broucker T. [Isoniazid induced neuropathy: consider prevention]. *Rev. Mal. Respir.* 23(2 Pt 1), 157–160 (2006).
100. Coodley G. Update on vitamins, minerals, and the carotenoids. *J. Physicians Assoc. AIDS Care* 2(1), 24–29 (1995).
101. Tagliati M, Grinnell J, Godbold J, Simpson DM. Peripheral nerve function in HIV infection: clinical, electrophysiologic, and laboratory findings. *Arch. Neurol.* 56(1), 84–89 (1999).
102. Bademosi O, Osuntokun BO. Diseases of peripheral nerves as seen in the Nigerian African. *Afr. J. Med. Med. Sci.* 10(1–2), 33–38 (1981).
103. Van Veen NH, Nicholls PG, Smith WC, Richardus JH. Corticosteroids for treating nerve damage in leprosy. *Cochrane Database Syst. Rev.* (2), CD005491 (2007).
104. Van Veen NH, Schreuders TA, Theuvenet WJ, Agrawal A, Richardus JH. Decompressive surgery for treating nerve damage in leprosy. *Cochrane Database Syst. Rev.* 12, CD006983 (2009).
105. Young P, De Jonghe P, Stogbauer F, Butterfass-Bahloul T. Treatment for Charcot–Marie–Tooth disease. *Cochrane Database Syst. Rev.* (1), CD006052 (2008).
106. Hubalek Z. Epidemiology of Lyme borreliosis. *Curr. Probl. Dermatol.* 37, 31–50 (2009).
107. Jowi JO, Gathua SN. Lyme disease: report of two cases. *East Afr. Med. J.* 82(5), 267–269 (2005).
108. Elamin M, Monaghan T, Mulllins G *et al.* The clinical spectrum of Lyme neuroborreliosis. *Ir. Med. J.* 103(2), 46–49 (2010).
109. Puntoni M, Sbrana F, Bigazzi F, Sampietro T. Tangier disease: epidemiology, pathophysiology, and management. *Am. J. Cardiovasc. Drugs* 12(5), 303–311 (2012).
110. Zyss J, Behin A, Couvert P *et al.* Clinical and electrophysiological characteristics of neuropathy associated with Tangier disease. *J. Neurol.* 259(6), 1222–1226 (2012).

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. You are medical volunteer at a hospital in the outskirts of Ghana, West Africa. You are working in the outpatient clinic. A 12-year-old girl is brought in by her mother to be evaluated for difficulty walking for 2 days. They come from a village that is 6 hours away on foot. Towards the end of their trek, her daughter required assistance. You suspect she has a peripheral neuropathy. Knowing that you are working in a resource-poor country (RPC), compared to more "developed" settings, which of the following statements is correct regarding the cause of peripheral neuropathy?

- ☐ **A** Neurotoxins are not observed since medications are lacking
- ☐ **B** Vitamin A deficiency is usually the cause of peripheral neuropathy in this setting
- ☐ **C** Greater numbers of infections such as tuberculosis and HIV type 1 are more often seen
- ☐ **D** Hereditary disorders do not occur in RPCs

2. Upon further history and physical exam, you suspect this child has acute inflammatory demyelinating polyradiculoneuropathy (AIDP). Which of the following would be consistent with this diagnosis?

- ☐ **A** Grey pharyngeal membrane
- ☐ **B** Ascending evolution of paralysis
- ☐ **C** History of toxin exposure
- ☐ **D** Urine darkening on exposure to daylight

3. Which of the following would be the most appropriate methods for diagnosing the cause of the peripheral neuropathy in this patient?

- ☐ **A** Neurophysiology studies
- ☐ **B** Molecular genetic analysis
- ☐ **C** Peripheral nerve biopsy
- ☐ **D** MRI

4. A few hours later, you examine your patient again and find that she is unable to ambulate and having more difficulty breathing. The best treatment option for this patient is:

- ☐ **A** Steroids
- ☐ **B** Carbamazepine
- ☐ **C** Gabapentin
- ☐ **D** Intravenous immunoglobulin