

# Peripheral nerve disease secondary to systemic conditions in children

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**Abstract:** This review is an overview of systemic conditions that can be associated with peripheral nervous system dysfunction. Children may present with neuropathic symptoms for which, unless considered, a causative systemic condition may not be recognized. Similarly, some systemic conditions may be complicated by comorbid peripheral neuropathies, surveillance for which is indicated. The systemic conditions addressed in this review are critical illness polyneuropathy, chronic renal failure, endocrine disorders such as insulin-dependent diabetes mellitus and multiple endocrine neoplasia type 2b, vitamin deficiency states, malignancies and reticuloses, sickle cell disease, neurofibromatosis, connective tissue disorders, bowel dysmotility and enteropathy, and sarcoidosis. In some disorders presymptomatic screening should be undertaken, while in others there is no benefit from early detection of neuropathy. In children with idiopathic peripheral neuropathies, systemic disorders such as celiac disease should be actively excluded. While management is predominantly focused on symptomatic care through pain control and rehabilitation, some neuropathies improve with effective control of the underlying etiology and in a small proportion a more targeted approach is possible. In conclusion, peripheral neuropathies can be associated with a diverse range of medical conditions and unless actively considered may not be recognized and inadequately managed.

**Keywords:** children, peripheral neuropathy, systemic disease

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## Introduction

Peripheral nervous system (PNS) dysfunction can complicate various systemic diseases. Whilst this is more common in the adult age group, children are also at risk. Children are exposed to multiple types of systemic dysfunction, especially from inflammation, secondary infections, toxins, and so on, which potentially lead to primary and secondary impact on the PNS.

Systemic involvement may be the presenting feature and an underlying neuropathy may not be detected unless screened for by targeted examination and neurophysiological studies. People with conditions such as lymphoma, diabetes mellitus and uremia are at risk of PNS dysfunction, which can be clinically striking and symptomatic. Patient management focuses on the systemic disease, with the risk that comorbid complications are missed.

In other situations, PNS dysfunction may be the instigator leading to presentation for medical assessment. In this setting exploration for an underlying systemic disease should be included as part of the diagnostic assessment.

This review focuses on systemic conditions affecting children, which may be associated with PNS dysfunction, but excludes peripheral nerve disease which is reported with neurodegenerative disorders, metabolic diseases, and infections. The key findings are summarized in Table 1. Recommended and explorative therapeutic interventions are assessed for each condition.

## Search strategy and methodology

Articles were searched for on PubMed with no date limitation and targeting human studies. Case

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**Table 1.** Systemic conditions associated with peripheral nervous system dysfunction in children.

Condition	Key clinical features	Clinical features of neuropathy	Nerve conduction studies	Biopsy/histology	Intervention/outcome
Critical illness Polyneuropathy Rare (0.02% pediatric ICU admissions)	Failure to wean from ventilation support due to generalized neuropathy 4–26 days post ICU admission <sup>1,2</sup>	Generalized weakness. Absent or reduced deep tendon reflexes	Denervation and axonal features <sup>1,3</sup>	Extensive muscle denervation and axonal degeneration <sup>1,3</sup>	Supportive care. Correction of impaired osmolar states, glycemic levels and electrolyte imbalance. Early rehabilitation. Spontaneous recovery occurs but long-term morbidity common. <sup>4–6</sup>
Chronic renal failure	Children in renal failure with chronic uremia, typically requiring dialysis <sup>7</sup>	Usually subtle features of neuropathy. Sensory abnormalities in the lower limbs, can evolve sensorimotor polyneuropathy with flaccid paraplegia or quadriplegia. A purely motor neuropathy also reported.	2/3 slowed common peroneal nerve conduction studies. <sup>8–10</sup> Prolonged latency of 'H' reflex. <sup>11</sup>	Axonal degenerative neuropathy typical. But any type of neuropathy (purely axonal, mixed, or predominantly demyelinating) may occur <sup>12</sup>	Symptoms improve with longer periods and frequency of dialysis. Renal transplantation resolve of the complication. <sup>13</sup>
<b>Endocrine Disorders</b>					
Diabetes mellitus	Incidence unclear. <sup>14,15</sup> Neuropathy often (not invariably) associated with longer duration/poorly controlled diabetes <sup>16</sup>	Subclinical in most. Polyneuropathy, or focal neuropathy, or autonomic neuropathy can occur. <sup>14,17</sup>	Mild slowing of nerve conduction more commonly seen in lower extremities. <sup>18</sup>	Axonal degeneration, segmental demyelination	Prevention remains related to good blood glucose control. <sup>19,20</sup>
Multiple Endocrine Neoplasia Type 2B	Marfanoid habitus, dysmorphic facial features, skeletal anomalies, <sup>21</sup> proximal/distal muscle wasting. <sup>22</sup>	Wrist or foot drop may be a presenting feature. Involvement of autonomic nerves can cause constipation or diarrhea. <sup>23,24</sup>	Mildly abnormal motor and sensory nerve conduction studies and chronic denervation on needle EMG. <sup>23,25</sup>	Moderate loss of small- and large-diameter myelinated fibers on sural nerve biopsy. Axonal degeneration. <sup>23</sup>	Treatment of neoplasia, screening for malignancies.

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**Table 1.** (Continued)

Condition	Key clinical features	Clinical features of neuropathy	Nerve conduction studies	Biopsy/histology	Intervention/outcome
Vitamin deficiencies					
B <sub>1</sub> (thiamine) deficiency	Infantile form: cardiac dysfunction, neck rigidity and acute peripheral neuritis. <sup>26–28</sup> Childhood form: ataxia, ophthalmoplegia, confusion.	Sensory ataxia, hypotonia and weakness. <sup>29</sup>	Sensory neuropathy with additional acute motor axonopathy. <sup>30</sup>	Large-fiber mainly axonal degeneration and subperineurial edema. <sup>31</sup>	T thiamine replacement therapy. Complete recovery not invariable. <sup>30</sup>
B <sub>2</sub> (riboflavin) deficiency	Acquired (dietary) deficiency. <sup>32</sup> Genetic form: (BVL): progressive pontobulbar palsy, sensorineural hearing loss, optic atrophy and muscle weakness <sup>33</sup>	Muscle weakness: upper limbs and axial. Preservation lower limb power. Sensory ataxia <sup>33</sup>	Axonal sensorimotor neuropathy <sup>33,34</sup>	Axonal degeneration <sup>34</sup>	Case series support limited response with early intervention to riboflavin replacement. Phrenic nerve involvement unlikely to resolve completely. <sup>35</sup>
B <sub>6</sub> (pyridoxine) deficiency	Can be associated with isoniazid induced deficiency. Rare complication in children. Excessive supplementation with pyridoxine can also cause neuropathy <sup>36,37</sup>	Painful sensory neuropathy related to isoniazid therapy. Pyridoxine toxicity is associated with a dorsal ganglionopathy.	Reduced sensory potentials. Sensory or sensorimotor axonal neuropathy <sup>38</sup>	Severe active axonal neuropathy with multifocal loss of large and small myelinated fibers. <sup>38</sup>	In deficiency states either withdrawing the toxic agent for example, isoniazid or early supplementation with pyridoxine (5–10 mg/day). Avoiding toxic levels above 50 mg/day <sup>39,40</sup>
B <sub>12</sub> deficiency	Anemia. Myelopathic features are more common but neuropathy is reported as well <sup>41</sup>	Clinical sensorimotor neuropathy in most <sup>42</sup>	Mixed axonal and demyelinating features <sup>42</sup>	Acute axonal degeneration early, chronic axonopathy with secondary demyelination late <sup>42</sup>	Response to therapy may be delayed. <sup>42</sup>

(Continued)

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Condition	Key clinical features	Clinical features of neuropathy	Nerve conduction studies	Biopsy/histology	Intervention/outcome
Vitamin E deficiency	Usually associated with malabsorption. Variable neurological features. <sup>43,44</sup> Onset often in the first decade but after 2 years of age.	Impaired position and vibration awareness. Reduced power, loss of deep tendon reflexes, and impaired proprioception.	Abnormal somatosensory evoked potential studies. <sup>45,46</sup> A sensory neuropathy with normal motor conduction and absent or markedly reduced sensory nerve action potentials (SNAPs). <sup>47,48</sup>	Axonal loss. <sup>45,47</sup>	Improves with dietary vitamin E supplementation. <sup>47,49</sup>
Malignancies and Reticuloses					
Lymphoma	Neuropathies unrelated to direct infiltration and chemotherapy toxicity are rare in children. <sup>50</sup>	Sensory type: pins and needles, altered unpleasant skin sensation, discomfort, and proprioceptive ataxia. Combined sensory and motor neuropathy, acute polyneuropathy of the acute inflammatory polyradiculoneuropathy (AIDP) phenotype more with Hodgkin's disease.	When differentiating between AIDP phenotype and vincristine toxicity, F waves are usually absent early in the course of AIDP. A more chronic demyelinating or axonal neuropathy also occurs in pediatric lymphoma. <sup>51</sup>	Small-fiber neuropathy is reported in a third of children with acute lymphoblastic leukemia who completed treatment protocols which include vincristine. <sup>52</sup>	AIDP phenotype may respond to intravenous immunoglobulin (IVIg). Some data supports glutamine prophylaxis. <sup>53</sup>
Paraneoplastic neuropathies	Rare cases of paraneoplastic neuropathy are reported in children. <sup>54-56</sup>	Features of an acute polyneuropathy. Can appear as atypical pediatric AIDP and CIDP <sup>55-58</sup>	Axonal pattern of conduction <sup>54</sup>	Axonal degeneration of nerves and dorsal funiculus with no evidence of metastatic spread or cellular inflammation.	Improvement following IVIG and supportive care is reported. <sup>57</sup>
Graft-versus-Host Disease (GVHD)	Patients with allogeneic hematopoietic stem cell transplantation are most at risk of neuropathies associated with GVHD <sup>59-63</sup>	Phenotype of Guillain-Barré syndrome, can also have a chronic phenotype <sup>60</sup>	Chronic inflammatory demyelinating neuropathy <sup>64</sup>	-	Good response to IVIG for cases typical of Guillain-Barré syndrome. Exclusion of indirect etiologies important <sup>60</sup>

(Continued)

Table 1. (Continued)

Condition	Key clinical features	Clinical features of neuropathy	Nerve conduction studies	Biopsy/histology	Intervention/outcome
Neurofibromatosis (NF)	NF type 1. Specific genetic markers predispose to development of malignant nerve sheath tumors <sup>65,66</sup>	Severe pain and rapid growth of the soft-tissue lesion are markers of malignant change. <sup>65</sup>	Both axonal and demyelinating neuropathies occur. <sup>67</sup>	Loss of axons and changes in myelination. Fibroblast-like cells accompanying the nerve fascicles. <sup>67</sup>	Serum markers. High-resolution ultrasound aid in early detection. Surgical interventions are performed where viable. Outcome often poor. <sup>67,68</sup>
Sickle cell disease	Prevalent in the African population	Neuropathy associated with lead toxicity in isolated case reports <sup>69</sup>	Demyelinating <sup>69</sup>	–	Avoidance and management of lead toxicity
Connective Tissue Disorders					
Rheumatoid Arthritis	Rare, but reported in children. <sup>70</sup>	More as nerve entrapments. Can be generalized but often subclinical in children	Normal or slowed nerve conduction in single nerves or denervation on EMG. <sup>8</sup>	Segmental demyelination, axonal degeneration	Symptoms worsen with age <sup>71</sup>
Systemic Lupus Erythematosus (SLE)	Autoimmune disorder, rarely leads to neuropathy in children. Clinical presentation 1–5 years after SLE diagnosed, develop foot drop or pain.	Most are subclinically affected. 3 main nerve diseases occur: Mononeuritis multiplex, an acute sensorimotor neuropathy similar to Guillain-Barré syndrome, and a distal sensory neuropathy.	Sensory and motor axonal pathology, which may be slowly progressive or may wax and wane. <sup>72,73</sup>	Axonal degeneration affecting myelinated and unmyelinated fibers, vasculitis <sup>74,75</sup>	Treatment may include immunomodulation and IVIG. <sup>76</sup>
Miscellaneous					
Chronic Idiopathic Intestinal Pseudo-Obstruction	Intestinal pseudo-obstruction can affect all ages from the neonates through to adults	A motor neuropathy may occur related to neuronal dysplasia in the myenteric plexus	Demyelinating changes are typically, axonal pathology also reported. <sup>77</sup>	–	Early recognition important for supportive care to reduce secondary complications.

(Continued)

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Condition	Key clinical features	Clinical features of neuropathy	Nerve conduction studies	Biopsy/histology	Intervention/outcome
<p>Waardenburg–Shah syndrome, which is subtype is allelic to Waardenburg syndrome type 4 due to recessive mutations in the <i>SOX10</i> gene.<sup>78,79</sup></p>	<p>Bowel dysmotility and peripheral neuropathy.</p>	<p>Neurocristopathy presents early in life as a combination of Waardenburg syndrome, central dysmyelination, Hirschsprung disease, and a hypomyelinating peripheral neuropathy.<sup>78–85</sup></p>	<p>Hypomyelinating</p>	<p>Hypoplasia and loss of axons<sup>82</sup></p>	<p>Early recognition important for supportive care to reduce secondary complications.</p>
<p>Celiac disease</p>	<p>Gluten-sensitive enteropathy</p>	<p>Recurring Guillain-Barré syndrome picture</p>	<p>Axonal or demyelinating sensory or sensory and motor neuropathy in some patients.<sup>86–88</sup></p>	<p>Marked reduction of myelinated fibers with no evidence of regeneration.<sup>89</sup></p>	<p>Electrophysiology screening is not recommended in asymptomatic patients with celiac disease.<sup>90</sup> Patients with idiopathic immune peripheral neuropathies should be screened for celiac disease.<sup>91</sup></p>
<p>Sarcoidosis</p>	<p>Cranial neuropathy, generalized chronic neuropathy, hilar lymphadenopathy, uveitis, parotitis and erythema nodosum.<sup>92</sup></p>	<p>Facial weakness less common than in adults. Generalized neuropathies are usually asymmetric, presenting as mononeuritis multiplex or Guillain-Barré syndrome.<sup>93</sup> Sensory loss may cause patchy pain or dysesthesia over the torso.<sup>94</sup></p>	<p>Nerve conduction studies can be normal or detect mild slowing of conduction.<sup>94</sup></p>	<p>Muscle or sural nerve biopsy may identify sarcoid granulomas.<sup>95</sup></p>	<p>Prognosis variable. Evidence for steroid effectiveness limited.<sup>96</sup></p>

reports were included for some conditions as these were the only resources with documented information. Where this occurred, it was noted in the text. Search terms included 'child' and 'neuropathy' as standard, and were linked to each of the system disease headings, which were searched for under the main title as well as each of their subconditions. For example 'vitamin deficiencies' was followed by searches under each type of vitamin deficiency, similarly 'endocrine disorders' was followed by a search under 'thyroid disease', 'hypothyroidism', 'hyperthyroidism', 'diabetes mellitus', and so on. Only conditions associated with peripheral neuropathy in children were included. Information, where available, was drawn from the text relating to prevalence, clinical features, neurophysiology, and histological findings as well as management and outcome. Studies on peripheral neuropathies associated with neurodegenerative disorders, metabolic diseases, and active infections were excluded.

### Critical illness polyneuropathy

Critical illness polyneuropathy (CIP) occurs as a result of systemic inflammation in patients with sepsis, severe respiratory illnesses, after transplantation of organs, and multiple systemic failure of organs, as well as those requiring extracorporeal life support.<sup>1,2</sup> The pathophysiology of CIP is poorly understood, but most probably includes a combination of microvascular (vasodilation, increased permeability), metabolic (hyperglycemia, mitochondrial failure, hypoalbuminemia) and electrical alterations (inactivation of sodium channels and change in resting membrane potential).<sup>1</sup> CIP is part of a group of disorders including critical illness myopathy (CIM) and combination-critical illness polyneuropathy (CIPNM).<sup>1</sup> The condition is rare in children, reported to affect 0.02% of pediatric intensive care unit (PICU) admissions, but this figure may be an underestimation.<sup>2</sup> Clinical presentation of CIP is often first considered following failure to wean from artificial ventilation support.<sup>97</sup> In the PICU environment the associated generalized weakness, muscle atrophy, and absent or reduced deep tendon reflexes may be difficult to detect. The condition can present within the first week of illness, with ranges between 4 and 26 days reported.<sup>97,98</sup> Children affected by severe burns have been reported to suffer a condition similar to CIP.<sup>99</sup> Differential diagnoses of CIP, include spinal cord pathology,

neuromuscular blockade, autoimmune myasthenia gravis, corticosteroid- or relaxant-induced myopathy, acute necrotizing myopathy, low blood phosphate levels, toxic and vitamin deficiencies (e.g. thiamine-deficiency), asthma-amiotrophy syndrome, and acute inflammatory demyelinating polyradiculoneuritis. Useful screening investigations include assessing magnesium and phosphate levels, serum creatine kinase levels, which are normal in most cases of CIP, neurophysiological studies, and relevant imaging modalities. Extensive muscle denervation and axonal degeneration is found on peripheral nerve studies and biopsy samples.<sup>1,3</sup>

Children who already have life-threatening conditions and are affected with CIP/CIM can suffer significant additional morbidity.<sup>97</sup> Supportive care is the mainstay of treatment; with prompt correction of impaired osmolar states, glycemic levels and electrolyte imbalance, in addition to early rehabilitation.<sup>4-6</sup> Spontaneous recovery occurs but may be delayed.<sup>97</sup> The updated 2014 Cochrane review found moderate quality evidence that use of insulin therapy could reduce symptoms of CIP/CIM, and high-quality evidence to support that it was associated with reduced duration of artificial ventilation, duration on ICU and mortality at 180 days, but identified potential risks associated with hypoglycemia.<sup>6</sup> Corticosteroid therapy is ineffective in CIP/CIM.<sup>6</sup> There is moderate evidence that early rehabilitation of CIP/CIM may facilitate weaning from ventilatory support.<sup>6</sup> No beneficial effect was evident from electrical muscle stimulation, based on very low-quality evidence.<sup>6</sup>

### Chronic renal failure

Nerve conduction studies in children with long-term dialysis-dependent renal failure are usually either normal or mildly neuropathic.<sup>7</sup> Two-thirds of uremic children with abnormal common peroneal nerve conduction studies have no symptoms of peripheral neuropathy.<sup>8-10</sup> Evaluation of the 'H' reflex is a useful marker in a child lacking clinical signs of uremic polyneuropathy.<sup>11</sup> As such this neurophysiological study is important to include in assessments as the complication is found in almost 60% of children with chronic renal failure.<sup>11</sup> An axonal degenerative neuropathy is usually found, although any type of neuropathy (purely axonal, mixed or predominantly demyelinating) may occur.<sup>12</sup>

Symptomatic children may experience sensory abnormalities in the lower limbs; these can, over time, evolve into a sensorimotor polyneuropathy with flaccid paraplegia or quadriplegia. A purely motor type of uremic neuropathy is also reported.<sup>100</sup> Symptoms may be improved through longer periods and frequency of dialysis. Even in patients with established uremic neuropathy, which may be due to chronic hyperpolarization secondary to altered potassium levels, renal transplantation can lead to resolution of the complication.<sup>13</sup>

### Endocrine disorders

Polyneuropathy may also occur in patients with hypothyroidism<sup>101</sup> and hypoglycemia,<sup>102</sup> as well as with diabetes and multiple endocrine neoplasia (MEN).

#### *Diabetes mellitus*

Studies report a wide range, namely between 10% and 68%, of children with diabetes who are affected with neuropathy.<sup>14,15</sup> One study of 146 children with diabetes found that whilst 27.4% had features of peripheral neuropathy, in 62.5% this was subclinical.<sup>19</sup> Diabetic neuropathy may manifest as a polyneuropathy, focal neuropathy, or autonomic neuropathy.<sup>14</sup> Autonomic neuropathy leads to the most serious clinical impact from lack of awareness of hypoglycemia and cardiovascular dysfunction, and is the most common neuropathy to occur. Rare cases of mononeuritis multiplex are also reported.<sup>103</sup> Whilst some affected patients believe themselves to be asymptomatic, their clinical assessment may identify sensory loss. Impaired vibrotactile sense is a useful clinical marker of neuropathy in children with diabetes.<sup>104</sup> Numbness was detected in 30.8% of subjects in one study, with large myelinated nerve fiber dysfunction found in 7–10%; pain or temperature sensation impairment was found in only 1.4%.<sup>19</sup> A length-dependent polyneuropathy in children may lead to distal sensory loss (numbness) and paresthesia with burning, aching, or pinprick dysesthesia. In addition, affected children may have motor dysfunction related to distal weakness and poor coordination as well as distal anhidrosis, post-eating bloating, constipation, diarrhea, and impaired awareness of hypoglycemia. Deep tendon reflexes may be absent and foot ulcers can occur. Mildly impaired autonomic nervous system function was reported in 30–50% of children with diabetes who were tested soon after diagnosis.<sup>105,106</sup>

Nerve conduction studies most often detect abnormal measurements from the peroneal and sural nerves.<sup>19,107,108</sup> A large prospective study of nerve conduction and autonomic nervous system function in diabetic children detected slowing of sensory nerve conduction and impaired autonomic function in 25% of children at the time of diagnosis.<sup>17</sup> Of 50 juvenile diabetics with a mean age of 13 years, 10% had decreased median nerve motor conduction velocities, 32% had slowed conduction in the posterior tibial nerves, and 44% slowing of sural nerve conduction.<sup>18</sup> Diabetic neuropathy appears to be more marked in those with poorly controlled diabetes, but is also reported in young children with a short illness duration and good glycemic control.<sup>16</sup> Based on this, duration of illness cannot be stated to be a key disease-inducing factor. The nerve dysfunction can occur acutely and rapidly in the early stages from diabetes onset, although following this the neuropathy progresses more slowly and may even plateau.<sup>19</sup> The best preventative strategy for diabetic neuropathy remains good blood glucose control.<sup>19,20</sup> Serial nerve conduction studies are recommended to identify onset of this high-impact disease complication.<sup>109</sup> Most interventional studies of the management of diabetic neuropathy are experimental, or in adults with type 2 diabetes.<sup>110</sup> The potential benefits of aldose reductase inhibitors, which act on enzymes in the polyol pathway involved in the metabolism of blood glucose, and benfotiamine, a fat-soluble analog of thiamine that in animal models inhibits vascular damage in diabetes, are of potential interest.<sup>111,112</sup> C-peptide, the 31 amino acid component of proinsulin, may reverse the structural and functional changes due to diabetes in rats and humans.<sup>113</sup> It improved sensory function in patients with type 1 diabetes and mild neuropathy.<sup>113</sup> Angiotensin-converting enzyme inhibitors may also have a role.<sup>110</sup> For symptomatic relief of painful neuropathy most guidelines recommend use of tricyclic agents, serotonin–norepinephrine reuptake inhibitors, or  $\gamma$ -aminobutyric acid analogs (gabapentin or pregabalin) as first-line agents followed by opioids and topical treatments; again, these recommendations are targeted at adult patients and predominantly based on expert opinion.<sup>114</sup>

#### *MEN type 2B*

MEN type 2B is a rare syndrome of autosomal dominant inheritance that accounts for 5% of all cases of MEN 2. The condition is associated with

medullary thyroid carcinoma, pheochromocytoma, ganglioneuromatosis, as well as various skeletal and connective tissue abnormalities.<sup>21</sup> Patients with MEN 2B usually carry either an *M918T* or *A883T* mutation of the RET (rearranged during transfection) oncogene.<sup>21,115</sup> Affected patients have a marfanoid habitus along with thick, fleshy everted lips and the appearance of eversion of the eyelids.<sup>21</sup> In addition, a high arched palate and firm pale neuromatous nodules on the tongue as well as atrophy of the fibula, pes cavus, scoliosis, and proximal or distal muscle wasting is reported.<sup>22</sup>

This disorder may present with neuropathy manifesting as weakness of ankle dorsiflexion or occasionally of the intrinsic hand muscles.<sup>25</sup> Motor and sensory nerve conduction studies reveal mild impairments and chronic denervation on needle electromyography (EMG).<sup>23,25</sup>

Moderate loss of small- and large-diameter myelinated fibers is seen on sural nerve biopsy. Hyperplastic interlacing bands of Schwann cells and myelinated fibers that overlie the posterior columns of the spinal cord are reported in post-mortem samples.<sup>23</sup> Involvement of autonomic nerves is also reported and leads to severe constipation or diarrhea.<sup>23,24</sup>

Owing to the high risk of malignancy, early diagnosis is vital, especially as medullary thyroid carcinoma is typically already established when the diagnosis is made.<sup>21,25</sup> There is no specific therapy for the neuropathy beyond standard management and supportive interventions with rehabilitation and orthotics. It is not evident from the literature how treatment of the underlying neoplasias relates to the manifestation and or resolution of the neuropathy.

## Vitamin deficiency states

### *Vitamin B<sub>1</sub> (thiamine) deficiency*

Thiamine deficiency occurs in infants who are breastfed by mothers with inadequate intake of thiamine or who receive low-thiamine-content formula,<sup>26,27</sup> and in children who undergo medical or surgical procedures such as gastrointestinal resections, parenteral nutrition, and chemotherapy that result in inadequate thiamine uptake.<sup>29,116–118</sup> The condition in infants is referred to as beriberi, while in children the

manifestation falls under the term Wernicke's encephalopathy.<sup>29</sup> Infantile encephalitic beriberi (IEBB) is a rare form of thiamine deficiency complicated by cardiac dysfunction, neck rigidity, and acute peripheral neuritis.<sup>28</sup> The life-threatening respiratory and encephalopathic symptoms can mimic Leigh syndrome. The childhood onset form, Wernicke's encephalopathy, presents with the triad of ophthalmoplegia, ataxia, and confusion.<sup>29,116–118</sup>

The study by Ortigoza-Escobar *et al.*, across 21 centers, reviewed the primary and secondary conditions leading to thiamine deficiency in infants and children.<sup>29</sup> The group identified 79 children with inherited thiamine defects associated with neurological manifestations. The majority were due to *SLC19A3* disease ( $n=70$ ), the phenotype of which includes biotin thiamine responsive basal ganglia disease, Leigh's syndrome (LS), infantile spasms with lactic acidosis, and Wernicke-like encephalopathy.<sup>29</sup> The remainder had *TPK1* disease ( $n=4$ ) with a LS phenotype, and *SLC25A19* disease ( $n=5$ ) associated with Amish microcephaly and bilateral striatal degeneration and progressive polyneuropathy.<sup>29</sup> Data was collected on 153 children ( $n=65$ ) and infants ( $n=88$ ) with secondary thiamine deficiency. Infantile and childhood thiamine deficiency is rare in resource-equipped settings. In low- and middle-income countries of Africa, staple foods of polished rice and incorrectly prepared cassava are deficient in thiamine, which leads to high risk for thiamine deficiency.<sup>119</sup>

A predominantly sensory neuropathy with an additional acute motor axonopathy is detected on nerve conduction studies.<sup>30</sup> Large-fiber mainly axonal degeneration and subperineurial edema is typically found on biopsy.<sup>31</sup>

Sustained clinical improvement is reported following thiamine supplementation in patients with secondary thiamine deficiency, with less than 20% suffering mortality or neurological sequelae, inclusive of their neuropathy.<sup>29,30</sup>

### *Vitamin B<sub>2</sub> (riboflavin) deficiency*

Adequate dietary intake of riboflavin is essential as it is not endogenously synthesized or stored in human tissues. Riboflavin is integral to a diverse range of metabolic pathways through its role as a precursor of essential cofactors flavin mononucleotide (FMN)

and flavin adenine dinucleotide (FAD). These flavoproteins are important in chromatin remodeling, DNA repair, protein folding, and apoptosis.<sup>32</sup> Dietary deficiency, or ariboflavinosis, causes night blindness, cataracts, lethargy, anemia, poor growth, migraines, peripheral neuropathy, and dermatological symptoms.<sup>32</sup> Whilst unlikely with a normal diet it is reported to occur during lactation, phototherapy in infants, in children with celiac disease, malignancies, or prescribed drugs that include phenothiazine-derived antipsychotic medications, the antimalarial drug quinacrine, phenobarbital, and the cancer chemotherapy agent adriamycin.<sup>32</sup>

The Brown–Vialletto–Van Laere syndrome (BVVL) is a rare neurodegenerative disorder with progressive pontobulbar palsy, sensorineural hearing loss, optic atrophy, and muscle weakness related to an axonal sensorimotor neuropathy.<sup>33</sup> Without recognition and early intervention the condition is life-threatening owing to respiratory disease in early childhood.<sup>33</sup>

BVVL is caused by homozygous or compound heterozygous mutations in the genes encoding the plasma membrane based riboflavin transporters leading to riboflavin transporter defect type 2 (RTD2) (*SLC52A2* gene mutation) and RTD3 (*SLC52A3* gene mutation).<sup>33,120,121</sup> Children with RTD3 deficiency have sensorineural hearing loss, generalized lower limb predominant muscle weakness, bulbar weakness and tongue fasciculations, and respiratory weakness.<sup>25,122</sup> RTD2 deficiency differs from the phenotype of RTD3, with sensory ataxia presenting in childhood as well as sensorineural hearing loss. Muscle weakness is limited to the upper limbs, leading to the ‘child-in-the-barrel’ phenotype. Serum acylcarnitines are elevated in about 50% of cases.<sup>123</sup> Neurophysiological studies typically show axonal sensory and motor changes with evidence of anterior horn dysfunction and chronic denervation.<sup>32</sup> Sural nerve biopsies confirm axonal neuropathy and degeneration preferentially affecting large-diameter myelinated fibers, which correlates with the sensory dysfunction in affected patients.<sup>34</sup> Muscle biopsy in isolated cases of children with RTD2 and RTD3 has shown evidence of mitochondrial dysfunction inclusive of complex II and III deficiency, and ragged red fibers consistent with mitochondrial myopathy.<sup>35,124</sup>

The pathogenesis of the hereditary disorder is being explored and may lead to novel therapies,

especially related to the mitochondrial function.<sup>34,125</sup> The ripple effect of the deficiency state leading to mitochondrial dysfunction is most likely a secondary effect rather than part of a primary mitochondrial disorder. The manifestation of features compatible with mitochondrial dysfunction highlights the importance of including RTD in the differential diagnosis.<sup>124</sup>

Early recognition of RTD is important, as treatment with high-dose riboflavin (30–80 mg/kg/day) is well tolerated and slows or reverses the neuropathy and hearing loss.<sup>35</sup>

#### *Vitamin B<sub>6</sub> (pyridoxine) deficiency*

Vitamin B<sub>6</sub>, a water-soluble vitamin found in many standard dietary products, is a coenzyme for many reactions and involved in neuronal signaling through the synthesis of neurotransmitters.<sup>39</sup> Deficiency states are associated with cardiovascular dysfunction and polyneuropathy.<sup>39</sup> Ascending acute (<4 weeks) or subacute (12 weeks) numbness, with neuropathic pain, balance impediment, and weakness, is reported.<sup>38</sup> Neurophysiological studies are markedly abnormal, showing length-dependent acute axonal sensorimotor polyneuropathy with denervation, or a sensory neuropathy.<sup>38</sup>

Sural nerve biopsy shows a severe active axonal neuropathy with multifocal loss of large and small myelinated fibers, with scant epineurial vascular proliferation and inflammation.<sup>38</sup> This loss of small myelinated fibers is a complication as highlighted by an adult patient with additional autonomic dysfunction.<sup>126</sup>

Isoniazid-induced painful sensory neuropathy is relatively common in adults, and has also been reported in a few childhood cases.<sup>36,37</sup> Supplemental pyridoxine (5–10 mg/day) is recommended in HIV-positive or malnourished children receiving treatment for tuberculosis to avoid this complication.<sup>127</sup>

Pyridoxine is converted into its active form, pyridoxal phosphate. High levels of pyridoxine are thought to inhibit pyridoxal-phosphate-dependent enzyme. Paradoxically this means that supplementation with vitamin B<sub>6</sub>, usually in doses above 50 mg day, is associated with the development of a painful sensory neuropathy.<sup>39,40</sup> To date this has only been reported in adults.<sup>128,129</sup> The toxicity of

vitamin B<sub>6</sub> is not only dose determined, but related to the vitamin in which it is taken. There is a proposal that pyridoxine should be replaced by pyridoxal or pyridoxal phosphate when vitamin B<sub>6</sub> supplements are required.<sup>39</sup>

#### *Vitamin B<sub>12</sub> deficiency*

Childhood onset of vitamin B<sub>12</sub> deficiency anemia owing to impaired absorption of cobalamin, or poor dietary intake, is well known, but more often with myelopathic rather than neuropathic symptoms.<sup>41</sup> Symptomatic vitamin B<sub>12</sub> deficient-neuropathy is more often seen in resource-poor settings.<sup>130–132</sup> Early recognition and intervention are important to prevent irreversible nerve injury.<sup>133</sup> A study of 66 adolescents and adults with a vitamin B<sub>12</sub> deficient neurological syndrome found that 69.7% had clinical features of neuropathy and 54.5% had abnormal nerve conduction studies, most of which had mixed features of axonal and demyelinating disease.<sup>42</sup> Nerve biopsy in the early stages was consistent with acute axonal degeneration, and in later stages showed a chronic axonopathy with secondary demyelination.

With appropriate supplementation and management of underlying etiologies, nerve conduction parameters, and clinical findings improve within 6 months.<sup>42</sup>

#### *Vitamin E deficiency*

Children with protein-energy malnutrition, longstanding obstructive liver disease, chronic intestinal malabsorption, and cystic fibrosis are at risk of a progressive neurological syndrome owing to defective or inadequate vitamin E absorption.<sup>43,134–136</sup> Vitamin E deficiency is also a major cause of the polyneuropathies that occur in children with abetalipoproteinemia or hypobetalipoproteinemia.<sup>137</sup> These conditions are autosomal recessive disorders of the synthesis of the beta-lipoprotein owing to mutations of the MTTP (microsomal triglyceride transfer protein) or APOB genes, respectively.<sup>138,139</sup> Affected children develop nystagmus, gaze palsies (especially vertical gaze), retinitis pigmentosa, night blindness, ataxia, areflexia as well as impaired position and vibration awareness.<sup>43,44</sup> Neurological features may be evident by 2 years of age, with a third of affected children being symptomatic by 10 years. Intellectual disability affects the same proportion.

The clinical phenotype can mimic Friedreich ataxia and other similar primary spinocerebellar ataxia diseases.<sup>47</sup> Abetalipoproteinemia is treatable through the supplementation of fat-soluble vitamins and dietary modification.<sup>139</sup>

Vitamin E malabsorption can also occur due to familial isolated vitamin E deficiency caused by mutations in the alpha-tocopherol transfer protein gene (*TTP1*) and referred to as ataxia with vitamin E deficiency (AVED)<sup>44,140</sup> Most patients are from the Mediterranean region.<sup>47</sup> The antioxidant properties of vitamin E have a role in modulating glutamate neurotoxicity. In this genetic condition, failure of uptake of vitamin E into plasma low-density lipoproteins impairs normal recycling of vitamin E. Clinical features of AVED include dysarthria, progressive ataxia, weakness, loss of deep tendon reflexes, and impaired proprioception, with absent or very low serum vitamin E levels in the absence of hypolipidemia or fat malabsorption. Symptoms usually commence between 3 and 13 years of age (range 2–37 years).<sup>47</sup> Patients with AVED do not usually have retinopathy or ophthalmoplegia.<sup>44,141</sup> Upgoing plantar responses, tremor (especially head tremor), and dystonia of movements may occur.<sup>45,47</sup>

Somatosensory evoked potential studies confirm the abnormal posterior column function.<sup>45,46</sup> A sensory neuronopathy with normal motor conduction and absent or markedly reduced sensory nerve action potentials (SNAPs) is typically recorded on neurophysiologic studies.<sup>47,48</sup> Nerve biopsy typically shows axon loss.<sup>45,47</sup> Clinical resolution, as well as improvement in abnormal sensory conduction and evoked potentials, is reported with dietary vitamin E supplementation (up to 800 mg/day).<sup>49</sup> Intervention early in the disease course generally leads to better outcomes, but some patients are resistant even with timely supplementation.<sup>47</sup>

#### **Malignancies and reticuloses**

Children with cancers are at risk of PNS dysfunction, for multiple reasons including direct invasion, paraneoplastic syndromes, nerve compression, the side-effects of chemotherapy, infection, and the sequelae of poor nutrition.<sup>50,65,142,143</sup> However, once drug side-effects and local malignant infiltration are excluded, neuropathies are a relatively rare complication of childhood malignancies.<sup>143</sup> In 49 childhood malignancy

patients who were not managed with vincristine, none of the group had evidence of clinical or electrophysiological features of neuropathy.<sup>144</sup> From the same study, in 47 children treated with vincristine there was a high rate of absent deep tendon reflexes and abnormal sensory conduction velocities, but in most cases children were not clinically compromised.<sup>144</sup>

### *Lymphoma*

Peripheral neuropathy manifests in about 5% of adults with lymphoma, but is much rarer in childhood.<sup>50</sup> A sensory neuropathy and a sensorimotor neuropathy occur as the two main carcinomatous neuropathies. Genetic markers of increased predisposition to development of vincristine-induced peripheral neuropathy (VIPN) in children with acute lymphoblastic leukemia (ALL) have recently been identified, and may offer a means to tailoring therapy to avoid this disease complication.<sup>145</sup>

Pure sensory neuropathy is more likely to be seen in association with carcinoma rather than lymphoma.<sup>144</sup> The symptoms of pins and needles, altered unpleasant skin sensation, discomfort, and proprioceptive ataxia are similar to those seen in carcinoma. Small-fiber neuropathy is reported in a third of children with ALL who completed treatment protocols, which include vincristine.<sup>52</sup> For patients with combined sensory and motor neuropathy, acute polyneuropathy of the acute inflammatory polyradiculoneuropathy (AIDP) phenotype is reported in patients with lymphoma, especially Hodgkin's disease. Differentiating between AIDP and vincristine toxicity can be challenging in children with ALL, non-Hodgkin's and Hodgkin's lymphoma<sup>57,146,147</sup> who present with a mainly lower limb sensory and motor neuropathy.<sup>57,146</sup> Early in the course of the condition, F waves may be absent in children with AIDP, and these children can have a good response to intravenous immunoglobulin (IVIG).<sup>146</sup> A more chronic demyelinating or axonal neuropathy also occurs in pediatric lymphoma.<sup>51</sup> Nerve roots and peripheral nerve malignant invasion occurs more often in lymphoma than in carcinoma. In most cases management of associated neuropathy is symptomatic and supportive. Glutamine supplementation is reported to be well tolerated with improvements in sensory function and overall quality of life.<sup>53</sup> Future research is needed to establish if glutamine should form part of the care for patients with vincristine-related sensory neuropathy.

### *Paraneoplastic neuropathies*

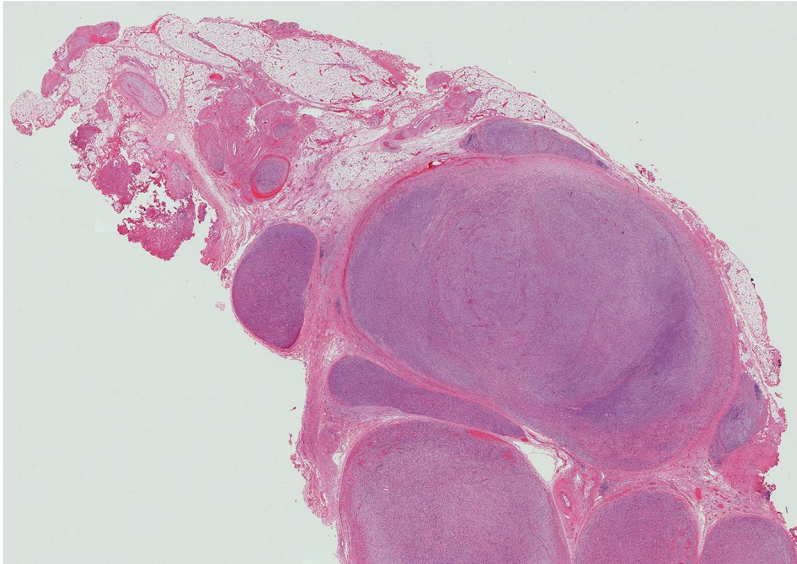
About 1% of cancer sufferers are affected by paraneoplastic neurological syndromes. Adults tend to develop peripheral neuropathies mediated by antibodies to intracellular (Hu-D and CV2-CRMP5) or cell membrane antigens (voltage-gated calcium channel, LG1 and CASPR2 proteins).<sup>65,142,148</sup> Children more typically develop autoimmune encephalitis rather than peripheral nerve dysfunction,<sup>149</sup> but rare cases of paraneoplastic neuropathy are reported.<sup>54-56</sup> A 13-year-old boy with Hodgkin's disease was reported with an acute polyneuropathy and autoimmune hemolytic anemia.<sup>54</sup> Axonal degeneration in the nerves and dorsal funiculus was identified on pathological assessment, and these nerves had no evidence of metastatic spread or cellular inflammation. Occasional cases of atypical pediatric AIDP and CIDP represent a paraneoplastic complication of lymphoreticular malignancies.<sup>55-58</sup> Improvement is reported with IVIG and supportive care.<sup>57</sup> Development of peripheral neuropathy in a patient with non-Hodgkin's malignant lymphoma (NHML) is an indication for intensification of chemotherapy. This approach can lead to significant regression of neuropathy.<sup>58</sup>

### *Graft-versus-host disease*

Allogeneic hematopoietic stem cell transplantation in children and adults can be complicated by acute immune-mediated neuropathies.<sup>59-63</sup> In relation to graft-versus-host disease (GVHD), all subtypes of Guillain-Barré syndrome can occur, often after intercurrent infections.<sup>60</sup> Affected patients typically have a good response to intervention with IVIG. A 7 month old girl post-bone marrow transplantation who developed severe GVHD, had her course further complicated by a chronic inflammatory demyelinating neuropathy.<sup>64</sup> Whilst a graft-versus-host response places children at risk of peripheral neuropathy, other direct or indirect causes (for example, toxins, infections, and paraneoplastic processes), should also be considered.<sup>150,151</sup> For example thalidomide is often used in the management of graft-versus-host response, and peripheral neuropathies can occur with use of this agent.<sup>152</sup>

### *Neurofibromatosis*

Neurofibromatosis type 1 (NF1), an autosomal dominant condition, may be complicated by peripheral nerve tumors [spinal neurofibromas,



**Figure 1.** Tumor is seen arising within a plexiform neurofibroma in a patient with of Neurofibromatosis type 1 (NF1) on low-power montage. (Image supplied by Associate Professor Duncan McGregor, Department Head of Anatomical Pathology, The Royal Children's Hospital, Melbourne, Australia)

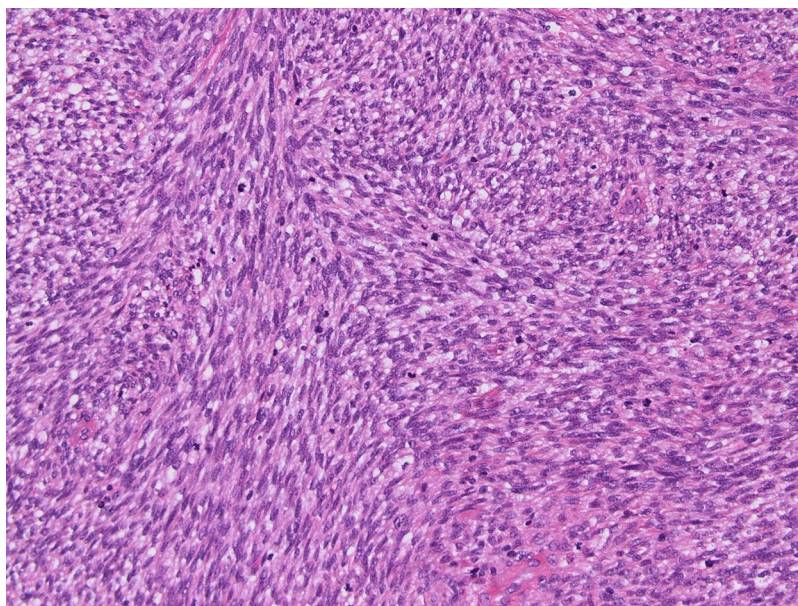
plexiform neurofibromas, and malignant peripheral nerve sheath tumors (MPNST)].<sup>153</sup> NF2, which is not as prevalent as NF1, less commonly manifests in childhood, but can also be associated with neuropathies. Sarcomatous malignant change occurs in some 8–13% of affected people with peripheral nerve sheath tumors, with a poor prognosis.<sup>67,68</sup> The histological appearance is illustrated by Figures 1 and 2. Mutations in the *p53* and *INK4a* genes, and aberrant signaling in the Notch pathway are factors leading to the development of MPNST.<sup>65,66</sup> Of 123 Chinese children with NF1, three patients (2.4%) developed had MPNST.<sup>66</sup> Severe pain and rapid growth of the soft-tissue lesion are markers of malignant change.<sup>65</sup> Early detection of this complication may be possible with serum markers.<sup>68</sup> High-resolution ultrasonography may be of value in detecting peripheral nerve involvement in NF1 and NF2.<sup>154,155</sup> There is no therapy to attenuate or prevent neuropathic symptoms of NF1,<sup>67</sup> but MEK and mTOR inhibitors have been proposed as possible interventions for tumor-associated neuropathic pain.<sup>67</sup> Surgical resection has been effective in some case reports where neuropathy is not associated with malignant transformation.<sup>156</sup> The use of high-resolution intraoperative ultrasound and contrast-enhanced ultrasound is reported to improve surgical outcomes.<sup>157</sup> Collaborative groups are developing research to aid establishment of effective management protocols.<sup>158</sup>

#### *Sickle cell disease*

Children with sickle cell disease, a condition prevalent throughout the African population, are predisposed to the development of a demyelinating peripheral neuropathy in the setting of lead intoxication.<sup>69</sup> In many resource-poor countries, lead intoxication remains a risk; this is an avoidable exacerbating factor to exclude in children presenting with neuropathy who have sickle cell disease. Chelation therapy was reported to result in improvement of the motor function in the two reported children over a period of months.<sup>69</sup> Sensory neuropathy in patients with sickle cell disease is reported more outside the childhood age range.<sup>159</sup>

#### *Connective tissue disorders*

*Rheumatoid arthritis.* Adults with rheumatoid arthritis are more likely to suffer polyneuropathy and entrapment neuropathies than children.<sup>70</sup> Carpal tunnel syndrome is occasionally seen in children with juvenile rheumatoid arthritis.<sup>160,161</sup> Delayed nerve conduction in single nerves was reported in 4 children from a cohort of 99 with juvenile rheumatoid arthritis.<sup>162</sup> Clinically there was no evidence of mononeuropathy, and conduction in the other nerves was normal.<sup>162</sup> A 14-year-old boy with established juvenile rheumatoid arthritis, over 4 months developed muscle weakness and reduced deep tendon reflexes, he had



**Figure 2.** The same patient with NF-1 as in Figure 1, in this view tumour is seen arising within a plexiform neurofibroma at high magnification illustrating the densely cellular spindle cell sarcoma is visible. (Image supplied by Associate Professor Duncan McGregor, Department Head of Anatomical Pathology, The Royal Children's Hospital, Melbourne, Australia)

denervation on EMG, but normal motor nerve conduction studies.<sup>8</sup> Symptoms, inclusive of neuropathic pain, experienced by patients with rheumatoid arthritis may be mild or unusual in childhood, but become more pronounced with time, such that 96% of adults have symptomatic neuropathy.<sup>71</sup> Children benefit from optimal care of their underlying rheumatoid arthritis and symptomatic relief of neuropathy where required.<sup>163</sup>

#### *Systemic lupus erythematosus and other vasculitic disorders*

Symptomatic peripheral nerve disease is uncommon in children with systemic lupus erythematosus (SLE), however subclinical nerve involvement is reported in up to 15% of affected children.<sup>164–169</sup> Whilst children may present with SLE owing to complications of a neuropathy, for example foot drop or pain,<sup>170</sup> most children with SLE who develop neuropathy do this between 1 and 5 years after the diagnosis.<sup>165</sup> The neuropsychiatric manifestations, which are common in the setting of SLE, can further complicate recognition of a neuropathy.<sup>170</sup> Mononeuritis multiplex, an acute sensorimotor neuropathy similar to GBS, and a distal sensory neuropathy are the three main types of nerve disease to occur. Nerve conduction studies usually show sensory and motor axonal pathology,

which may be slowly progressive or may wax and wane over time, generally worsening with age.<sup>72,73</sup> Axonal degeneration affecting myelinated and unmyelinated fibers is found on sural nerve samples, in addition to vasculitis in most cases.<sup>74,75</sup> Pathogenetic mechanisms suggested for the peripheral neuropathy in SLE include vasculitis of the vasa nervorum, endoneurial immune complex deposition and antiphospholipid antibody-mediated damage to components of neural tissue.<sup>75,164,165,168,171</sup> The vasculitis leads to ischemic infarction of blood vessels, which results in Wallerian degeneration of nerve fibers.<sup>172,173</sup> Treatment may include immunomodulation and IVIG.<sup>76</sup> Children with SLE should undergo regular nerve conduction studies to monitor for development of subclinical neuropathy.<sup>164,170</sup>

Vasculitic mononeuritis multiplex has been described in children with SLE, Churg–Strauss syndrome, and polyarteritis nodosa.<sup>174–180</sup> Sjögren's syndrome is an autoimmune exocrinopathy primarily affecting the salivary and lacrimal glands. This condition is also associated with development of a sensory neuropathy possibly related to vasculitis or ganglionitis of the dorsal roots.<sup>181</sup> Occasional pediatric cases are reported.<sup>181</sup> Immunosuppression and immunomodulation are part of standard care. Children with polyarteritis

need aggressive immunosuppression, especially in the setting of progressive gangrene related to the sensory vasculitic neuropathy.<sup>182</sup> There are conflicting studies in relation to the role of the tumor necrosis factor- $\alpha$  agent, etanercept.<sup>183,184</sup>

### *Miscellaneous systemic disorders*

*Chronic idiopathic intestinal pseudo-obstruction.* Intestinal pseudo-obstruction can affect all ages from the neonates through to adults. A motor neuropathy may occur related to neuronal dysplasia in the myenteric plexus, as well as in association with Duchenne muscular dystrophy, myotonic dystrophy, mitochondrial cytopathy, myxedema, porphyria, scleroderma, amyloidosis, and Chagas disease.<sup>77,185–187</sup> Familial visceral neuropathy is the hereditary form of the disorder.<sup>77</sup> Nonintestinal abnormalities are reported, including pupillary abnormalities.<sup>188–190</sup> There is overlap with the features of the condition familial visceral myopathy.<sup>77,185</sup> Demyelinating changes are typically recorded on nerve conduction studies, although axonal pathology is also reported.<sup>77</sup> The mode of inheritance is not defined.<sup>77</sup>

Waardenburg–Shah syndrome also combines bowel dysmotility and peripheral neuropathy; this subtype is allelic to Waardenburg syndrome type 4 due to recessive mutations in the *SOX10* gene.<sup>78,79</sup> This neurocristopathy presents early in life with Waardenburg syndrome, central dysmyelination, Hirschsprung disease, and a hypomyelinating peripheral neuropathy.<sup>78–85</sup> Hypoplasia and markedly reduced axonal fibers were detected on sural nerve biopsy of an infant with Waardenburg–Shah syndrome.<sup>82</sup>

Whilst peripheral neuropathy is common in the setting of mitochondrial disease, especially mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) and myoclonic epilepsy with ragged-red fibers (MERRF), mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) invariably causes peripheral neuropathy.<sup>191</sup> MNGIE is a rare multisystemic recessive disorder which is complicated by progressive external ophthalmoplegia, gastrointestinal impaired motility, extreme weight loss, muscle wasting, peripheral neuropathy and leukoencephalopathy, due to mutations in the *TMMMP* gene, encoding for thymidine phosphorylase.<sup>192</sup> Onset of the condition is in childhood or adolescence.<sup>193</sup> The peripheral

neuropathy is usually demyelinating but mixed axonal/demyelinating or predominantly axonal cases are reported.<sup>192</sup> Delay in diagnosis of MNGIE is common.<sup>192</sup> Allogeneic haemopoietic stem cell transplantation may improve the neuropathy as well as improving body mass index and gastrointestinal manifestations.<sup>194</sup>

Celiac disease is a gluten-sensitive enteropathy complicated by an axonal or demyelinating sensory or sensory and motor neuropathy in some patients.<sup>86–88</sup> Recurrent Guillain–Barré syndrome occurred in a single patient which was considered due to molecular mimicry.<sup>195,196</sup> A 3-year-old child who had celiac disease developed an evolving polyneuropathy that was unresponsive to a gluten-free diet, vitamin E and folic acid supplementation, and on sural nerve biopsy had marked reduction of myelinated fibers and no evidence of regeneration.<sup>89</sup> A Wallerian degeneration mechanism was supported by the distal involvement and the nerve biopsy findings, further the failure to respond to a gluten-free diet supported that direct toxicity of gliadin had not occurred.<sup>89</sup> Neurophysiologic screening is not recommended in asymptomatic patients with celiac disease.<sup>90</sup> A large Swedish population study, however, concluded that patients with idiopathic immune peripheral neuropathies should be screened for celiac disease.<sup>91</sup>

### *Sarcoidosis*

Peripheral neuropathy involvement in sarcoidosis may be isolated or part of the overall systemic disease complications.<sup>93</sup> Adults, in particular, are at risk of facial nerve palsy, which is the most common neurological manifestation of the condition.<sup>93</sup> Generalized neuropathies are usually asymmetrical and present as mononeuritis multiplex or Guillain–Barré syndrome.<sup>93</sup> Sensory loss, with altered skin sensation or pain, over large areas of the torso, can also occur.<sup>94</sup>

Cranial neuropathy in addition to generalized chronic neuropathy is very supportive of a diagnosis of sarcoidosis. This is typically in the setting of a patient with hilar lymphadenopathy, uveitis, parotitis, and erythema nodosum.<sup>92</sup> Overall peripheral nerve disease in children is rare but has been reported as young as 13 years of age, with two cases presenting with Guillain–Barré syndrome.<sup>92,197</sup> Neurosarcoidosis was reported in 53 children who most often manifested with cranial neuropathy (in 21% of cases).<sup>96</sup>

Nerve conduction studies can be normal or detect mild slowing of conduction.<sup>94</sup> Muscle or sural nerve biopsy may identify sarcoid granulomas.<sup>95</sup> Mild pleocytosis and raised total protein can occur in cerebrospinal fluid.<sup>94</sup>

Whilst the long-term outcome of sarcoid neuropathy is better than that of central nervous system sarcoidosis, the overall prognosis cannot be predicted. Although corticosteroids are used, the evidence to support this intervention is not established.<sup>96</sup>

### Conclusion

This review provides an overview of systemic conditions that can be associated with PNS dysfunction. Some neuropathies associated with systemic disease, such as CIP and autonomic dysfunction with diabetes mellitus, can have a profound clinical effect and compromise. In other settings, screening for evidence of nerve dysfunction can be an indicator of chronic poor disease control. In some conditions, such as celiac disease, peripheral neuropathy may be the presenting feature warranting active exclusion of the systemic condition. In all cases early recognition and symptomatic care of neuropathy is important for mobility and pain control. In many conditions, neuropathy will improve in tandem with the optimal management of the underlying disease. In conclusion, peripheral neuropathies can be associated with a diverse range of medical conditions and unless actively considered may not be recognized and, thus, inadequately managed.

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### References

1. Shepherd S, Batra A and Lerner DP. Review of critical illness myopathy and neuropathy. *Neurohospitalist* 2017; 7: 41–48.
2. Field-Ridley A, Dharmar M, Steinhorn D, *et al.* ICU-Acquired weakness is associated with differences in clinical outcomes in critically ill children. *Pediatr Crit Care Med* 2016; 17: 53–57.
3. Vondracek P and Bednarik J. Clinical and electrophysiological findings and long-term outcomes in paediatric patients with critical illness polyneuropathy. *Eur J Paediatr Neurol* 2006; 10: 176–181.
4. Gheith O, Al Otaibi T, Halim M, *et al.* Successful management of critical illness polyneuropathy and myopathy in renal transplant recipients. *Exp Clin Transplant* 2012; 10: 62–66.
5. Hermans G, De Jonghe B, Bruyninckx F, *et al.* Interventions for preventing critical illness polyneuropathy and critical illness myopathy. *Cochrane Database Syst Rev* 2009; 1: CD006832.
6. Hermans G, De Jonghe B, Bruyninckx F, *et al.* Interventions for preventing critical illness polyneuropathy and critical illness myopathy. *Cochrane Database Syst Rev* 2014: CD006832.
7. de Beaufort CE, Andre JL, Heimans JJ, *et al.* Peripheral nerve function in children with end-stage renal failure. *Pediatr Nephrol* 1989; 3: 175–178.
8. Evans OB. Polyneuropathy in childhood. *Pediatrics* 1979; 64: 96–105.
9. Elzouki A, Carroll J, Butinar D, *et al.* Improved neurological outcome in children with chronic renal disease from infancy. *Pediatr Nephrol* 1994; 8: 205–210.
10. Mentser MI, Clay S, Malekzadeh MH, *et al.* Peripheral motor nerve conduction velocities in children undergoing chronic hemodialysis. *Nephron* 1978; 22: 337–341.
11. Mendoza-Guevara L, Cervantes A, Aguilar-Kitsu A, *et al.* “H” reflex as a measure of subclinical uremic polyneuropathy in children with chronic renal failure. *Adv Perit Dial* 1997; 13: 285–290.
12. Said G, Boudier L, Selva J, *et al.* Different patterns of uremic polyneuropathy: clinicopathologic study. *Neurology* 1983; 33: 567–574.
13. Krishnan AV and Kiernan MC. Uremic neuropathy: clinical features and new pathophysiological insights. *Muscle Nerve* 2007; 35: 273–290.

14. Trotta D, Verrotti A, Salladini C, *et al.* Diabetic neuropathy in children and adolescents. *Pediatr Diabetes* 2004; 5: 44–57.
15. Bao XH, Wong V, Wang Q, *et al.* Prevalence of peripheral neuropathy with insulin-dependent diabetes mellitus. *Pediatr Neurol* 1999; 20: 204–209.
16. Moser JT, Langdon DR, Finkel RS, *et al.* The evaluation of peripheral neuropathy in youth with type 1 diabetes. *Diabetes Res Clin Pract* 2013; 100: e3–e6.
17. Solders G, Thalme B, Aguirre-Aquino M, *et al.* Nerve conduction and autonomic nerve function in diabetic children. A 10-year follow-up study. *Acta Paediatr* 1997; 86: 361–366.
18. Gallai V, Firenze C, Mazzotta G, *et al.* Neuropathy in children and adolescents with diabetes mellitus. *Acta Neurol Scand* 1988; 78: 136–140.
19. Hasani N, Khosrawi S, Hashemipour M, *et al.* Prevalence and related risk-factors of peripheral neuropathy in children with insulin-dependent diabetes mellitus. *J Res Med Sci* 2013; 18: 132–136.
20. Ghaemi N, Hasanabadi H, Ashrafzadeh F, *et al.* Peripheral neuropathy in children and adolescents with insulin-dependent diabetes mellitus. *Iran J Child Neurol* 2018; 12: 83–90.
21. Moline J and Eng C. Multiple endocrine neoplasia type 2: an overview. *Genet Med* 2011; 13: 755–764.
22. Carney JA, Bianco AJ Jr, Sizemore GW, *et al.* Multiple endocrine neoplasia with skeletal manifestations. *J Bone Joint Surg Am* 1981; 63: 405–410.
23. Dyck PJ, Carney JA, Sizemore GW, *et al.* Multiple endocrine neoplasia, type 2b: phenotype recognition; neurological features and their pathological basis. *Ann Neurol* 1979; 6: 302–314.
24. Mass E, Lapidot M and Gadoth N. Case report: multiple endocrine neoplasia type 2B misdiagnosed as familial dysautonomia. *Eur J Paediatr Dent* 2005; 6: 48–50.
25. Ramos-Levi AM, Diaz-Perez A, Sobrido MJ, *et al.* Axonal neuropathy, long limbs and bumpy tongue: think of MEN2B. *Muscle Nerve* 2012; 46: 961–964.
26. Mimouni-Bloch A, Goldberg-Stern H, Strausberg R, *et al.* Thiamine deficiency in infancy: long-term follow-up. *Pediatr Neurol* 2014; 51: 311–316.
27. Oguz SS, Ergenekon E, Tumer L, *et al.* A rare case of severe lactic acidosis in a preterm infant: lack of thiamine during total parenteral nutrition. *J Pediatr Endocrinol Metab* 2011; 24: 843–845.
28. Rao SN, Mani S, Madap K, *et al.* High prevalence of infantile encephalitic beriberi with overlapping features of Leigh's disease. *J Tropical Pediatr* 2008; 54: 328–332.
29. Ortigoza-Escobar JD, Alfadhel M, Molero-Luis M, *et al.* Thiamine deficiency in childhood with attention to genetic causes: survival and outcome predictors. *Ann Neurol* 2017; 82: 317–330.
30. Ishibashi S, Yokota T, Shiojiri T, *et al.* Reversible acute axonal polyneuropathy associated with Wernicke-Korsakoff syndrome: impaired physiological nerve conduction due to thiamine deficiency? *J Neurol Neurosurg Psychiatry* 2003; 74: 674–676.
31. Koike H, Iijima M, Sugiura M, *et al.* Alcoholic neuropathy is clinicopathologically distinct from thiamine-deficiency neuropathy. *Ann Neurol* 2003; 54: 19–29.
32. Balasubramaniam S, Christodoulou J and Rahman S. Disorders of riboflavin metabolism. *J Inherit Metab Dis* 2019; 42: 608–619.
33. Bosch AM, Stroek K, Abeling NG, *et al.* The Brown-Vialletto-Van Laere and Fazio Londe syndrome revisited: natural history, genetics, treatment and future perspectives. *Orphanet J Rare Dis* 2012; 7: 83.
34. O'Callaghan B, Bosch AM and Houlden H. An update on the genetics, clinical presentation, and pathomechanisms of human riboflavin transporter deficiency. *J Inherit Metab Dis* 2019; 42: 598–607.
35. Chaya S, Zampoli M, Gray D, *et al.* The first case of riboflavin transporter deficiency in sub-Saharan Africa. *Semin Pediatr Neurol* 2018; 26: 10–14.
36. Shetty NS and Shah I. Isoniazid-induced neuropathy in a pre-pubertal child. *Paediatr Int Child Health* 2018: 1–3.
37. Baxter P. Pyridoxine-dependent and pyridoxine-responsive seizures. *Dev Med Child Neurol* 2001; 43: 416–420.
38. Hamel J and Logigian EL. Acute nutritional axonal neuropathy. *Muscle Nerve* 2018; 57: 33–39.
39. Vrolijk MF, Opperhuizen A, Jansen EHJM, *et al.* The vitamin B<sub>6</sub> paradox: supplementation with high concentrations of pyridoxine leads to decreased vitamin B<sub>6</sub> function. *Toxicol In Vitro* 2017; 44: 206–212.

40. Ghavanini AA and Kimpinski K. Revisiting the evidence for neuropathy caused by pyridoxine deficiency and excess. *J Clin Neuromuscul Dis* 2014; 16: 25–31.
41. MacLean WC Jr and Graham GG. Vegetarianism in children. *Am J Dis Child* 1980; 134: 513–519.
42. Kalita J, Chandra S, Bhoi SK, *et al.* Clinical, nerve conduction and nerve biopsy study in vitamin B<sub>12</sub> deficiency neurological syndrome with a short-term follow-up. *Nutr Neurosci* 2014; 17: 156–163.
43. Muller DP. Vitamin E and neurological function. *Mol Nutr Food Res* 2010; 54: 710–718.
44. Di Donato I, Bianchi S and Federico A. Ataxia with vitamin E deficiency: update of molecular diagnosis. *Neurol Sci* 2010; 31: 511–515.
45. Jackson CE, Amato AA and Barohn RJ. Isolated vitamin E deficiency. *Muscle Nerve* 1996; 19: 1161–1165.
46. Muller DP and Goss-Sampson MA. Neurochemical, neurophysiological, and neuropathological studies in vitamin E deficiency. *Crit Rev Neurobiol* 1990; 5: 239–263.
47. El Euch-Fayache G, Bouhlal Y, Amouri R, *et al.* Molecular, clinical and peripheral neuropathy study of Tunisian patients with ataxia with vitamin E deficiency. *Brain* 2014; 137: 402–410.
48. Harding AE, Muller DP, Thomas PK, *et al.* Spinocerebellar degeneration secondary to chronic intestinal malabsorption: a vitamin E deficiency syndrome. *Ann Neurol* 1982; 12: 419–424.
49. Puri V, Chaudhry N, Tatke M, *et al.* Isolated vitamin E deficiency with demyelinating neuropathy. *Muscle Nerve* 2005; 32: 230–235.
50. Hughes RA, Britton T and Richards M. Effects of lymphoma on the peripheral nervous system. *J Royal Soc Med* 1994; 87: 526–530.
51. McLeod JG and Walsh JC. Peripheral neuropathy associated with lymphomas and other reticulososes. In: Dyck PJ, Thomas PK, Lambert EH, *et al.* (eds) *Peripheral neuropathy*. Philadelphia, PA: Saunders, 1984, pp. 2192–2203.
52. Lieber S, Blankenburg M, Apel K, *et al.* Small-fiber neuropathy and pain sensitization in survivors of pediatric acute lymphoblastic leukemia. *Eur J Paediatr Neurol* 2018; 22: 457–469.
53. Sands S, Ladas EJ, Kelly KM, *et al.* Glutamine for the treatment of vincristine-induced neuropathy in children and adolescents with cancer. *Support Care Cancer* 2017; 25: 701–708.
54. Kurczynski TW, Choudhury AA, Horwitz SJ, *et al.* Remote effect of malignancy on the nervous system in children. *Dev Med Child Neurol* 1980; 22: 205–222.
55. Rowland LP and Schneck SA. Neuromuscular disorders associated with malignant neoplastic disease. *J Chronic Dis* 1963; 16: 777–795.
56. Chandar R, Seetharam S, Gopakumar KG, *et al.* Paraneoplastic demyelinating sensorimotor neuropathy delaying the diagnosis of an underlying acute lymphoblastic leukemia in a child. *J Oncol Pract* 2018; 14: 629–631.
57. Bahl A, Chakrabarty B, Gulati S, *et al.* Acute onset flaccid quadriplegia in pediatric non-Hodgkin lymphoma: vincristine induced or Guillain-Barre syndrome? *Pediatr Blood Cancer* 2010; 55: 1234–1235.
58. Vallat JM, De Mascarel HA, Bordessoule D, *et al.* Non-Hodgkin malignant lymphomas and peripheral neuropathies—3 cases. *Brain* 1995; 118 (Pt 5): 1233–1245.
59. Bulsara KR, Baron PW, Tuttle-Newhall JE, *et al.* Guillain-Barre syndrome in organ and bone marrow transplant patients. *Transplantation* 2001; 71: 1169–1172.
60. Wen PY, Alyea EP, Simon D, *et al.* Guillain-Barre syndrome following allogeneic bone marrow transplantation. *Neurology* 1997; 49: 1711–1714.
61. Rabinstein AA and Wijidicks EF. Weaning from the ventilator using BiPAP in myasthenia gravis. *Muscle Nerve* 2003; 27: 252–253.
62. Rodriguez V, Kuehnle I, Heslop HE, *et al.* Guillain-Barre syndrome after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2002; 29: 515–517.
63. Ostronoff F, Perales MA, Stubblefield MD, *et al.* Rituximab-responsive Guillain-Barre syndrome following allogeneic hematopoietic SCT. *Bone Marrow Transplant* 2008; 42: 71–72.
64. Adams C, August CS, Maguire H, *et al.* Neuromuscular complications of bone marrow transplantation. *Pediatr Neurol* 1995; 12: 58–61.
65. Antoine JC and Camdessanche JP. Peripheral nervous system involvement in patients with cancer. *Lancet Neurol* 2007; 6: 75–86.
66. Cheuk DK, Chiang AK, Ha SY, *et al.* Malignancies in Chinese patients with neurofibromatosis type 1. *Hong Kong Med J* 2013; 19: 42–49.

67. Schulz A, Grafe P, Hagel C, *et al.* Neuropathies in the setting of neurofibromatosis tumor syndromes: complexities and opportunities. *Exp Neurol* 2018; 299: 334–344.
68. Park SJ, Sawitzki B, Kluwe L, *et al.* Serum biomarkers for neurofibromatosis type 1 and early detection of malignant peripheral nerve-sheath tumors. *BMC Med* 2013; 11: 109.
69. Imbus CE, Warner J, Smith E, *et al.* Peripheral neuropathy in lead-intoxicated sickle cell patients. *Muscle Nerve* 1978; 1: 168–171.
70. Kaymak B, Bilginer Y, Ozcakar L, *et al.* Effect of wrist involvement on median nerve electrophysiology in juvenile idiopathic arthritis. *Acta Reumatol Port* 2009; 34: 614–617.
71. Filatova ES and Erdes SF. Etiopathogenetic factors of peripheral neuropathic pain in rheumatoid arthritis. *Zh Nevrol Psikhiatr Im S S Korsakova* 2017; 117: 67–71.
72. Omdal R, Loseth S, Torbergesen T, *et al.* Peripheral neuropathy in systemic lupus erythematosus—a longitudinal study. *Acta Neurol Scand* 2001; 103: 386–391.
73. Jasmin R, Sockalingam S, Ramanaidu LP, *et al.* Clinical and electrophysiological characteristics of symmetric polyneuropathy in a cohort of systemic lupus erythematosus patients. *Lupus* 2015; 24: 248–255.
74. Goransson LG, Tjensvoll AB, Herigstad A, *et al.* Small-diameter nerve fiber neuropathy in systemic lupus erythematosus. *Arch Neurol* 2006; 63: 401–404.
75. McCombe PA, McLeod JG, Pollard JD, *et al.* Peripheral sensorimotor and autonomic neuropathy associated with systemic lupus erythematosus. Clinical, pathological and immunological features. *Brain* 1987; 110(Pt 2): 533–549.
76. Levy Y, Uziel Y, Zandman GG, *et al.* Intravenous immunoglobulins in peripheral neuropathy associated with vasculitis. *Ann Rheum Dis* 2003; 62: 1221–1223.
77. Roper EC, Gibson A, McAlindon ME, *et al.* Familial visceral neuropathy: a defined entity? *Am J Med Genet A* 2005; 137A: 249–254.
78. Chaoui A, Watanabe Y, Touraine R, *et al.* Identification and functional analysis of SOX10 missense mutations in different subtypes of Waardenburg syndrome. *Hum Mutat* 2011; 32: 1436–1449.
79. Falah N, Posey JE, Thorson W, *et al.* 22q11.2q13 duplication including SOX10 causes sex-reversal and peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome, and Hirschsprung disease. *Am J Med Genet A* 2017; 173: 1066–1070.
80. Inoue K, Shilo K, Boerkoel CF, *et al.* Congenital hypomyelinating neuropathy, central dysmyelination, and Waardenburg-Hirschsprung disease: phenotypes linked by SOX10 mutation. *Ann Neurol* 2002; 52: 836–842.
81. Mahmoudi A, Rami M, Khattala K, *et al.* Shah-Waardenburg syndrome. *Pan Afr Med J* 2013; 14: 60.
82. Parthey K, Kornhuber M, Kunze C, *et al.* SOX10 mutation with peripheral amyelination and developmental disturbance of axons. *Muscle Nerve* 2012; 45: 284–290.
83. Shimotake T, Tanaka S, Fukui R, *et al.* Neuroglial disorders of central and peripheral nervous systems in a patient with Hirschsprung's disease carrying allelic SOX10 truncating mutation. *J Pediatr Surg* 2007; 42: 725–731.
84. Unzicker A, Pingault V, Meyer T, *et al.* A novel SOX10 mutation in a patient with PCWH who developed hypoxic-ischemic encephalopathy after E. coli sepsis. *Eur J Ped* 2011; 170: 1475–1480.
85. Verheij JB, Sival DA, van der Hoeven JH, *et al.* Shah-Waardenburg syndrome and PCWH associated with SOX10 mutations: a case report and review of the literature. *Eur J Paediatr Neurol* 2006; 10: 11–17.
86. Lionetti E, Francavilla R, Pavone P, *et al.* The neurology of coeliac disease in childhood: what is the evidence? A systematic review and meta-analysis. *Dev Med Child Neurol* 2010; 52: 700–707.
87. Cakir D, Tosun A, Polat M, *et al.* Subclinical neurological abnormalities in children with celiac disease receiving a gluten-free diet. *J Pediatr Gastroenterol Nutr* 2007; 45: 366–369.
88. Ruggieri M, Incorpora G, Polizzi A, *et al.* Low prevalence of neurologic and psychiatric manifestations in children with gluten sensitivity. *J Pediatr* 2008; 152: 244–249.
89. Simonati A, Battistella PA, Guariso G, *et al.* Coeliac disease associated with peripheral neuropathy in a child: a case report. *Neuropediatrics* 1998; 29: 155–158.
90. İşıkay Ş, İşıkay N, Kocamaz H, *et al.* Peripheral neuropathy electrophysiological screening in children with celiac disease. *Arq Gastroenterol* 2015; 52: 134–138.


91. Thawani SP, Brannagan TH, Lebowitz B, *et al.* Risk of neuropathy among 28,232 patients with biopsy-verified celiac disease. *JAMA Neurol* 2015; 72: 806–811.
92. Wurzel DF, Steinfert DP, Massie J, *et al.* Paralysis and a perihilar protuberance: an unusual presentation of sarcoidosis in a child. *Pediatr Pulmonol* 2009; 44: 410–414.
93. Sharma OP. Neurosarcoidosis: a personal perspective based on the study of 37 patients. *Chest* 1997; 112: 220–228.
94. Matthews WB. Sarcoid neuropathy. In: Dyck PJ, Thomas PK, Lambert EH, *et al.* (eds) *Peripheral neuropathy*, Vol. 2. Philadelphia, PA: Saunders, 1984, pp. 2018–2026.
95. Nemni R, Galassi G, Cohen M, *et al.* Symmetric sarcoid polyneuropathy: analysis of a sural nerve biopsy. *Neurology* 1981; 31: 1217–1223.
96. Rao R, Dimitriadis VR, Weimer M, *et al.* Neurosarcoidosis in pediatric patients: a case report and review of isolated and systemic neurosarcoidosis. *Pediatr Neurol* 2016; 63: 45–52.
97. Williams S, Horrocks IA, Ouvrier RA, *et al.* Critical illness polyneuropathy and myopathy in pediatric intensive care: a review. *Pediatr Crit Care Med* 2007; 8: 18–22.
98. Banwell BL, Mildner RJ, Hassall AC, *et al.* Muscle weakness in critically ill children. *Neurology* 2003; 61: 1779–1782.
99. Tamam Y, Tamam C, Tamam B, *et al.* Peripheral neuropathy after burn injury. *Eur Rev Med Pharmacol Sci* 2013; 17(Suppl. 1): 107–111.
100. McGonigle RJ, Bewick M, Weston MJ, *et al.* Progressive, predominantly motor, uraemic neuropathy. *Acta Neurol Scand* 1985; 71: 379–384.
101. Nemni R, Bottacchi E, Fazio R, *et al.* Polyneuropathy in hypothyroidism: clinical, electrophysiological and morphological findings in four cases. *J Neurol Neurosurg Psychiatry* 1987; 50: 1454–1460.
102. Mohseni S. Hypoglycemic neuropathy. *Acta Neuropathol* 2001; 102: 413–421.
103. Ouvrier RA and Shield L. Focal lesions in peripheral nerves. In: Ouvrier RA, McLeod JG and Pollard J (eds) *Peripheral neuropathy in childhood*. 2nd ed. London: Mac Keith Press, 1999, pp. 244–264.
104. Ising E, Dahlin LB and Elding Larsson H. Impaired vibrotactile sense in children and adolescents with type 1 diabetes - signs of peripheral neuropathy. *PLoS One* 2018; 13: e0196243.
105. Verrotti A, Chiarelli F, Blasetti A, *et al.* Autonomic neuropathy in diabetic children. *J Paediatr Child Health* 1995; 31: 545–548.
106. Donaghue KC, Fung AT, Fairchild JM, *et al.* Prospective assessment of autonomic and peripheral nerve function in adolescents with diabetes. *Diabet Med* 1996; 13: 65–71.
107. Karsidag S, Morali S, Sargin M, *et al.* The electrophysiological findings of subclinical neuropathy in patients with recently diagnosed type 1 diabetes mellitus. *Diabetes Res Clin Pract* 2005; 67: 211–219.
108. Meh D and Denislic M. Subclinical neuropathy in type I diabetic children. *Electroencephalogr Clin Neurophysiol* 1998; 109: 274–280.
109. Holiner I, Haslinger V, Lutschg J, *et al.* Validity of the neurological examination in diagnosing diabetic peripheral neuropathy. *Pediatr Neurol* 2013; 49: 171–177.
110. Javed S, Petropoulos IN, Alam U, *et al.* Treatment of painful diabetic neuropathy. *Ther Adv Chronic Dis* 2015; 6: 15–28.
111. Hotta N, Akanuma Y, Kawamori R, *et al.* Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy: the 3-year, multicenter, comparative aldose reductase inhibitor-diabetes complications trial. *Diabetes Care* 2006; 29: 1538–1544.
112. Stracke H, Gaus W, Achenbach U, *et al.* Benfotiamine in diabetic polyneuropathy (BENDIP): results of a randomised, double blind, placebo-controlled clinical study. *Exp Clin Endocrinol Diabetes* 2008; 116: 600–605.
113. Cotter MA, Ekberg K, Wahren J, *et al.* Effects of proinsulin C-peptide in experimental diabetic neuropathy: vascular actions and modulation by nitric oxide synthase inhibition. *Diabetes* 2003; 52: 1812–1817.
114. Spallone V. Management of painful diabetic neuropathy: guideline guidance or jungle? *Curr Diab Rep* 2012; 12: 403–413.
115. Nakao KT, Usui T, Ikeda M, *et al.* Novel tandem germline RET proto-oncogene mutations in a patient with multiple endocrine neoplasia type 2B: report of a case and a literature review of tandem RET mutations with in silico analysis. *Head Neck* 2013; 35: E363–E368.
116. Han JW, Lim S, Shin HS, *et al.* Two cases of Wernicke's encephalopathy in young age patients receiving allogeneic hematopoietic stem cell transplantation. *Yonsei Med J* 2012; 53: 1049–1053.

117. Masumoto K, Esumi G, Teshiba R, *et al.* Need for thiamine in peripheral parenteral nutrition after abdominal surgery in children. *JPEN J Parenter Enteral Nutr* 2009; 33: 417–422.
118. Salloum S, Goenka A and Mezoff A. Beriberi disease in an 11-year-old girl with total colectomy. *Oxf Med Case Reports* 2018; 2018: omy091.
119. Adamolekun B and Hiffler L. A diagnosis and treatment gap for thiamine deficiency disorders in Sub-Saharan Africa? *Ann N Y Acad Sci* 2017; 1408: 15–19.
120. Johnson JO, Gibbs JR, Megarbane A, *et al.* Exome sequencing reveals riboflavin transporter mutations as a cause of motor neuron disease. *Brain* 2012; 135: 2875–2882.
121. Ciccolella M, Corti S, Catteruccia M, *et al.* Riboflavin transporter 3 involvement in infantile Brown-Vialetto-Van Laere disease: two novel mutations. *J Med Genet* 2013; 50: 104–107.
122. Green P, Wiseman M, Crow YJ, *et al.* Brown-Vialetto-Van Laere syndrome, a ponto-bulbar palsy with deafness, is caused by mutations in c20orf54. *Am J Hum Genet* 2010; 86: 485–489.
123. Bosch AM, Abeling NG, Ijlst L, *et al.* Brown-Vialetto-Van Laere and Fazio Londe syndrome is associated with a riboflavin transporter defect mimicking mild MADD: a new inborn error of metabolism with potential treatment. *J Inherit Metab Dis* 2011; 34: 159–164.
124. Nimmo GAM, Ejaz R, Cordeiro D, *et al.* Riboflavin transporter deficiency mimicking mitochondrial myopathy caused by complex II deficiency. *Am J Med Genet A* 2018; 176: 399–403.
125. Manole A, Jaunmuktane Z, Hargreaves I, *et al.* Clinical, pathological and functional characterization of riboflavin-responsive neuropathy. *Brain* 2017; 140: 2820–2837.
126. Bacharach R, Lowden M and Ahmed A. Pyridoxine toxicity small fiber neuropathy with dysautonomia: a case report. *J Clin Neuromuscul Dis* 2017; 19: 43–46.
127. Stop TB Partnership Childhood TB Subgroup World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Chapter 1: introduction and diagnosis of tuberculosis in children. *Int J Tuberc Lung Dis* 2006; 10: 1091–1097.
128. Malek E, Doumiati H and Salameh JS. Pyridoxine-induced sensory ataxic ganglionopathy: a case report and literature review. *Acta Neurol Belg.* Epub ahead of print 28 April 2018. DOI: 10.1007/s13760-018-0919-7.
129. Echaniz-Laguna A, Mourot-Cottet R, Noel E, *et al.* Regressive pyridoxine-induced sensory neuropathy in a patient with homocystinuria. *BMJ Case Rep* 2018; 2018. DOI: 10.1136/bcr-2018-225059.
130. Conway SP, Gillies DR and Littlewood JM. Vitamin B<sub>12</sub> neuropathy in a 6 year old. *Arch Dis Child* 1984; 59: 575–576.
131. van Loon M, Postels DG, Heikens GT, *et al.* Severe pernicious anaemia in an 8-year-old African girl. *Ann Trop Paediatr* 2009; 29: 231–234.
132. Grattan-Smith PJ, Wilcken B, Procopis PG, *et al.* The neurological syndrome of infantile cobalamin deficiency: developmental regression and involuntary movements. *Mov Disord* 1997; 12: 39–46.
133. Dobrozi S, Flood VH, Panepinto J, *et al.* Vitamin B<sub>12</sub> deficiency: the great masquerader. *Pediatr Blood Cancer* 2014; 61: 753–755.
134. Chakrabarty B, Kabra SK, Gulati S, *et al.* Peripheral neuropathy in cystic fibrosis: a prevalence study. *J Cyst Fibros* 2013; 12: 754–760.
135. Ueda N, Suzuki Y, Rino Y, *et al.* Correlation between neurological dysfunction with vitamin E deficiency and gastrectomy. *J Neurol Sci* 2009; 287: 216–220.
136. Kalra V, Grover JK, Ahuja GK, *et al.* Vitamin E administration and reversal of neurological deficits in protein-energy malnutrition. *J Trop Pediatr* 2001; 47: 39–45.
137. Hentati F, El-Euch G, Bouhhal Y, *et al.* Ataxia with vitamin E deficiency and abetalipoproteinemia. *Handb Clin Neurol* 2012; 103: 295–305.
138. Hooper AJ and Burnett JR. Update on primary hypobetalipoproteinemia. *Curr Atheroscler Rep* 2014; 16: 423.
139. Lee J and Hegele RA. Abetalipoproteinemia and homozygous hypobetalipoproteinemia: a framework for diagnosis and management. *J Inherit Metab Dis* 2014; 37: 333–339.
140. Fusco C, Frattini D, Pisani F, *et al.* Isolated vitamin E deficiency mimicking distal hereditary motor neuropathy in a 13-year-old boy. *J Child Neurol* 2008; 23: 1328–1330.
141. Hentati A, Deng HX, Hung WY, *et al.* Human alpha-tocopherol transfer protein: gene structure and mutations in familial vitamin E deficiency. *Ann Neurol* 1996; 39: 295–300.
142. Antoine JC and Camdessanche JP. Treatment options in paraneoplastic disorders of the

- peripheral nervous system. *Curr Treat Options Neurol* 2013; 15: 210–223.
143. Bjornard KL, Gilchrist LS, Inaba H, *et al.* Peripheral neuropathy in children and adolescents treated for cancer. *Lancet Child Adolesc Health* 2018; 2: 744–754.
  144. Lowitzsch K, Gutjahr P and Ottens H. Clinical and neurophysiological findings in 47 long-term survivors of childhood malignancies treated with various doses of vincristine. In: Canal N and Pozza PG (eds) *Peripheral neuropathies*. Amsterdam: Elsevier, 1978, pp. 459–466.
  145. Abaji R, Ceppi F, Patel S, *et al.* Genetic risk factors for VIPN in childhood acute lymphoblastic leukemia patients identified using whole-exome sequencing. *Pharmacogenomics* 2018; 19: 1181–1193.
  146. Brigo F, Balter R, Marradi P, *et al.* Vincristine-related neuropathy versus acute inflammatory demyelinating polyradiculoneuropathy in children with acute lymphoblastic leukemia. *J Child Neurol* 2012; 27: 867–874.
  147. Apjok E, Marosi A and Magyarosy E. Guillain-Barre syndrome in patients treated for Hodgkin disease. *Orv Hetil* 2003; 144: 1039–1040.
  148. Dalmau J, Graus F, Rosenblum MK, *et al.* Anti-Hu-associated paraneoplastic encephalomyelitis/sensory neuronopathy. A clinical study of 71 patients. *Medicine* 1992; 71: 59–72.
  149. Honnorat J, Didelot A, Karantoni E, *et al.* Autoimmune limbic encephalopathy and anti-Hu antibodies in children without cancer. *Neurology* 2013; 80: 2226–2232.
  150. Lavoratore SR, Navarro OM, Grunebaum E, *et al.* Cyclosporine-induced pain syndrome in a child undergoing hematopoietic stem cell transplant. *Ann Pharmacother* 2009; 43: 767–771.
  151. Onozawa M, Hashino S, Haseyama Y, *et al.* Incidence and risk of postherpetic neuralgia after varicella zoster virus infection in hematopoietic cell transplantation recipients: Hokkaido hematology study group. *Biol Blood Marrow Transplant* 2009; 15: 724–729.
  152. Yang CS, Kim C and Antaya RJ. Review of thalidomide use in the pediatric population. *J Am Acad Dermatol* 2015; 72: 703–711.
  153. Gutmann DH, Ferner RE, Listernick RH, *et al.* Neurofibromatosis type 1. *Nat Rev Dis Primers* 2017; 3: 17004.
  154. Telleman JA, Stellingwerff MD, Brekelmans GJ, *et al.* Nerve ultrasound in neurofibromatosis type 1: a follow-up study. *Clin Neurophysiol* 2017; 129: 354–359.
  155. Farschtschi S, Gelderblom M, Buschbaum S, *et al.* Muscle action potential scans and ultrasound imaging in neurofibromatosis type 2. *Muscle Nerve* 2017; 55: 350–358.
  156. Shetty GM, Murari AS, Song HR, *et al.* Neurofibromatous sensory neuropathy of the thigh in a 7-year-old boy. *Arch Orthop Trauma Surg* 2008; 128: 1093–1097.
  157. Pedro MT, Antoniadis G, Scheuerle A, *et al.* Intraoperative high-resolution ultrasound and contrast-enhanced ultrasound of peripheral nerve tumors and tumorlike lesions. *Neurosurg Focus* 2015; 39: E5.
  158. Reilly KM, Kim A, Blakely J, *et al.* Neurofibromatosis type 1-associated MPNST state of the science: outlining a research agenda for the future. *J Natl Cancer Inst* 2017; 109.
  159. Kehinde MO, Temiye EO and Danesi MA. Neurological complications of sickle cell anemia in Nigerian Africans—a case-control study. *J Natl Med Assoc* 2008; 100: 394–399.
  160. Unal O, Ozcakar L, Cetin A, *et al.* Severe bilateral carpal tunnel syndrome in juvenile chronic arthritis. *Pediatr Neurol* 2003; 29: 345–348.
  161. De Smet L and Wouters C. Severe carpal tunnel syndrome in a patient with juvenile idiopathic arthritis due to proximal migration of hypertrophic lumbrical muscles. *Clin Rheumatol* 2004; 23: 552–554.
  162. Puusa A, Lang HA and Makela AL. Nerve conduction velocity in juvenile rheumatoid arthritis. *Acta Neurol Scand* 1986; 73: 145–150.
  163. An Y, Liu T, He D, *et al.* The usage of biological DMARDs and clinical remission of rheumatoid arthritis in China: a real-world large scale study. *Clin Rheumatol* 2017; 36: 35–43.
  164. Bhowmik A and Banerjee P. Mononeuritis multiplex complicating systemic lupus erythematosus. *Indian Pediatr* 2012; 49: 581–582.
  165. Harel L, Mukamel M, Brik R, *et al.* Peripheral neuropathy in pediatric systemic lupus erythematosus. *Pediatr Neurol* 2002; 27: 53–56.
  166. Loh WF, Hussain IM, Soffiah A, *et al.* Neurological manifestations of children with systemic lupus erythematosus. *Med J Malaysia* 2000; 55: 459–463.
  167. Ryan M. Peripheral neuropathy in pediatric systemic lupus erythematosus. *Pediatr Neurol* 2003; 28: 236.

168. Steinlin MI, Blaser SI, Gilday DL, *et al.* Neurologic manifestations of pediatric systemic lupus erythematosus. *Pediatric Neurol* 1995; 13: 191–197.
169. Sibbitt WL Jr, Brandt JR, Johnson CR, *et al.* The incidence and prevalence of neuropsychiatric syndromes in pediatric onset systemic lupus erythematosus. *J Rheumatol* 2002; 29: 1536–1542.
170. Sridhar AV, Gosalakal J, Pye IF, *et al.* Peripheral neuropathy—a rare complication of paediatric systemic lupus erythematosus. *Eur J Paediatr Neurol* 2004; 8: 253–256.
171. Seaman DE, Londino AV Jr, Kwok CK, *et al.* Antiphospholipid antibodies in pediatric systemic lupus erythematosus. *Pediatrics* 1995; 96: 1040–1050.
172. Scheinberg L. Polyneuritis in systemic lupus erythematosus; review of the literature and report of a case. *N Engl J Med* 1956; 255: 416–421.
173. Bodi I, Varadi P, Pokorny G, *et al.* Polyneuropathy with endoneurial immune complex deposition as the first manifestation of systemic lupus erythematosus. *Acta Neuropathologica* 1998; 96: 297–300.
174. Guillevin L, Cohen P, Gayraud M, *et al.* Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine* 1999; 78: 26–37.
175. Ford FR. *Diseases of the nervous system in infancy, childhood and adolescence*. Springfield, IL: Charles C Thomas, 1966, pp. 825–829.
176. Draaisma JM, Fiselier TJ and Mullaart RA. Mononeuritis multiplex in a child with cutaneous polyarteritis. *Neuropediatrics* 1992; 23: 28–29.
177. Wang SJ, Yang YH, Lin YT, *et al.* Childhood Churg-Strauss syndrome: report of a case. *J Microbiol Immunol Infect* 2000; 33: 263–266.
178. Penas PF, Porras JI, Fraga J, *et al.* Microscopic polyangiitis. A systemic vasculitis with a positive P-ANCA. *Br J Dermatol* 1996; 134: 542–547.
179. Ryan MM, Tilton A, De Girolami U, *et al.* Paediatric mononeuritis multiplex: a report of three cases and review of the literature. *Neuromuscul Disord* 2003; 13: 751–756.
180. Andrade R, Moya Machado A, Gomez Conde S, *et al.* Neuropathies due to vasculitis in infancy. *Rev Neurol* 2004; 38: 619–624.
181. Kumon K, Satake A, Mizumot M, *et al.* A case of sensory neuropathy associated with childhood Sjogren syndrome. *Eur J Pediatr* 2000; 159: 630–631.
182. Mondal R, Sarkar S, Pal P, *et al.* Childhood Polyarteritis Nodosa: a prospective multicentre study from eastern India. *Indian J Pediatr* 2014; 81: 371–374.
183. Valor L, Monteagudo I, de la Torre I, *et al.* Young male patient diagnosed with cutaneous polyarteritis nodosa successfully treated with etanercept. *Mod Rheumatol* 2014; 24: 688–689.
184. Jing S, Yang C, Zhang X, *et al.* Efficacy and safety of etanercept in the treatment of sciatica: a systematic review and meta-analysis. *J Clin Neurosci* 2017; 44: 69–74.
185. Kapur RP. Neuronal dysplasia: a controversial pathological correlate of intestinal pseudo-obstruction. *Am J Med Genetics A* 2003; 122A: 287–293.
186. Garcia Aroca J, Sanz N, Alonso JL, *et al.* Intestinal pseudo-obstruction secondary to systemic neuropathies and myopathies. *Cir Pediatr* 1994; 7: 115–120.
187. Byrne WJ, Cipel L, Euler AR, *et al.* Chronic idiopathic intestinal pseudo-obstruction syndrome in children—clinical characteristics and prognosis. *J Pediatr* 1977; 90: 585–589.
188. Arrindell EL, Trobe JD, Sieving PA, *et al.* Pupillary and electroretinographic abnormalities in a family with neuronal intranuclear hyaline inclusion disease. *Arch Ophthalmol* 1991; 109: 373–378.
189. Barnett JL, McDonnell WM, Appelman HD, *et al.* Familial visceral neuropathy with neuronal intranuclear inclusions: diagnosis by rectal biopsy. *Gastroenterology* 1992; 102: 684–691.
190. Faber J, Fich A, Steinberg A, *et al.* Familial intestinal pseudoobstruction dominated by a progressive neurologic disease at a young age. *Gastroenterology* 1987; 92: 786–790.
191. Luigetti M, Sauchelli D, Primiano G, *et al.* Peripheral neuropathy is a common manifestation of mitochondrial diseases: a single-centre experience. *Eur J Neurol* 2016; 23: 1020–1027.
192. Garone C, Tadesse S and Hirano M. Clinical and genetic spectrum of mitochondrial neurogastrointestinal encephalomyopathy. *Brain* 2011; 134: 3326–3332.
193. Libernini L, Lupis C, Mastrangelo M, *et al.* Mitochondrial neurogastrointestinal encephalomyopathy: novel pathogenic mutations in thymidine phosphorylase gene in two Italian brothers. *Neuropediatrics* 2012; 43: 201–208.

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194. Halter JP, Michael W, Schüpbach M, *et al.* Allogeneic haematopoietic stem cell transplantation for mitochondrial neurogastrointestinal encephalomyopathy. *Brain* 2015; 138: 2847–2858.
195. Gupta V and Kohli A. Celiac disease associated with recurrent Guillain Barre syndrome. *Indian Pediatr* 2010; 47: 797–798.
196. Pacitto A, Paglino A, Di Genova L, *et al.* Celiac disease presenting with peripheral neuropathy in children: a case report. *Int J Environ Res Public Health* 2017; 14: 785.
197. Le Luyer B, Devaux AM, Dailly R, *et al.* Polyradiculoneuritis as a manifestation of childhood sarcoidosis. *Arch Fr Pediatr* 1983; 40: 175–178.