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# On the differential diagnosis of neuropathy in neurogenetic disorders

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**Abstract:** Neuropathy might be the presenting or accompanying sign in many neurogenetic and metabolic disorders apart from the classical-peripheral neuropathies or motor-neuron diseases. This causes a diagnostic challenge which is of particular relevance since a number of the underlying diseases could be treated. Thus, we attempt to give a clinical overview on the most common genetic diseases with clinically manifesting neuropathy.

**Keywords:** neuropathy, neurogenetic diseases, metabolic diseases, motor-neuron diseases

## Introduction

The hereditary peripheral neuropathies have been classified based upon clinical characteristics, mode of inheritance, electrophysiological features, metabolic defects, and specific genetic loci. The primary hereditary neuropathies predominantly affect peripheral nerves and produce symptoms of peripheral nerve dysfunction. Other hereditary neuropathies affect both the central and peripheral nervous systems, and, in some cases, other organs; in such patients, symptoms related to the peripheral neuropathy may be overshadowed by additional manifestations of the disease (Table 1). While polyneuropathy, mostly axonal neuropathy, might be a significant manifestation of an inherited or acquired disease in child-

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hood, it may be neither well recognized nor clinically confirmed. On the other hand, polyneuropathy might be detected by nerve conduction velocity measurements during the clinical work-up, but might misguide the diagnosis towards primary motor-sensory and sensory–autonomic neuropathies. Thus, awareness of additional clinical clues/signs and therapeutic proceedings in pediatric neurology is of utmost importance for clinical genetics of neuromuscular symptoms.

In this context, we would like to emphasize that this field is currently under rapid development due to the availability and diagnostics of genetic disorders based on next-generation sequencing strategies [1–10]. Especially, exome and genome analyses have provided a reverse genetics approach leading to breakthroughs and to the fall of old paradigms in genotype–phenotype correlations.

## Overlap of spinocerebellar ataxias, Friedreich ataxia, amyotrophic lateral sclerosis, and spastic paraplegias with polyneuropathies

The spinocerebellar ataxias (SCA) are a heterogeneous group of inherited disorders with different neuropathological profiles reflecting the degree of cerebellar and brainstem dysfunction or degeneration. A peripheral neuropathy is described in some but not all forms so far. Peripheral neuropathy has been best characterized in SCA4, in which a prominent axonal neuropathy is present [11]. A mild peripheral neuropathy with decreased deep tendon reflexes and reduced vibration sense has been described in SCA1, SCA2, SCA3, and SCA6 but may also be observed in other forms of SCA [12]. Overall, many forms of hereditary spastic paraplegia (HSP), amyotrophic lateral sclerosis (ALS), motor neuron diseases (hereditary motor neuropathies), and Charcot-Marie-Tooth (CMT) disease seem to be allelic diseases presenting with specific phenotypes depending on the mutation or genetic background [13], thus it would not be surprising to observe a neuropathy in a patient with ALS.

**Friedreich ataxia (FRDA) (#229300)** is an autosomal-recessive hereditary ataxia with a frequency of 4–50 per

**Table 1:** Chronic predominantly demyelinating (low NCV) and predominantly axonal (normal NCV) diseases.

Name	Neuro-pathy*	Manifesting age	NCV demyelinating	Clinical Clues/Symptoms	OMIM	Gene Name (Gene symbol, *OMIM Number)	Inheritance pattern	Treatment
<b>Predominantly demyelinating (low NCV)</b>								
Refsum disease	P	late childhood to adulthood	Yes	ataxia, ichthyosis, cardiomyopathy, serum phytanic acid and CSF protein high	#266500	phytanoyl-CoA hydroxylase (PHYH, *602026)	AR	phytanic acid reduced diet
X-ALD/AMN	P	childhood to adulthood	Yes	behavioral problems, mental decline, spasticity, paralysis due to adrenomyeloneuropathy, ACTH and VLCFA high	#300100	ATP-binding cassette (ABCD1, *300371)	X-linked recessive	early bone marrow transplantation
Austin disease/Multiple Sulfatase deficiency	A	congenital or childhood	Yes	mimics mucopolysaccharidosis, leukodystrophie with ichthyosis	#272200	Sulfatase Modifying Factor 1 (SUMF1, *607939)	AR	NA
Mannosidosis	A	childhood	Yes	learning difficulties, short stature, hepatosplenomegaly, thick bones, sometimes hearing loss	#248510	Mannosidase Beta (MANBA, *609489) and alpha-mannosidosis MAN2B1 (*609458)	AR	NA
Farber lipogranulomatosis	A	infancy	Yes	hoarseness, irritability, restricted joint movements, nodules joints, lungs, progressive, cerebral infarcts	#228000	N-Acylsphingosine Amidohydrolase 1 (ASAH1, *613468)	AR	NA
Homocysteine remethylation defects (MTHFR, CbIC)	A	infancy	Yes	MTHFR defects, increased homocysteine in urine, secondary microcephaly, seizures, lower motoneuron sign	#277400	Metabolism Of Cobalamin Associated C (MMACHC, *609831), Peroxiredoxin 1 (PRDX1, *176763)	AR	Pyridoxime or Vitamin B12 depending on the mutation and defect
Krabbe disease	A	infancy to childhood	Yes	initially irritability, dyskinesia, regression, spasticity, motor neuron involvement, demyelination in brain-MRI with high T2 signal	#245200	Galactosylceramidase (GALC, *606890)	AR	NA
Metachromatic Leukodystrophy	A	early childhood	Yes	early ataxia, regression of motor skills, later optic atrophy, mixed motoneuron signs	#250100	Arylsulfatase A (ARSA, *607574)	AR	NA

Table 1: (continued)

Name	Neuro-pathy*	Manifesting age	NCV demyelinating	Clinical Clues/Symptoms	OMIM	Gene Name (Gene symbol, *OMIM Number)	Inheritance pattern	Treatment
Mitochondrial neurogastrointestinal encephalopathy (MNGIE)	A	early childhood	Yes	Ptosis, progressive external ophthalmoplegia (PEO), gastrointestinal dysmotility (often pseudoobstruction), cachexia, diffuse leukoencephalopathy, peripheral neuropathy	#603041	Thymidine Phosphorylase (TYMP, *131222), DNA polymerase gamma (POLG, *174763), Ribonucleotide Reductase M2B (RRM2B, *604712)	AR	NA
Tangier disease	A**	childhood to adulthood	Yes	orange mucosa tonsils, hepato-splenomegaly, cataracts	#205400	ATP Binding Cassette Subfamily A Member 1 (ABCA1, *600046)	AR	NA
<b>Predominantly axonal (normal NCV)</b>								
Abetalipoproteinemia	P	childhood	Yes	diarrhea early, later retinitis and late ophthalmoplegia, acanthocytosis, low vitamin E, cerebellar atrophy	#200100	Microsomal Triglyceride Transfer Protein (MTTP, *157147), Apolipoprotein B (APOB, *107730)	AR	Substitution with Vitamin E
Alpha-methylacyl-CoA-racemase deficiency (AMACRD)	P	teenage age to adulthood	Yes	seizures, visual failure, sensorimotor neuropathy, spasticity, migraine, and white matter hyperintensities on brain imaging. Serum pristanic acid and C27 bile acid intermediates are increased	#614307	Alpha-methylacyl-CoA racemase (AMACR*604489)	AR	NA
Congenital Disorder of Glycosylation (CDG) type I	P	congenital	Yes	global delay, fatpads, thrombosis, strabism, cerebellar hypoplasia, abnormal profile of transferrin	#212065	Phospho-mannomutase-2 (PMM2, *601785)	AR	NA
GM2 Gangliosidosis	P**	infancy to childhood	Yes	regression, infantile spasm, cherry-red spot frequent, dysarthria, decrebration, motor neuron involvement	#272750	GM2 Activator (GM2A, *613109)	AR	NA

Table 1: (continued)

Name	Neuro-pathy*	Manifesting age	NCV axonal	Clinical Clues/Symptoms	OMIM	Gene Name (Gene symbol, *OMIM Number)	Inheritance pattern	Treatment
Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase deficiency (LCHAD)	P	childhood to adulthood	Yes	cardiomyopathy, hepatopathy, mild muscle weakness, fatigue, rhabdomyolysis	#609016	<i>Hydroxyacyl-CoA Dehydrogenase Trifunctional Multienzyme Complex Subunit Alpha</i> (HADHA, *600890)	AR	NA
Peroxisomal biogenesis defects	P	congenital to childhood	Yes	seizures, large forehead, hepatomegaly, VLCFA, Phytanic Acid	#614866	<i>Peroxisome Biogenesis Factor 1</i> , (PEX1, *602136) <i>Peroxisome Biogenesis Factor 2</i> , (PEX2, *170993)	AR	NA
Polyglucosan body disease Polyglucosan Body Neuropathy	P	adulthood	Yes	slow progressive cognitive impairment, pyramidal tetraparesis, peripheral neuropathy, and neurogenic bladder. Dyspraxia, ataxia and extrapyramidal signs	#263570	<i>Glycogen Branching Enzyme</i> (GBE1, *607839)	AR	NA
Vitamin E malabsorption due to tocopherol carrier defect / Vitamin E, Familial isolated deficiency of (VED)	P	adulthood	Yes	ataxia, areflexia, loss of proprioception, mimics Friedreich Ataxia	#277460	<i>Alpha Tocopherol Transfer Protein</i> (TTPA, *600415)	AR	NA
Tyrosinemia type I (TYRSN1), Tyrosinemia type II (TYRSN2), Tyrosinemia type III (TYRSN3)	P	adulthood	Yes	attacks	#276700, #276600, #276710	<i>Fumarylacetoacetate Hydrolase</i> (FAH, *613871), <i>Tyrosine Amino transferase</i> (TAT, *613018), <i>4-Hydroxyphenylpyruvate dioxygenase</i> (HPD, *609695)	AR	NA
Cerebrotendinous xantomatosis (CTX)	A	late childhood to adolescence	Yes	Xanthomas in tendons (achilles), mental confusion	#213700	<i>Cytochrome P450 Family 27 Subfamily A Member 1</i> (CYP27A1, *606530)	AR	bile acid substitution

Table 1: (continued)

Name	Neuro-pathy*	Manifesting age	NCV axonal	Clinical Clues/Symptoms	OMIM	Gene Name (Gene symbol, *OMIM Number)	Inheritance pattern	Treatment
Neuroaxonal Dystrophy (Neurodegeneration with brain iron accumulation, NBIA1)	A	early childhood	Yes	regression and dementia, optic atrophy, mixed motoneuron signs, denervation in EMG, cerebellar atrophy. Progressive iron accumulation in the basal ganglia and other regions of the brain, resulting in extrapyramidal movements and dystonia	#256600	<i>Pantothenate kinase 2</i> (PANK2, *606157) and expanding other genes	AR	NA
Gyrate atrophy of choroid and retina, GACR (Ornithine aminotransferase)	A	late	Yes	progressive chorioretinal degeneration, early cataract formation, and type II muscle fiber atrophy	#258870	<i>Ornithine Aminotransferase</i> (OAT, *613349)	AR	NA
P5C synthase	A	late childhood	Yes	cataracts, hypermobile joints, mental retardation		<i>Pyroline-5-carboxylate reductase</i> (PYCR1, *179035)	AR	NA
Porphyria (Acute intermittent, AIP)	A**		Yes	recurrent attacks of abdominal pain, gastrointestinal dysfunction, and neurologic disturbances	#176000	<i>Hydroxymethylbilane synthase</i> (HMBSS, *609806) or <i>porphobilinogen deaminase</i> (PBGD)	AD	NA
Pyroglutamic aciduria, 5-Oxoprolinuria deficiency	A	childhood to adulthood	Yes	variable, learning difficulties, kidney stones, diarrhea	#260005	<i>5-oxoprolinase</i> (OPLAH, *614243), <i>Glutathione synthase</i> (GSS, *601002)	AR, AD	NA
OXPHOS (Neurodevelopmental disorder, mitochondrial, with abnormal movements and lactic acidosis, with or without seizures)	A	congenital to childhood	Dem./ axo.	multisystemic disorder characterized by delayed psychomotor development, intellectual disability, and abnormal motor function, including hypotonia, dystonia, ataxia, and spasticity	#617710, #617171, #256000	<i>Tryptophanyl-Trna Synthetase 2</i> (WARS2, *604733), <i>Deaf1 Transcription Factor</i> , (DEAF1, *602635) <i>Bcs1 Homolog</i> , <i>Ubiquinol-Cytochrome C Reductase Complex Chaperone</i> , (BCS1L, *603647)	AR or mtDNA	NA

Table 1: (continued)

Name	Neuro-pathy*	Manifesting age	NCV axonal	Clinical Clues/Symptoms	OMIM	Gene Name (Gene symbol, *OMIM Number)	Inheritance pattern	Treatment
Serine deficiency syndrome/ phosphoserine aminotransferase deficiency (PSATD)	A	congenital	Yes	characterized biochemically by low plasma and cerebrospinal fluid (CSF) concentrations of serine and glycine and clinically by intractable seizures, secondary microcephaly, spasticity, and psychomotor retardation	#610992	<i>Phosphoserine aminotransferase (PSAT1, *610936)</i>	AR	Serine substitution
Fabry disease	A **	childhood to adulthood	Yes	pain in arms and legs, angiokeratoma corporis diffusum, poor vision, and renal failure	#301500	<i>Alpha-galactosidase (GLA, *300644)</i>	X-linked	NA
Non-ketotic hyperglycinemia/ Glycine encephalopathy (GCE)	A	congenital		neonatal phenotype, presenting in the first few days of life with lethargy, hypotonia, and myoclonic jerks, and progressing to apnea, and often to death. Those who regain spontaneous respiration develop intractable seizures and profound mental retardation	#605899	<i>Aminomethyltransferase (AMT, *238310), Glycine Decarboxylase (GLDC, *238300), Glycine Cleavage System Protein H (GCSH, *238330)</i>	AR	NA

Presenting the Chronic predominantly demyelinating (low NCV) and predominantly axonal (normal NCV) diseases. The information in the table showing for each disease the manifesting age, the NCV being demyelinating (dem.) in the upper part of the table and axonal (axo.) in the lower part of the table. The most typical clinical symptoms for each disease is shown as well accompanied by the OMIM number for the disease (\*) and the Gene (#) with Gene name. Additionally, we noted the known inheritance pattern for the different diseases and if available, the ways of treatment. (NA = Not available)

\* P = presenting neuropathy; A = accompanying neuropathy.

\*\* Involvement of small fibres/autonomic nervous system.

100,000 and is mostly sporadic. It is caused by a homozygous GAA trinucleotide repeat expansion greater than 200 copies (normal, 7–22 copies) in the Frataxin (*FXN*) (\*606829) gene. However, rare small mutations such as missense mutations have also been reported [14–17]. Although the disease has well-defined clinical features, a polyneuropathy might begin before the typical FRDA phenotype occurs. Initial symptoms of some patients, such as gait abnormality, might be firstly attributed to polyneuropathy. The patients typically present after 5 years of age with progressive sensory ataxia of the gait and also dysarthria. Since patients suffer from central spinocerebellar degeneration and peripheral neuropathy with pes cavus, they present a positive Babinski sign and absent deep tendon reflexes (DTR) in the lower limbs; the sensory nerves are more affected than the motor nerves. In a subset of FRDA cases the DTR are conserved [18]. Involvement of the central and peripheral nervous systems and the musculoskeletal, cardiac, and endocrine systems is also observed. Cardiomyopathy is present in the majority of cases but is initially often asymptomatic. Diabetes could also be a clinical feature.

### Ponto-cerebellar hypoplasias (PCH) and diseases with cerebellar atrophy and axonal motor neuropathy

While all PCH types share the common feature of motor developmental delay, the reported phenotypes show a broad range from lethal cases in neonates with polyhydramnios, congenital contractures, respiratory failure, and severe generalized hypotonia, to patients that survive with muscular hypotonia or progressive cerebellar ataxia well into adolescence and beyond [19]. The most severe courses of PCH and earliest onsets are found in PCH1, which is largely associated with generalized hypotonia, motor neuron degeneration, and peripheral neuropathy, and PCH2 is more likely associated with other neuromotor symptoms, e. g., chorea, dystonia, and ataxia.

Both lower and upper neuron atrophy appear in the subtypes PCH1A (#607596), PCH1C (#616081), and PCH1D (#618065), all of which are reported with early lethality (mean age at death 3 months). Patients with PCH1C and *EXOSC8* (\*606019) mutations generally present with severe generalized hypotonia, spasticity, motor neuron degeneration, and hearing and vision impairment during the first six months after birth [20]. Patients with other PCH1 subtypes may already present with an onset of symptoms during the neonatal period and harbor mutations in the genes exosome component 3 (*EXOSC3*, \*606489) [21–23]

and vaccinia-related kinase 1 (*VRK1*, \*602168) [24]. Other PCH types may also be associated with motor neuron involvement, e. g., PCH9 (#615809) with *AMPD2* (\*102771) mutations [25, 26] and PCH10 (#615803) with mutations in the cleavage and polyadenylation factor I subunit 1 gene (*CLP1*, \*608757) [27, 28].

PCH2 is associated with mutations in the tRNA splicing endonuclease 54 gene (*TSEN54*, \*608755). PCH2 may present with a severe early-onset generalized hypotonia, progressive microcephaly, and respiratory and feeding problems. Dyskinetic symptoms such as dystonia and chorea were also reported in mutations in *TSEN54*, and also *EXOSC3* and *AMPD2* [29]. Although cerebellar symptoms may not be present in every case, certain symptoms may serve as guiding points for differential diagnoses such as dyspraxia, nystagmus (*EXOSC3* and *EXOSC9*, \*606180) [30], and cerebellar ataxia (*VRK1*). Patients with mutations in charged multivesicular body protein 1A (*CHMP1A*, \*164010; PCH8 [#614961]) may present with these symptoms and little to no disease progression [31].

We would like to mention the presentation of PCH with lower motor neuron involvement due to mutations in other genes like prune exopolyphosphatase 1 (*PRUNE1*, \*617413) [32], *AGTPBP1*, which encodes cytosolic carboxypeptidase 1 (ATP/GTP-binding protein 1, \*606830) [33], kinesin family member 26B (*KIF26B*, \*614026) [34], RNA-binding motif protein 7 (*RBM7*, \*612413) [35], and solute carrier family 25, member 46 (*SLC25A46*, \*610826) [36]. These patients usually have more severe central nervous system involvement, like microcephaly, severe psychomotor developmental delay, and epilepsy. Of note, they also have spinal lower motor neuron involvement and varying degrees of cerebellar atrophy.

## Neurodegenerative diseases with neuropathy

**Infantile neuroaxonal dystrophy (INAD; #256600)**, also called *PLA2G6*-associated neurodegeneration or Seitelberger disease, is an autosomal recessive disorder. It is considered one of the subtypes of neurodegeneration with brain iron accumulation (NBIA [37, 38]). Mutations in the *PLA2G6* (\*603604) gene have also been detected in patients previously diagnosed with other subtypes of NBIA, and it now appears that the mutations in *PLA2G6* are associated with a characteristic clinical and radiologic phenotype called *PLA2G6*-associated neurodegeneration (PLAN). INAD typically manifests after the age of 2 years. The disease is typically rapidly progressive, causing

death prior to teenage age. Symptoms related to infantile neuroaxonal dystrophy reflect involvement of the peripheral nerves, central nervous system, and autonomic nervous system. The peripheral neuropathy is characterized by loss of distal sensation, which may lead to limb mutilation and muscle atrophy. Hypotonia and loss of motor milestones are associated with an early onset of the disease. Deep tendon reflexes typically are reduced. Central nervous system manifestations include cognitive deterioration, spasticity, optic atrophy, and hypothalamic dysfunction with diabetes insipidus and hypothyroidism. Autonomic symptoms may include urinary retention, decreased tear production, and dysfunction of temperature regulation. Seizures are rare but may occur at late preterminal stages of the disease. Cerebellar atrophy and gliosis are universally present, with an increased signal on fluid-attenuated inversion recovery (FLAIR) and T2-weighted MRI sequences. Other common MRI findings include hypointensity of the globus pallidus, dentate nuclei, and substantia nigra [39, 40]. The genetic diagnosis of infantile neuroaxonal dystrophy could be supported by the demonstration of spheroids in a peripheral nerve or conjunctiva biopsy [41]. The differential diagnosis of INAD includes other subtypes of NBIA, showing a broad phenotypic overlap [42, 43].

## Metabolic diseases

Metabolic diseases manifesting as or accompanied by neuropathy as one of their symptoms are listed in Tables 1 and 2. Several diseases for which treatment exists are listed in the section of treatable disorders below.

### Peroxisomal disorders

The peroxisomal disorders are usually classified into three groups according to the presence or absence of intact peroxisomes and whether one or more peroxisomal enzymes or functions are affected.

**Adrenomyeloneuropathy (AMN)/adrenoleukodystrophy (ALD, #300100)** is an X-linked peroxisomal disorder, which leads to dysfunction of the central and peripheral nervous systems. Clinical clues are behavioral problems in early childhood. It is characterized by accumulation of very long-chain fatty acids (VLCFA) in the adrenal gland and in the central and peripheral nervous systems and is caused by mutations in the *ABCD1* (\*300371) gene, which encodes the peroxisomal ABC half

transporter. There are variable [44] subphenotypes depending on the manifesting symptoms. Childhood-onset cerebral ALD and AMN, comprising 80 % of cases, are the most prevalent forms. Starting in adulthood, ALD leads to slowly progressive paraplegia, and central nervous system dysfunction occurs later in life. Female carriers may also develop late-onset neurological symptoms and the VLCFA profiles may appear normal, thus for atypical female patients with neuropathy ALD should be considered as a rare differential diagnosis. Male patients can be diagnosed easily by the VLCFA profile and typical leukodystrophy on brain MRI [45].

**Bi-allelic mutations in *HSD17B4* (\*601860) gene cause D-bifunctional protein (DBP) (#261515) deficiency and Perrault syndrome (#233400).** DBP deficiency is typically characterized by hypotonia, seizures, dysmorphism, and hearing and vision loss beginning in the neonatal period. Psychomotor development can be severely affected. Patients often die before 2 years of age. However, juvenile forms with a milder clinical course have been reported recently and described by some authors as a form of Perrault syndrome. Ataxia, intellectual disability, polyneuropathy, hypergonadotropic hypogonadism, and cerebellar atrophy can be seen in both juvenile DBP and Perrault syndrome. Routine peroxisomal screening tests such as VLCFA and phytanic acid levels are low in infantile DBP deficiency, and these findings may differentiate it from Perrault syndrome. Perrault syndrome is distinguished by sensorineural deafness in both males and females and by ovarian dysgenesis in females. However, in the juvenile form, the VLCFA and phytanic acid levels are normal [46–48].

**Refsum disease (#266500)**, previously also known as hereditary motor and sensory neuropathy IV, is a disorder of peroxisomal function. Refsum disease has been classified into classic and infantile forms. Classic Refsum disease (heredopathia atactica polyneuritiformis) is an autosomal recessive disorder associated with the accumulation of phytanic acid in plasma and tissues. Phytanic acid is a branched-chain fatty acid present in normal human diet. Normally it is metabolized by transformation to its CoA ester, phytanoyl-CoA, and then by alpha-oxidation to pristanic acid. Patients with Refsum disease are unable to degrade phytanic acid because of deficient activity of phytanoyl-CoA hydroxylase (*PHYH* or *PAHX*, \*602026), a peroxisomal enzyme that catalyzes the first step of phytanic acid alpha-oxidation; the enzyme dysfunction is caused by mutations in the *PHYH* gene [49]. A small number of patients with classic adult Refsum disease have defects in the *PEX7* (\*601757) gene rather than the *PHYH* gene [50]. The *PEX7* gene encodes the peroxin 7 receptor



protein, which is required for peroxisomal import of proteins playing a role in incorporation of PHYH protein into peroxisomes. Defects in the *PEX7* gene are also found in another hereditary disorder, rhizomelic chondrodysplasia punctata type 1. Infantile Refsum disease belongs to the group of lethal peroxisome biogenesis disorders (the others being Zellweger syndrome and neonatal ALD). This disorder is characterized by mutations in *PEX1* (\*602136) or *PEX6* (\*601498), which encode members of the AAA protein family (ATPases associated with multiple cellular activities) [51]. Classic Refsum disease is characterized by the presence of four clinical abnormalities: retinitis pigmentosa, peripheral polyneuropathy, cerebellar ataxia, and elevated cerebrospinal fluid protein concentrations (100 to 600 mg/dl) without an increase of cells. Affected patients also may have sensorineural deafness, ichthyosis, anosmia, and cardiac conduction defects. Nerve conduction studies typically show a slowed conduction velocity. Peripheral nerve biopsy reveals hypertrophic changes with onion bulb formation and paracrystalline inclusions on electron microscopy. The diagnosis is usually made clinically and can be confirmed by elevated serum phytanic acid concentrations. Strict reduction of dietary phytanic acid intake is of benefit for patients with classical Refsum disease; plasmapheresis could be performed to reduce the phytanic acid levels, too [52, 53].

### Polyglucosan body disease

Recessive mutations in *GBE1* (\*607839) lead to **branching enzyme deficiency (GSD IV, #232500)**, which is characterized by liver cirrhosis and failure to thrive. Patients often also develop extra-hepatic manifestations like myopathy and neuropathy; the most severe cases may present with fetal akinesia. Branching enzyme is responsible for converting  $\alpha$ -1,4-linked glucosyl chains into  $\alpha$ -1,6-glucosidic links, adding branches to the growing glycogen molecule. In adults another form of this disease is observed: adult polyglucosan body disease (#263570). Bladder dysfunction usually is the first symptom; later patients develop spastic gait, peripheral neuropathy, and mild cognitive impairment. Other manifestations include cerebellar dysfunction and extrapyramidal signs. The disease usually manifests between 40 and 60 years of age and is common in Ashkenazi Jews with a specific founder mutation in the *GBE1* gene. The pathologic hallmark of the disorder is the widespread accumulation of round, intracellular polyglucosan bodies throughout the nervous system, which are confined to neuronal and astrocytic processes [54–56].

### Tyrosinemia and porphyria

Four autosomal recessive disorders are caused by enzyme deficiencies in the tyrosine catabolic pathway: hereditary tyrosinemia types 1, 2, and 3 and alkaptonuria.

**Tyrosinemia type 1 (HT1) (#276700)** is the most severe disorder of tyrosine metabolism. It is characterized by severe progressive liver disease and renal tubular dysfunction. HT1 is caused by mutations in the fumarylacetoacetate hydrolase gene (*FAH*, \*613871), which encodes the last enzyme in the tyrosine catabolic pathway.

**Tyrosinemia type 2 (Richner–Hanhart syndrome, #276600)** is characterized by keratitis, palmoplantar hyperkeratosis, intellectual disability (mental retardation), and elevated blood tyrosine levels. The disease is caused by deficiency in hepatic tyrosine aminotransferase (*TAT*, \*613018).

**Tyrosinemia type 3 (#276710)** is caused by deficiency of 4-hydroxyphenylpyruvate dioxygenase (*HPD*, \*609695). It is an extremely rare disorder associated with hypertyrosinemia and elevated urinary excretion of 4-hydroxyphenyl derivatives. Affected patients have neurologic symptoms, including ataxia, seizures, and mild psychomotor retardation, but no other systemic involvement.

Severe neurologic manifestations may occur in children with **porphyria**. These are due to the accumulation of succinylacetone, which is a potent inhibitor of **ALA dehydratase (porphobilinogen synthase)**. Thus, patients may have symptoms of ALA dehydratase porphyria, which might cause acute hepatic forms of porphyria with sudden forms of colic abdominal pain, polyneuropathy with paresthesia, mental confusion, psychiatric episodes, and cardio-vascular symptoms, such as tachycardia, resembling panic attacks. Other forms of porphyria should be also considered, diagnosis should be made by quantifying  $\alpha$ -aminolevulinic acid and porphyrin metabolites in collected urine and stool samples, which must be light-protected and frozen immediately [57].

In a study investigating 48 children with tyrosinemia identified by neonatal screening, neurologic symptoms resembling the crises of neuropathic porphyrias occurred in 20 of them (42%) [58]. These acute episodes of peripheral neuropathy were characterized by severe pain with increased muscle tone in the calves (in 75%), vomiting with or without paralytic ileus (69%), muscle weakness (29%), and self-mutilation (8%). Eight children required mechanical ventilation because of paralysis. After crises, most survivors regained normal function. Electrophysiologic studies and nerve biopsies showed axonal degeneration and secondary demyelination [58].

## Mitochondrial diseases

Defects in structure or function of mitochondria, mainly involving the oxidative phosphorylation, mitochondrial biogenesis, and other metabolic pathways, are associated with a wide spectrum of clinical phenotypes. Peripheral neuropathy is a prominent feature in several of them. From the genetic perspective one has to distinguish defects of mtDNA and mutations in nuclear-encoded genes essential for mitochondrial function.

**Leigh syndrome (subacute necrotizing encephalomyelopathy) (#256000)** is an inherited neurodegenerative disorder of infancy or childhood [59]. The pathologic hallmarks of Leigh syndrome are bilateral, symmetric necrotizing lesions with spongy changes and microcysts in the basal ganglia, thalamus, brainstem, and spinal cord. It is characterized by developmental delay or psychomotor regression, signs of brainstem dysfunction, ataxia, dystonia, external ophthalmoplegia, seizures, lactic acidosis, vomiting, and weakness. Peripheral neuropathy with reduced nerve conduction velocity and demyelination also are frequent findings. The genetic basis is expanding rapidly [60, 61]. A specific form of an mtDNA defect, Leber hereditary amaurosis, is discussed in the section on treatable diseases.

## Neurodevelopmental disorders and polyneuropathy

There is a growing list of neurodevelopmental and neurodegenerative early-onset diseases with involvement of the peripheral nervous system, mostly with axonal neuropathy. The neuropathy might not be the clinically leading symptom and go unnoticed. Often neurons are vulnerable to genetic mutations, altering basic cellular functions, axonal transport, synaptic processes, or neuromuscular transmission. Since most of the motor neurons do not divide after birth, the system cannot repair itself, leading to neuropathy and ultimately to neuronal death.

Neurodevelopmental disorders are a group of disorders affecting neuronal maintenance and survival (neurodegenerative forms and genes) or are due to mutation in genes essential for the development of the motor networks and circuits. These neurodevelopmental genes regulate or are involved in the development and maturation of the motor network. They are organized in modules with critical hubs (regulators) and have specific temporal and spatial expression patterns in the developing brain. They affect movements, emotion, memory, learning ability, and

self-control [62]. Some patients may also have dysfunction of the peripheral nervous system. This group is currently rapidly expanding, thus we recommend strongly to re-assess unsolved cases once per year based on the most recent publications. Here we present only a few selected ones in Table 2.

## Neuromuscular disorders presenting with variable predominance/co-occurrence of myopathy and neuropathy

Co-occurrence of myopathy and neuropathy is not so rare. The causes may be inherited or acquired. Distinguishing myopathy from neuropathy based on clinical features alone may be insufficient. Nerve conduction studies, needle electromyography, and muscle and nerve biopsies are frequently needed to distinguish myopathy and neuropathy. Rare occurrence of immune-mediated neuromuscular disorders like myasthenia gravis, inflammatory neuropathy, and myositis have also been reported.

There are also inherited causes of combined myopathy and polyneuropathy. Myotonic dystrophy type 1 (#160900) and 2 (#602668), several mitochondrial disorders, myofibrillar myopathy (#601419), merosin negative congenital muscular dystrophy (#607855), and lamin A/C disorders (\*150330) are classical examples of inherited myopathies associated with polyneuropathy. Polyneuropathy (#613710) is present in one-third of the myotonic dystrophy type 1 patients and has also been described in myotonic dystrophy type 2 [63, 64].

Mutations in *LMNA* (\*150330) have been associated with myopathy (Emery–Dreifuss, limb girdle muscular dystrophy, congenital muscular dystrophy), neuropathy (Charcot-Marie-Tooth disease 2B), familial partial lipodystrophy, mandibulo-acral dysplasia, and progeria syndromes. Coexistence of muscular dystrophy and axonal neuropathy has also been associated with dominant *LMNA* mutations. These patients have histological evidence of combined neuropathic and myopathic phenotypes, which suggests a common etiology. Merosin-negative congenital muscular dystrophy (#607855) is an autosomal recessive muscle disorder caused by mutations in *LAMA2* (\*156225). It is a progressive muscular dystrophy and patients also have mild to moderate demyelinating neuropathy, in addition to brain abnormalities. It is not clear whether peripheral neuropathy contributes to

Table 2: Neurodevelopmental disorders with accompanying polyneuropathy.

Phenotype	OMIM Phenotype IDs	Gene name	Clinical clues	Inheritance pattern	Type of neuropathy	Treatable
Neurodevelopmental disorder with movement abnormalities, abnormal gait and autistic features (NEDMAGA)	#617865	ZSWIM6	Global developmental delay Intellectual disability Movement abnormalities Abnormal gait Autistic features	AD	Mixed axonal-demyelinating	No
Neurodevelopmental disorder with hypotonia, neuropathy, deafness (NEDHND)	#617519	SPTBN4	Congenital hypotonia Areflexia Intellectual disability Respiratory and feeding problems	AR	Mixed axonal and demyelinating motor neuropathy	No
Neurodevelopmental disorder with central and peripheral motor dysfunction	#609145	NFASC	Intellectual disability Motor impairment Speech difficulties	AR	Demyelinating neuropathy	No
Neurodegeneration, childhood-onset, stress-induced, with variable ataxia and seizures	#618170	ADPRS	Stress-induced neurodegeneration Ataxia Peripheral neuropathy Respiratory insufficiency	AR	Sensorimotor axonal polyneuropathy	No
Peripheral neuropathy, autosomal recessive, with or without impaired intellectual disability	#618124	MCM3AP	Motor and cognitive developmental delay Ophthalmoparesis Scoliosis Pes cavus	AR	Axonal polyneuropathy	No
Agensis of corpus callosum with peripheral neuropathy (Andermann Syndrome)	#218000	SLC12A6	Developmental retardation Agensis of corpus callosum Peripheral neuropathy	AR	Axonal polyneuropathy	No
Giant axonal neuropathy	#256850	GAN	Developmental delay Kinky hair Leukodystrophy Polyneuropathy	AR	Sensory-dominant axonal neuropathy	Intrathecal delivery of sCAAV9/letT-GAN (phase 1)

muscle weakness in affected patients. Abnormal maturation of myelin sheets and segmental demyelination are the suggested mechanism leading to neuropathy [65]. Dominant mutations in *DNM2* (\*602378) are disease-causing in around 50% of patients with centronuclear myopathy (#160150). The way of inheritance is autosomal dominant and clinical findings are milder than the X-linked neonatal forms caused by myotubularin gene. *DNM2* mutations affecting the pleckstrin-homology domain cause Charcot-Marie-Tooth disease, dominant intermediate B (#606482) and Charcot-Marie-Tooth disease, axonal type 2M (#606482). Lethal congenital contracture syndrome 5 (#615368), characterized by lack of spontaneous movement and respiratory insufficiency, is caused by homozygous missense mutations in *DNM2*. Some *DNM2*-related centronuclear myopathy patients also have accompanying peripheral neuropathy [66].

Mutations in *BICD2* (\*609797) are associated with autosomal dominant lower extremity-predominant spinal muscular atrophy type 2 (#615290), hereditary spastic paraplegia, arthrogyriosis multiplex congenita and perilymbian polymicrogyria, cerebellar hypoplasia, and distal myopathy [67]. Another gene causing overlapping phenotypes to *BICD2* is *DYNCH1* (\*600112). Overlapping features include polymicrogyria, hereditary spastic paraplegia, and spinal muscular atrophy, predominantly in the lower extremities, depending on the localization of the mutation in the gene. In recent years, phenotypes mimicking a congenital myopathy caused by *DYNCH1* mutations have also been described [68–70].

Myofibrillar myopathies are a group of myopathies characterized by muscle weakness, myalgia, cardiomyopathy, arrhythmia, respiratory failure, and peripheral neuropathy. Symptoms could begin in any period of life. Muscle weakness begins in distal muscles and then spreads to proximal and facial muscles. Genes associated with myofibrillar myopathies include *BAG3* (\*603883), *CRYAB* (\*123590), *DES* (\*125660), *FLNC* (\*102565), *LDB3/ZASP* (\*605906), *MYOT* (\*604103), *DNAJB6* (\*611332), and *TTN* (\*188840). The mutations in these genes cause aggregation of various proteins which disrupt the linking between neighboring sarcomeres. Patients with myofibrillar myopathies associated with *BAG3* mutations may have a mixed axonal and demyelinating peripheral myopathy [71, 72].

*PYROXD1* (\*617220) encodes a pyridine nucleotide-disulfide oxidoreductase (PNDR) with two putative enzymatic domains, i. e., a pyridine nucleotide-disulfide oxidoreductase domain and an NADH-dependent nitrite reductase domain. It is one of the new genes implicated in congenital myopathies. It may also present with a milder

limb girdle muscular dystrophy- or myofibrillar myopathy-resembling phenotype. Nerve conduction studies in some patients show a mild length-dependent axonal sensory neuropathy. The significance of this finding is uncertain but the patients should be followed up for the development of neuropathy with increasing age [73, 74].

Several proteins involved in membrane remodeling have been reported to be associated with neuromuscular diseases. Among these, mutations in *myotubularin* (*MTM1*, \*300415), *amphiphysin 2* (*AMPH*, \*600418), *bridging integrator 1* (*BIN1*, \*601248), and *DNM2* (\*602378) lead to different forms of centronuclear myopathy (CNM). More interestingly, mutations in *DNM2* can also cause a dominant form of Charcot-Marie-Tooth neuropathy, and recently it was reported that mutations in another dynamin family member, dynamin 1, cause encephalopathy [75]. Moreover, mutations in *INPP5K* (\*607875), which encodes the inositol polyphosphate-5-phosphatase K, also known as skeletal muscle and kidney enriched inositol phosphatase (SKIP), cause congenital muscular dystrophy [76] with LGMD and neuropathic features. Therefore, the literature to date suggests that mutations in proteins involved in membrane remodeling and trafficking might act through a shared pathological pathway [77]. We would like to mention a new emerging gene: striated muscle preferentially expressed protein kinase (*SPEG*, \*615959). It interacts with *MTM1*, and we have recently described it as a cause of neuropathy and congenital myopathy [78].

## Fetal akinesia (FA) spectrum

FA is an etiological term describing a clinical syndromic entity characterized by reduced or absent fetal movement caused by intrauterine movement limitation leading to multiple phenotypic abnormalities [79]. This phenotypical spectrum includes both the clinical entities of arthrogyriosis multiplex congenita (AMC) and the fetal akinesia deformation sequence (FADS). Therefore, we propose to use FA as an overarching term covering the entire phenotypical spectrum from a mild AMC phenotype to a severe FADS phenotype with a prenatally lethal outcome [79]. While many genetically defined Mendelian FA disease entities are caused by mutations in genes causing bona-fide neuropathy, our recent large study based on systematic next-generation sequencing showed that approximately 30% of the FA cases have a neurogenic etiology [79]. Thus, the clinical work-up of FA should include the measurement of nerve conduction velocities for differential diagnosis.

## Other syndromes with significant neuropathy

**Chediak–Higashi syndrome (CHS, #214500)** is an autosomal recessive disorder characterized by recurrent infections, partial albinism, hepatosplenomegaly, an increased risk of lymphoreticular malignancy, and multiple neurologic abnormalities. It is caused by recessive mutations in the lysosomal trafficking regulator (*LYST*) (\*606897). Patients who survive early childhood despite serious infections develop severe neurologic manifestations in adolescence and early adulthood. Both the peripheral and central nervous systems are involved [80]. Neurologic features may include nystagmus, photosensitivity, seizures, intellectual disability (mental retardation), generalized weakness, spinocerebellar degeneration, and Parkinsonism. Biopsy of peripheral nerves reveals perivascular intracytoplasmic inclusions, loss of myelinated sensory fibers, and the presence of peroxidase-positive granules in Schwann cells, similar to those seen in leukocytes, which are thought to be giant lysosomes [81].

The DNA repair disorders are characterized by susceptibility to chromosomal breakages, increased frequency of breaks, and interchanges occurring either spontaneously or following exposure to various DNA damaging agents. The underlying defect in these syndromes is the inability to repair a particular type of DNA damage. The inheritance of these disorders is autosomal recessive and they show an increased tendency to develop malignancies. **Xeroderma pigmentosum (#278730)** is a multigenic, multiallelic autosomal recessive disease [82]. Neurologic features may be mild or severe and can include progressive cognitive impairment, ataxia, choreoathetosis, sensorineural hearing loss, spasticity, seizures, and peripheral neuropathy with diminished or absent deep tendon reflexes [83].

**Cockayne syndrome (#216400)** is characterized by severe physical and mental retardation, short stature, microcephaly, progressive neurologic dysfunction caused by demyelination, retinal degeneration with a pigmented retinopathy and optic atrophy, kyphoscoliosis, gait defects, and sun sensitivity but no increased frequency of cancer [84]. Various polyneuropathies have been described in Cockayne syndrome [85], but the most common form is a sensorimotor demyelinating polyneuropathy [86]. Affected patients have white matter demyelination in the central nervous system, with atrophy of the cerebrum and cerebellum. Perivascular calcifications are seen in the basal ganglia and cerebellum. Brain-MRI scans have shown increased signals in the white matter with T2 images [87, 88].

## Treatable diseases

### Lysosomal storage disorders

**Fabry disease (#301500)** is an X-linked glycolipid storage disease caused by deficiency of alpha-galactosidase A (*GLA*, \*300644) [89]. It is classically associated with a painful small-fiber peripheral neuropathy. Additional clinical clues are angiokeratoma (buttocks and genital region), corneal clouding, and cardiac hypertrophy with conduction defects. Stroke and renal failure may lead to premature death at 40 to 50 years of age; heterozygous women manifest milder symptoms. Fabry disease is treatable by enzyme replacement therapy (agalsidase-beta) or the chemical chaperone migalastat hydrochloride.

**Krabbe disease (#245200)** is an autosomal recessive disorder caused by the deficiency of galactocerebrosidase (*GALC*, \*606890). The neuropathy associated with Krabbe disease is demyelinating, and nerve conduction studies typically show a uniform pattern of slowing. Most patients present within the first 6 months of life, but later onset (adults included) may occur. Infantile Krabbe patients present with dystonic attacks together with irritability, poor feeding, motor regression, and seizures. Apart from the diagnostic leukodystrophy images on brain MRI, calcification of the basal ganglia has also been described. Clinical clues are the regression triggered by febrile illnesses, decreased visual perception, and spastic posturing but with areflexia with demyelinating neuropathy. Histopathology shows inclusion bodies in monocytes and biopsies of other tissues; interestingly the protein level in CSF is elevated. CNVs are common in *GALC*, thus suitable techniques should be included in the genetic work-up [90–92]. Treatment with hematopoietic stem cell transplantation is based on disease burden and manifestations.

**Metachromatic leukodystrophy (#250100)** is an autosomal recessive lysosomal storage disease that occurs due to mutation in Arylsulfatase A (*ARSA*, \*607574) in 1 of 40,000 births. The neuropathy that accompanies metachromatic leukodystrophy is demyelinating, with either uniform or non-uniform slowing of conduction velocities on nerve conduction studies [90–92]. Treatment by bone marrow transplantation has been reported [90–92].

**Niemann–Pick disease (NPD, sphingomyelin-cholesterol lipidosis)** is a group of autosomal recessive disorders associated with splenomegaly, cholestasis with jaundice, and variable neurologic deficits due to the excessive storage of sphingomyelin.

Four different forms exist. NPD type A (#257220) is caused by recessive mutations in *acid sphingomyelinase (SMPD1, \*607608)*. NPD type B (#607616) is also caused by

recessive mutations in *SMPD1*, but does not manifest with neurological symptoms in early childhood but rather with unspecific gastro-intestinal symptoms throughout all ages and neurological symptoms manifest at older age [93, 94].

NPC type C1 (#257220) may present in school age with seizures and learning difficulties and as a diagnostic clue with a vertical gaze palsy. A cherry red spot on the retina is observed in only 50 % of the cases; other neurological symptoms manifest variably during the disease course with ataxia, dystonia, narcolepsy, and cataplexy. Lymphocytes and the bone marrow show so-called foam cells due to accumulation of lipids, thus the enzyme activity can be measured from peripheral blood lymphocytes for diagnosis. The disease occurs due to mutations in the *intracellular cholesterol transporter 1 (NPC1, \*607623)* gene. About 5 % of the cases have recessive mutations in the epididymal secretory protein (*HE1, NPC2, \*601015*) [95–97]. NPC is treatable by misglutamate, which is an inhibitor of glucosylceramid-synthase, avoiding the accumulation of toxic metabolites in lysosomes.

**Cerebrotendinous Xanthomatosis (#213700)** is a recessive condition, leading to abnormal accumulation of cholesterol and xanthomas in late childhood or adolescence due to bi-allelic mutations in *CYP27A1 (\*606530)*. The disease is slowly progressive. Xanthomas may manifest in tendons early in disease progression and mental deterioration may occur slowly together with cataracts and myoclonic seizures during disease course. At late stages of the disease cerebellar dysfunction and also bulbar paralysis and peripheral neuropathy may manifest [98].

**Leber hereditary optic neuropathy (LHON)** is a maternally inherited bilateral subacute optic neuropathy caused by mutations in the mitochondrial genome. It is the first human disease to be associated with a mitochondrial DNA point mutation. Three LHON mtDNA mutations at nucleotide positions 3460, 11778, and 14484 are specific for LHON. These mutations account for more than 90 % of worldwide cases and are designated as primary. LHON typically produces severe and permanent visual loss and predominantly affects males. The initial symptoms include visual dysfunction with blurring of vision and loss of central vision, most often beginning in the late teens. Additional findings that can occur in children include an extrapyramidal syndrome, seizures, ataxia, spasticity, intellectual disability (mental retardation), and peripheral neuropathy. In the central nervous system, demyelination of the optic tracts and cell loss and gliosis of the geniculate bodies occur, but the visual cortex is normal. Axonal depletion centrally in the optic nerve is present as well as loss of ganglion cells in the retina. The diagnosis typically is made by

mtDNA sequencing from lymphocytes. In addition, the defects in respiratory enzymes in the abnormal mitochondria could be measured on fresh or frozen muscle biopsies.

There is a possible treatment for LHON (#535000) [99]. Studies suggest the possibility of benefits with the antioxidant Idebenone [100]. This drug has been approved and is relatively safe to use, but further post-marketing studies are needed to prove the clinical efficacy.

**Brown-Vialetto-van Laere syndrome (BVVLS)** is characterized by progressive sensorimotor neuropathy, optic atrophy, hearing loss, bulbar dysfunction, and respiratory failure due to variants in *SLC52A2 (\*607882)* and *SLC52A3 (\*613350)* genes, which encode riboflavin transporter 2 and 3 proteins, respectively [101, 102]. RVFT2 is a brain transporter and RVFT3 is an intestinal transporter. Riboflavin is the precursor of flavo-coenzymes involved in fatty acid oxidation. Defects in riboflavin transport result in impaired mitochondrial membrane potential and respiratory chain activity. There is severe neuronal loss in the lower cranial nuclei and anterior horns. There is also atrophy of spinothalamic, spinocerebellar, and posterior column-medial lemniscus pathways. Symptoms of the disease frequently start in childhood with cranial nerve involvement. Sensorineural hearing loss is a frequently presenting symptom, followed by impaired vision and bulbar and facial weakness. Limb weakness follows, which is more severe in the upper extremities. Gait ataxia and epilepsy are also common. Most of the patients develop respiratory insufficiency in advanced stages of the disease. Electromyography revealed sensorimotor axonal polyneuropathy. Riboflavin treatment is lifesaving. Oral riboflavin treatment is started at a dosage ranging from 10 to 60 mg/kg/day. Clinical improvement after treatment occurs in 74 % of cases and stabilization occurs in 26 % of cases. One critical point is that if a riboflavin-responsive neuropathy is suspected, treatment should be started immediately while awaiting genetic confirmation.

**Homocystinuria** occurs frequently due to recessive mutations in cystathionine synthase (*CBS*) [103] or other defects of the methyl-B<sub>12</sub> biosynthesis N<sup>5</sup>-methyltetrafolate methyltransferase. **Methylenetetrahydrofolate reductase (MTHFR) deficiency** may manifest as homocystinuria as well. Of patients with CBS defects, 50 % are mentally retarded; clinical clues to CBS deficiency may be arachnodactyly, osteopetrosis, lens dislocation, and in particular thromboembolic events like stroke. Axonal neuropathy might be a feature of especially MTHFRD; those patients do not thrive well, and may develop microcephaly and seizures in early childhood. The treatment depends on the genetic defect and the levels of

the metabolites and may include supplementation with vitamin B12, vitamin B6, and folic acid.

In this context one needs to mention **cobalamin C (vitamin B12) deficiency**, through genetic defects in either the biosynthesis or receptors, which may apart from megaloblastic anemia also lead to sensory-motor neuropathy. Apart from intestinal malabsorption it may also occur in vegetarians or breast-fed children of vegetarian mothers. Treatment includes the supplementation of vitamin B12.

**Abetalipoproteinemia (Bassen-Kornzweig syndrome) (#200100)** [104] is a rare autosomal recessive disorder caused by mutations in microsomal triglyceride transfer protein (*MTTP*, \*157147). A similar disease is familial hypobetalipoproteinemia-1 (#615558), caused by mutations in the *APOB* gene (\*107730). The neurologic manifestations result from the inability to absorb and transport vitamin E and include progressive ataxia, sensory-motor neuropathy, and vision impairment with retinitis pigmentosa. Other clinical manifestations include acanthocytosis along with fat malabsorption and steatorrhea. Diarrhea in childhood could be an early sign. The diagnosis is made in the setting of the typical clinical findings accompanied by laboratory findings of acanthocytosis, very low triglyceride and low total cholesterol levels, and absent betalipoproteins. It must be distinguished from other forms of neuroacanthocytosis [105]. Neurologic manifestations can be prevented and partially reversed with the administration of vitamin E (150 mg/kg per day) along with other fat-soluble vitamins [106, 107].

**Tangier disease (#205400)** is an autosomal codominant condition in which homozygotes have no serum high density lipoprotein (HDL) and heterozygotes have serum HDL concentrations of approximately one-half of those in normal individuals [108–110]. HDL-mediated cholesterol efflux from macrophages and intracellular lipid trafficking are impaired, leading to the presence of foam cells in macrophages and other cells/tissues. Tangier disease is caused by mutations in the ATP-binding cassette transporter A1 (*ABCA1*, \*600046) gene, which encodes for the cholesterol efflux regulatory protein. Homozygotes may develop cholesterol ester deposition in the tonsils (orange tonsils), liver, spleen, gastrointestinal tract, lymph nodes, bone marrow, and Schwann cells. The main clinical manifestations are hepatosplenomegaly and premature coronary disease; a neuropathy occurs in at least 50% of patients and is the most debilitating feature of the disease [111]. Two major types of neurologic syndromes are seen: a peripheral neuropathy in childhood with fluctuating numbness, tingling, distal sensory loss, and distal weakness with muscle atrophy [112], or a progressive loss of sensory and motor function in the upper body in a pattern

similar to that which occurs in syringomyelia (a cystic degeneration of the spinal cord) [112]. The major pathologic findings on nerve biopsy are loss of smaller myelinated and unmyelinated nerve fibers and lipid vacuole accumulation in Schwann cells. Initiation of a low-fat diet may reduce the number of abnormal HDL particles and can be associated with symptomatic improvement in the peripheral neuropathy. The administration of drugs that can increase serum HDL in other patients (gemfibrozil, niacin, or a statin) had only little effect in those with Tangier disease [108–110].

## Conclusion

Neuropathy could be a presenting or accompanying manifestation and sign of various genetic disorders [5]. In order to diagnose it, one should seek a holistic approach to the patient and not just focus on a few clinical findings, keeping in mind that atypical cases may occur. Depending on the clinical specialty certain clinical findings could be overemphasized while others which could have led to the diagnosis might be overlooked. We are living in exciting times, especially sequencing of larger next-generation sequencing panels or whole exomes teaches us many clinical lessons in reverse genetics (unexpected pathogenic variants in unexpected diseases which in retrospect explain a number of the clinical problems of the patient) to remain humble and be open for constant learning. Neuromuscular clinicians should be aware of diseases which may manifest as overlapping phenotypes between neuropathy and myopathy.

Especially, the currently treatable disease should not be overlooked and diagnosed in time (see also Table 1).

We would like to emphasize also that many neuropathies might not be primarily genetic but rather autoimmune, paraneoplastic, or acquired. In children one should also consider toxin intake or vitamin deficiencies, especially if the child previously developed normally. Secondary neuropathies may occur in metabolic conditions (diabetes, hypoglycemia, uremia, porphyria, hypothyroidism, acromegaly), through toxins (arsenic, lead, mercury, thallium, vincristine, isoniazid), in nutritional deficiencies (vitamins B1, B6, B12, and E), in paraproteinemias (myeloma, Waldenstrom), connective tissue disorders (polyarteritis nodosa, Wegener granulomatosis, Sjögren syndrome, lupus, rheumatoid conditions, scleroderma), through infection (HIV, Lyme borreliosis, and leprosy), and in older age (amyloid neuropathy). Fractures,

trauma, and tumors may lead to local entrapment neuropathies even in infants or children.

Our review could only give an overview about the most common or treatable genetic neuropathies; however, every week a few additional novel neurodevelopmental diseases are currently published and in many of them a neuropathy is at least an accompanying sign.

As an outlook in order to solve the etiology of the unsolved neuropathies, we should also consider an oligogenic approach, as shown recently by Züchner's group [113], or overcome the limitations of exome sequencing by combining whole genome sequencing, RNA sequencing or long-read sequencing.

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