

REVIEW

Demyelinating prenatal and infantile developmental neuropathies

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Abstract The prenatal and infantile neuropathies are an uncommon and complex group of conditions, most of which are genetic. Despite advances in diagnostic techniques, approximately half of children presenting in infancy remain without a specific diagnosis. This review focuses on inherited demyelinating neuropathies presenting in the first year of life. We clarify the nomenclature used in these disorders, review the clinical features of demyelinating forms of Charcot-Marie-Tooth disease with early onset, and discuss the demyelinating infantile neuropathies associated with central nervous system involvement. Useful clinical, neurophysiologic, and neuropathologic features in the diagnostic work-up of these conditions are also presented.

Key words: Charcot-Marie-Tooth disease, Déjérine–Sottas disease, demyelination, paediatric, peripheral neuropathy

Introduction

The prenatal and infantile neuropathies are an uncommon and complex group of conditions with broad phenotypic and genotypic diversity. Most infantile neuropathies have a genetic basis. This review focuses on inherited demyelinating neuropathies presenting in the first year of life. Axonal neuropathies presenting during this period will be reviewed separately. Whilst progress has been made in the diagnosis of prenatal and infantile neuropathies, at this point more than half of children presenting in the first year of life remain without a specific diagnosis. With advances in molecular genetic techniques, the already rapidly expanding number of genes attributed to infantile neuropathies is set to further increase.

Aetiology

In a large cohort of 260 children with biopsy-confirmed peripheral neuropathy, 50 (19.2%) were symptomatic in infancy, of whom 48% had a demyelinating and 42% an axonal disorder (*Wilmshurst et al., 2003*). Whilst many of these cases presented prior to the era of genetic diagnosis, 20 children fell under the rubric of Charcot-Marie-Tooth disease (CMT), 19 of whom had a demyelinating form of CMT. Children with a demyelinating phenotype were more likely to receive a definitive diagnosis (six had heterozygous point mutations in *PMP22* or *MPZ*). More recently, in a series of 77 children with infantile neuropathies (58% demyelinating, 20% axonal, and 22% undefined), 35 children (45%) received a diagnosis involving mutations in 1 of 11 genes, most of which were associated with demyelinating forms of CMT (*Baets et al., 2011*). This emphasises the genetic heterogeneity of the infantile neuropathies, but also the fact that over half of children remain without a definitive diagnosis.

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Clinical Presentation

Most infants with early onset neuropathies tend to display one of two phenotypes. The first group has clear prenatal/neonatal onset and presents at birth with hypotonia, arthrogryposis, and respiratory insufficiency. The second (and more common) group presents later in infancy with delayed motor development and/or foot deformities, after an uneventful neonatal period (Baets *et al.*, 2011).

In the first group a history of decreased foetal movements, intra-uterine growth retardation and polyhydramnios may be obtained, and delivery of a hypotonic infant may result in obstetric complications such as obstructed labour and birth asphyxia, masking the underlying peripheral neuropathy. Ventilatory support is often required and early mortality common.

In contrast to adults, in whom distal weakness and sensory loss are the predominant features of a neuropathy, infants in the second group usually have delayed motor milestones (an indicator of infantile onset) and areflexia. Proximal weakness, foot deformity, scoliosis, and congenital hip dysplasia may be apparent, and the clinical features may mimic myopathy. Facial weakness and tongue fasciculations may be present, reflecting a severe neuropathic process. Nerve hypertrophy is visible or palpable in some hypertrophic neuropathies, but is difficult to assess and not always present. Some distinguishing clinical features of infantile demyelinating neuropathies are presented in Table 1. Features of axonal infantile neuropathies will be reviewed separately.

Once a neuropathy is diagnosed, the assessment should focus on identifying a specific diagnosis, as

well as detecting and managing complications of the neuropathy.

Diagnostic Process

To aid diagnosis, it is important to determine: (1) whether the infant has an isolated peripheral neuropathy or neuropathy in association with a central nervous system (CNS) disorder; (2) whether the neuropathy is primarily demyelinating/hypomyelinating or axonal; (3) the inheritance pattern; and (4) if there are any distinguishing features on clinical, neurophysiologic, or neuropathologic examination.

Nerve conduction studies provide vital information in determining if a neuropathy is primarily demyelinating or axonal. It is important to remember that conduction velocities increase during the first 2–3 years of life. Normative values for age should always be referenced (Miller and Kuntz, 1986; Parano *et al.*, 1993). Nerve conduction studies, particularly sensory studies, can be technically difficult in infants and neonates, so absent sensory responses should be interpreted with caution. Infants with severe neuropathies may have unobtainable motor and sensory responses, making it difficult to discriminate between a primarily demyelinating or axonal process. Testing of more proximal nerves (such as the phrenic nerve) can be helpful in this instance, while needle electromyography (EMG) helps to distinguish myopathies from neuropathies. In addition, conduction slowing may be so severe that the time base for nerve conduction testing needs to be adjusted to identify very delayed responses.

Nerve biopsy can be very informative in determining the basis of prenatal and infantile neuropathies.

Table 1. Clinical clues to the diagnosis of infantile demyelinating neuropathies.

Clinical feature	Clinical phenotype	Gene
Pupillary abnormalities	CHN, DSD, CMT1B CMT4C	MPZ SH3TC2
Multiple cranial neuropathies	CHN, DSD, CMT4E	EGR2
Prominent foot and hand deformities	CMT4A, CMT2H/K CMT4C	GDAP1 SH3TC2
Severe spinal deformities	CMT4C	SH3TC2
Asymmetric weakness	DSD, CMT4J	FIG4
Post-traumatic rapid progression of weakness	DSD, CMT4J	FIG4
Vocal cord paresis	CMT4A, CMT2H/K CMT4B1	GDAP1 MTMR2
Diaphragmatic involvement	CMT4A, CMT2H/K	GDAP1
Glaucoma	CMT4B2	MTMR13
Prominent sensory involvement	DSD, CMT4F	PRX
Congenital cataracts	HCC CCFDN	DRCTNNB1A CTDP1
Raised creatine kinase	Merosin-deficient CMD	LAMA2

CCFDN, congenital cataracts facial dysmorphism neuropathy syndrome; CHN, congenital hypomyelinating neuropathy; CMD, congenital muscular dystrophy; CMT, Charcot-Marie-Tooth disease; DSD, Déjérine–Sottas disease; HCC, hypomyelination and congenital cataract.

Table 2. Neuropathologic clues in the diagnosis of infantile demyelinating neuropathies.

Neuropathologic feature	Clinical/genetic phenotypes
Focal myelin folding	<i>Frequently present</i> MPZ-related CHN/DSD CMT4B1 (<i>MTMR2</i>) CMT4B2 (<i>MTMR13</i>) CMT4F (<i>PRX</i>) CMT4H (<i>FGD4</i>) <i>Occasionally present</i> EGR2-related neuropathies GDAP1-related neuropathies
Uncompacted myelin Long Schwann cell cytoplasmic processes	MPZ-related CHN/DSD CMT4C (<i>SH3TC2</i>)
Node of Ranvier disorganisation	CMT4C (<i>SH3TC2</i>)
Paranodal abnormalities	CMT4F (<i>PRX</i>) CMTX1 (<i>Cx32</i>)

CHN, congenital hypomyelinating neuropathy; CMT, Charcot-Marie-Tooth disease; DSD, Déjérine–Sottas disease.

Specific neuropathologic abnormalities may point to particular genetic syndromes; distinguishing nerve biopsy features of demyelinating neuropathies are presented in Table 2. Acquired and potentially treatable causes of neuropathies such as infantile CIDP (although rare), may mimic or occur superimposed on genetic neuropathies, and can be diagnosed on nerve biopsy.

Cerebral neuroimaging is not always required in the work-up of infants presenting with a purely peripheral process. However, magnetic resonance imaging (MRI) can sometimes provide important diagnostic clues in both demyelinating and axonal neuropathies.

Assessment and Management of Complications

Despite the genetic heterogeneity of infantile neuropathies, they tend to share typical management issues. Respiratory insufficiency may be related to diaphragmatic weakness (caused by involvement of the phrenic nerve), intercostal muscle weakness or spinal deformity. Ventilatory support may be required from birth or later in the disease course, and assessment for respiratory insufficiency is warranted in most cases.

Bulbar weakness may cause poor feeding and recurrent aspiration. Gastro-oesophageal reflux is probably more common than is recognised. Skeletal deformities including foot deformity, developmental hip dysplasia and scoliosis are common and should be appropriately managed. Visual disturbance due to optic atrophy or cataracts occurs in some conditions,

and some are associated with sensorineural hearing loss.

The long-term prognosis of individuals with early onset demyelinating neuropathies is variable and not well documented. Outcomes are dependent not only on the underlying genetic mutation, but likely also environmental and epigenetic factors given the inter- and intra-familial variability often present. Individuals with significant respiratory involvement tend to have a poorer prognosis than those without respiratory compromise.

Appropriate genetic counselling should always be provided to families.

Demyelinating Forms of CMT with Early Onset

Terminology

Congenital hypomyelinating neuropathy (CHN), Déjérine–Sottas disease (DSD, also referred to as CMT3 or hereditary motor and sensory neuropathy (HMSN) III) and CMT4 (also referred to as autosomal recessive CMT1, ARCMT1) are all forms of demyelinating CMT with early onset. The nomenclature is very confusing, as the original descriptions and classification were made prior to the availability of genetic testing, and use of the terms (in particular DSD and CHN) is often inconsistent. A single gene can cause multiple phenotypes of variable severity, and a single phenotype can be caused by mutations in more than one gene.

The features of DSD were defined by Dyck and Lambert (1968) and then by Ouvrier *et al.* (1987) as: recessive or sporadic inheritance, onset in infancy or the first two years of life, delayed motor development, extremely slow nerve conduction (motor nerve conduction velocity, MNCV < 12 m/s), elevated cerebrospinal fluid protein, and nerve biopsy features of a marked reduction in myelinated fibre density, thin myelin sheaths and onion bulb formations. Most children are areflexic. Foot deformity is common.

Many children with DSD have *de novo* dominant mutations in *MPZ* (Hayasaka *et al.*, 1993), *PMP22* (Roa *et al.*, 1993), or *EGR2* (Warner *et al.*, 1998). In addition, individuals with CMT4 (autosomal recessive CMT) sometimes have a DSD phenotype. Thus the term DSD is probably best used to describe the clinical syndrome of a severe demyelinating genetic neuropathy manifesting before two years of age with hypotonia or delayed motor development, with a median MNCV of 12 m/s or less (Benstead *et al.*, 1990; Gabreels-Festen, 2002).

CHN is rare and less well characterised than DSD. It is thought to reflect a defect in myelin synthesis. In

its classic form, CHN is characterised pathologically by complete absence of peripheral nerve myelin without onion bulb formations, although some individuals have severe hypomyelination and/or unusual “basal lamina onion bulbs” consisting of concentric whorls of double-layered Schwann cell basement membrane (Charnas *et al.*, 1988; Phillips *et al.*, 1999). In these “atypical” onion bulbs, Schwann cell processes are thought to have degenerated, leaving behind their basal laminae (Schroder, 2006). Evidence of myelin degeneration is absent. In comparison, nerve biopsies in DSD show evidence of hypomyelination and demyelination–remyelination, classic onion bulb formation and myelin breakdown products (Gabreels-Festen, 2002; Wilmshurst *et al.*, 2003).

Severe cases of CHN present at birth with profound weakness, hypotonia, arthrogryposis, and respiratory insufficiency (Charnas *et al.*, 1988; Boylan *et al.*, 1992). Nerve conduction is very slow or responses are absent. Tongue fasciculations may be present (Hahn *et al.*, 2001b). Less severe cases present in infancy with hypotonia and motor delay (Phillips *et al.*, 1999; McMillan *et al.*, 2010). Complete absence of peripheral nerve myelination does not always predict prenatal or neonatal onset, or early demise, and survival into adulthood is documented (Kasman *et al.*, 1976; Smit *et al.*, 2008). Hence the discrepancy between biopsy findings and clinical features, as well as overlap in genetic causation, makes the distinction between CHN and DSD of limited utility in the diagnosis and management of these patients, particularly in the era of genetic testing in which nerve biopsy may not be required (Fig. 1). It is likely that CHN and DSD lie on a continuum of “myelinopathies”, as mutations (sometimes even identical mutations) in *MPZ* (Warner *et al.*, 1996), *PMP22* (Roa *et al.*, 1993; Simonati *et al.*, 1999), and *EGR2* (Warner *et al.*, 1998; Boerkoel *et al.*, 2001a) can cause both phenotypes. It may be more appropriate to refer to these early onset disorders as infantile- or prenatal-onset neuropathies associated with a particular genetic cause if known.

A summary of the clinical and neurophysiologic phenotypes associated with each gene discussed below is presented in Table 3.

Early onset neuropathies due to *PMP22* mutations

Heterozygous duplications involving *PMP22* cause CMT1A, the most frequent type of CMT (Lupski *et al.*, 1991), while the reciprocal deletion causes hereditary neuropathy with liability to pressure palsies (HNPP) (Chance *et al.*, 1993). In the context of infantile neuropathies, heterozygous (often *de novo*) point mutations in *PMP22* are associated with DSD (Roa *et al.*, 1993; Ionasescu *et al.*, 1995) and, less

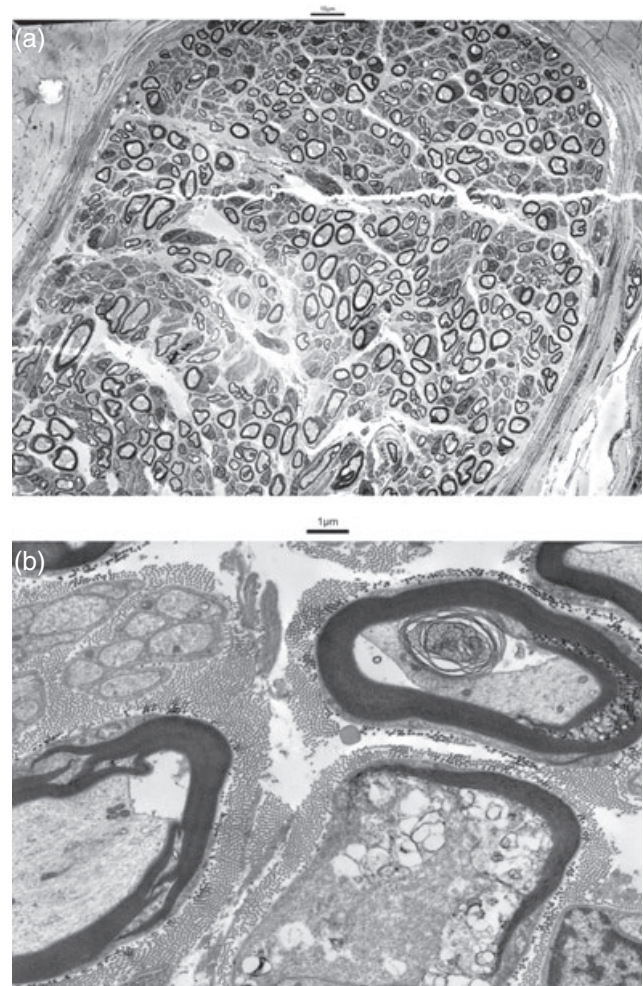


Figure 1. Post-mortem sural nerve of a male infant with a severe prenatal-onset demyelinating neuropathy. He had severe hypotonia, weakness, respiratory distress and areflexia from birth, and died from progressive respiratory failure at seven weeks of age. Electron micrographs at low (a) and high (b) power show generalised uniform thinning of the myelin sheaths in intermediate and large fibres. Focal myelin breakdown is also seen in (b). Genetic testing for mutations in *MPZ*, *PMP22*, and *EGR2* were negative. Whilst this infant had a severe congenital phenotype, myelin is still present, illustrating the discrepancy sometimes seen between clinical severity and degree of hypomyelination.

commonly, CHN (Simonati *et al.*, 1999; Fabrizi *et al.*, 2001).

Almost all children with DSD/CHN due to *PMP22* mutations have delayed development; many do not walk until 3–4 years of age, and some only with assistance (Tyson *et al.*, 1997; Marques *et al.*, 1998). A small number never achieve independent ambulation (Ionasescu *et al.*, 1995; Marques *et al.*, 1998). Increasing weakness may result in wheelchair dependency in later life (Ikegami *et al.*, 1998; Gabreels-Festen, 2002). There may be marked intrafamilial variability in severity and course (Gabreels-Festen, 2002).

Table 3. Clinical features of demyelinating forms of CMT with early onset.

Gene	Clinical phenotypes in infancy	Inheritance	MNCV (m/s)	Other features	Other clinical phenotypes
<i>PMP22</i> (point mutation)	CHN, DSD	AD, AR	<12	SNHL, facial weakness, nystagmus, vestibular dysfunction	CMT1A, HNPP
<i>PMP22</i> (duplication)	DSD	AD	9–20		CMT1A
<i>PMP22</i> (deletion)	DSD	AR*	<10	SNHL	HNPP
<i>MPZ</i>	CHN, DSD	AD, AR	<12	Pupillary abnormalities, SNHL, facial weakness	CMT1B, Intermediate CMT, CMT2
<i>EGR2</i>	CHN, DSD, CMT4E	AD, AR	3–20	Cranial neuropathies frequent	CMT1D
<i>NEFL</i>	DSD, CMT1F, CMT2E	AD, AR	12–35	Intellectual disability, pyramidal signs, SNHL	CMT1F, CMT2E
<i>Cx32</i>	CMTX1	X-linked	20–50	SNHL, tremor, transient CNS disturbances	CMTX1
<i>GDAP1</i>	CMT4A, CMT2H, CMT2K (AR)	AR	20–60	Vocal cord paresis and diaphragmatic involvement. Severe distal weakness, prominent foot deformity and claw hands	CMT2K (AD)
<i>MTMR2</i>	CMT4B1	AR	9–20	Facial weakness	
<i>MTMR13/SBF2</i>	CMT4B2	AR	16–21	Congenital or juvenile onset glaucoma	
<i>SH3TC2/KIAA1985</i>	CMT4C	AR	4–37	Early onset spinal deformities. Foot deformities, SNHL, abnormal pupillary responses	
<i>PRX</i>	DSD, CMT4F	AR	2–20	Prominent sensory involvement	
<i>FGD4</i>	DSD, CMT4H	AR	5–13	Slow progression	
<i>FIG4</i>	DSD, CMT4J	AR	3–41	Asymmetric weakness, rapid progression following trauma	

AD, autosomal dominant; AR, autosomal recessive; CHN, congenital hypomyelinating neuropathy; CMT, Charcot-Marie-Tooth disease; CNS, central nervous system; DSD, Déjérine–Sottas disease; HNPP, hereditary neuropathy with liability to pressure palsies; SNHL, sensorineural hearing loss.

*Only compound heterozygous deletions associated with infantile neuropathies.

Scoliosis and restrictive lung disease may be seen in individuals with *PMP22* point mutations (Gabreels-Festen, 2002); rarely respiratory involvement leads to early death (Ikegami et al., 1998). Other features reported with *PMP22* mutations include sensorineural hearing loss (Ionasescu et al., 1996; Russo et al., 2011), facial weakness (Tyson et al., 1997), and rarely nystagmus (Russo et al., 2011), vestibular dysfunction (Jen et al., 2005), ptosis, limited extraocular movements (Marques et al., 2004), and bladder symptoms (Marques et al., 1998).

On nerve conduction studies MNCV is almost always <10–12 m/s (Simonati et al., 1999; Gabreels-Festen, 2002). Sensory responses are often absent and compound muscle action potentials (CMAPs) are usually low amplitude, reflecting secondary axonal loss. Findings on nerve biopsy are usually typical

of DSD with thin myelin sheaths, myelinated fibre loss, increased total transverse fascicular area (due to increased collagen fibres), and prominent onion bulb formations, composed of thin Schwann cell lamellae or basal membranes or both. In those cases designated as CHN, hypomyelination is more marked (Simonati et al., 1999; Gabreels-Festen, 2002).

Less commonly recessive *PMP22* mutations (homozygous point mutations) (Parman et al., 1999) or compound heterozygous deletions (Al-Thihli et al., 2008; Abe et al., 2010) cause classic DSD. Hence children with a severe phenotype carrying a *PMP22* deletion should be analysed for mutations in the other *PMP22* allele. In addition, heterozygous *PMP22* duplications (usually associated with a classic CMT1 phenotype) can also cause a phenotype resembling DSD, accounting for 7% of all infantile neuropathies in

the series by Baets *et al.* compared to 1% for *PMP22* point mutations, although the MNCV may lie in the CMT1A rather than DSD range (Gabreels-Festen, 2002; Baets *et al.*, 2011). Congenital foot deformities in the presence of otherwise normal early development are a common presentation in these infants (Baets *et al.*, 2011). Nerve biopsies have a lower g-ratio (thicker myelin sheaths) compared to *PMP22* point mutations (Gabreels-Festen, 2002). Homozygous duplications of *PMP22*, albeit rare, can also cause DSD (Lupski *et al.*, 1991; Kaku *et al.*, 1993; Sturtz *et al.*, 1997), although curiously, the homozygous state does not always cause greater clinical severity or additional slowing of motor nerve conduction (LeGuern *et al.*, 1997).

PMP22, a 22-kDa glycoprotein with four putative transmembrane domains, accounts for 2%–5% of compact myelin of the peripheral nervous system (Snipes *et al.*, 1992; Haney *et al.*, 1996). *PMP22* may play a role in proliferation and differentiation of Schwann cells. Whilst altered gene dosage (CMT1A, HNPP) causes abnormal growth and differentiation of these cells, missense mutations within the transmembrane domains (where the majority of point mutations lie) are thought to result in a number of toxic gain-of-function effects including impaired intracellular protein trafficking, accumulation of mutant *PMP22* in the endoplasmic reticulum (ER), inhibition of post-endoplasmic reticulum protein degradation and cell apoptosis (Colby *et al.*, 2000; Khajavi *et al.*, 2007).

Early onset neuropathies due to *MPZ* mutations

The number of clinical phenotypes associated with *MPZ* mutations (CHN, DSD, CMT1B, intermediate CMT, and a CMT2-like phenotype) exemplifies the limitations of the current CMT classification, but also provides insight into the possible roles of *MPZ* in peripheral myelin. Nevertheless, most affected individuals have either an early onset demyelinating neuropathy, or a later onset neuropathy with axonal features. Most mutations are associated with a specific phenotype (Shy *et al.*, 2004; Shy, 2006). In a recent series, *MPZ* mutations accounted for 6% of all infantile neuropathies (Baets *et al.*, 2011).

Most children with early onset demyelinating *MPZ* neuropathies have a DSD phenotype, presenting with hypotonia or delayed motor development. Most do not walk until three to four years of age, and some as late as ten years. Increasing weakness and scoliosis may develop and some require wheelchairs for mobility (Shy *et al.*, 2004; Shy, 2006). A few cases designated as CHN have been reported (Warner *et al.*, 1996; Mandich *et al.*, 1999), including two presenting at birth with hypotonia, arthrogryposis, respiratory failure and almost no myelin on nerve biopsy (Szigeti *et al.*, 2003; Smit *et al.*, 2008). Pupillary

abnormalities such as Adie's pupil may be seen with both early and late onset *MPZ* mutations, providing an important diagnostic clue (Gabreels-Festen, 2002). Facial weakness, sensorineural hearing loss, bulbar problems, and rarely ptosis with limited extraocular movements (Fabrizi *et al.*, 1999) are also reported. Whilst data on long-term outcomes is limited, most subjects survive into adulthood, albeit requiring mobility assistance (Bird *et al.*, 1997; Shy, 2006).

Motor conduction velocities are usually less than 12 m/s. CMAP and sensory nerve action potential (SNAP) amplitudes are reduced (and sometimes unobtainable) in all patients (Shy, 2006). Apart from the expected neuropathologic findings of myelinated fibre loss, myelin thinning (or absent myelin in some cases of CHN), and onion bulb formations, two distinct and mutually exclusive ultrastructural abnormalities have been described in some patients: focally folded myelin sheaths, or areas of uncompacted myelin, reflecting the role of *MPZ* in myelin adhesion and compaction (Gabreels-Festen *et al.*, 1996; Shy, 2006) (Fig. 2).

Whilst the overwhelming majority of early onset neuropathies associated with *MPZ* are because of dominant heterozygous (often *de novo*) mutations, recessive homozygous or compound heterozygous mutations are occasionally identified. In these cases, heterozygous parents have a milder neuropathy, with MNCVs ranging from 29 to 54 m/s (Ikegami *et al.*, 1996; Warner *et al.*, 1996).

MPZ is a member of the immunoglobulin gene superfamily with a single extracellular, intracellular, and cytoplasmic domain. It functions as a homophilic adhesion molecule, playing an important role in myelin adhesion and compaction. Most mutations causing early onset demyelinating neuropathies are in the extracellular domain and likely to alter the *MPZ* tertiary structure and interfere with myelination (Shy *et al.*, 2004). A dominant negative effect of mutant *MPZ* at the plasma membrane has been demonstrated, as has impaired mutant protein trafficking with ER accumulation, which can induce apoptosis and protein degradation (Filbin *et al.*, 1999; Khajavi *et al.*, 2005; Grandis *et al.*, 2008).

Early onset neuropathies due to *EGR2* mutations

Mutations in *EGR2* account for less than 1% of CMT cases overall (Boerkoel *et al.*, 2002) and 1% of infantile neuropathies (Baets *et al.*, 2011). Approximately 11 cases of CHN/DSD have been reported, the majority with *de novo* heterozygous missense mutations (Warner *et al.*, 1998; Timmerman *et al.*, 1999; Boerkoel *et al.*, 2001a; Vandenberghe *et al.*, 2002; Numakura *et al.*, 2003; Szigeti *et al.*, 2007). Recessive inheritance was identified in one family with

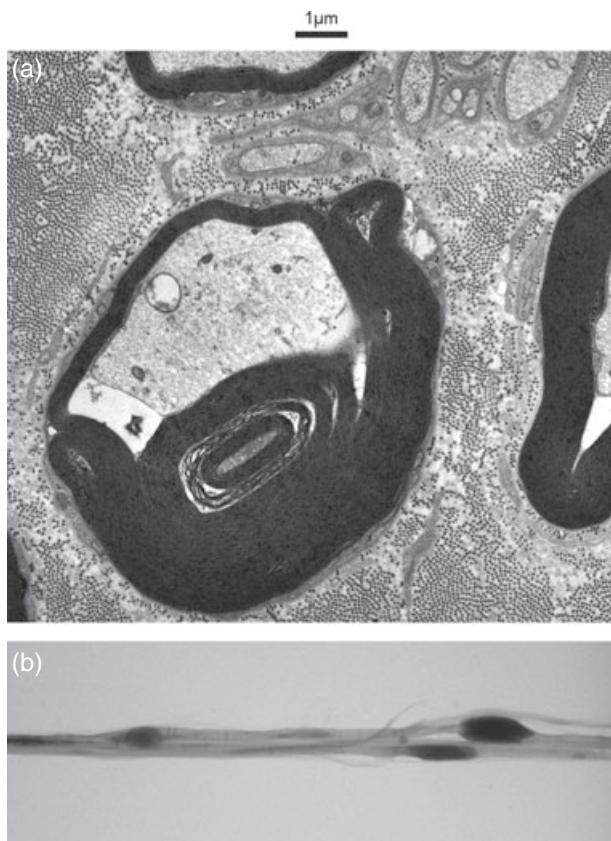


Figure 2. Sural biopsy of a 12-month-old female infant with an infantile-onset demyelinating neuropathy (Déjérine–Sottas disease phenotype) due to a heterozygous *de novo* mutation of *MPZ*. (a) Electron micrograph showing focal folding and thickening of myelin sheath. Axonal structure is preserved. (b) Teased fibres showing areas of focally folded myelin, with loss of myelin in intervening axonal segments (Osmium $\times 400$).

three affected siblings (designated CMT4E) (Warner *et al.*, 1998), and a clinical phenotype similar to the heterozygous cases. One patient with DSD had concurrent *EGR2* and *GJB1* mutations (Chung *et al.*, 2005). CMT1D is also associated with *EGR2* mutations but appears less common than the infantile syndromes (Warner *et al.*, 1998; Briani *et al.*, 2010).

Most cases present in the first few months of life with hypotonia and delayed motor development (Warner *et al.*, 1998; Boerkoel *et al.*, 2001a). One child with hip dysplasia never walked, had facial diplegia, bulbar difficulties, dysphagia, and died of respiratory failure at 6 years of age (Boerkoel *et al.*, 2001a). Peculiar to *EGR2*-related neuropathies is a high frequency of cranial nerve involvement (Pareyson *et al.*, 2000; Szigeti *et al.*, 2007). Ptosis (Warner *et al.*, 1998; Szigeti *et al.*, 2007), eye movement abnormalities (including Duane syndrome (Vandenbergh *et al.*, 2002), lateral rectus palsy (Boerkoel *et al.*, 2001a), nystagmus (Vandenbergh *et al.*, 2002)), pupillary abnormalities

(Szigeti *et al.*, 2007), tongue fasciculations (Warner *et al.*, 1998), and facial weakness (Boerkoel *et al.*, 2001a; Szigeti *et al.*, 2007) have all been described. The course is slowly progressive in most. Motor conduction velocities are usually < 12 m/s (Warner *et al.*, 1998; Timmerman *et al.*, 1999) but may be as high as 20 m/s (Szigeti *et al.*, 2007). Nerve biopsies show a range of hypomyelination (from almost complete myelin absence to thinly myelinated axons), as well as myelinated fibre loss, demyelination/remyelination, and onion bulb formations (Warner *et al.*, 1998; Timmerman *et al.*, 1999). Focally folded myelin sheaths were described in one patient (Timmerman *et al.*, 1999). Neuroimaging is normal in patients with cranial neuropathies (Pareyson *et al.*, 2000).

EGR2 is a zinc finger transcription factor which binds regulatory domains of target genes, including those critical for myelin formation and maintenance such as *MPZ*, *PMP22*, *Cx32*, *periaxin*, and *myelin basic protein* (Musso *et al.*, 2001; Nagarajan *et al.*, 2001; Jang and Svaren, 2009). Most mutations lie in the zinc finger domains, likely affecting DNA binding and transcription of these genes (Warner *et al.*, 1999). Knock-out *EGR2* mice display hypomyelination of the peripheral nervous system and abnormal hindbrain development (Schneider-Maunoury *et al.*, 1993; Topilko *et al.*, 1994), an interesting finding given the frequent cranial neuropathies associated with *EGR2* mutations.

Early onset neuropathies due to *NEFL* mutations

Dominant mutations in neurofilament light chain polypeptide (*NEFL*) cause CMT1F and CMT2E (Mersiyanova *et al.*, 2000; De Jonghe *et al.*, 2001; Jordanova *et al.*, 2003). Whilst most individuals with *NEFL* mutations become symptomatic in childhood or adolescence, a number of severe early onset cases have been caused by dominant, or occasionally recessive mutations (Jordanova *et al.*, 2003; Abe *et al.*, 2009; Yum *et al.*, 2009). *NEFL* mutations accounted for 1% of infantile neuropathies in one series (Baets *et al.*, 2011). Affected children present before the age of two years with hypotonia, delayed motor development or foot deformity (usually pes cavus). Distal weakness and wasting can be severe, and proximal weakness may be present. Additional features in early onset patients include intellectual disability, pyramidal signs, and hearing loss (Jordanova *et al.*, 2003; Abe *et al.*, 2009; Yum *et al.*, 2009). Ataxia and tremor have also been reported (Fabrizi *et al.*, 2007; Miltenberger-Miltenyi *et al.*, 2007).

Neurophysiologic findings are variable in *NEFL*-related neuropathies. Mixed axonal and demyelinating features may be present. MNCVs range from 12 to 56 m/s; in those with the early onset phenotype, MNCVs are between 12 and 35 m/s. CMAPs are usually moderately to severely reduced, and distal motor

latencies may be significantly prolonged (*Jordanova et al., 2003; Fabrizi et al., 2007; Yum et al., 2009*).

NEFL mutations probably do not cause a true “demyelinating” neuropathy, but rather an axonal neuropathy with secondary myelin loss. NEFL assembles into heteropolymers with heavy and medium neurofilaments, forming the major intermediate filament in axons. Neurofilaments determine axonal diameter and therefore conduction velocity (*Lee and Cleveland, 1996*). NEFL mutations disrupt neurofilament assembly and axonal transport, resulting in decreased axonal diameter, contributing to slowed conduction (*Brownlee et al., 2002; Sasaki et al., 2006*). On nerve biopsy the predominant finding is loss of large myelinated fibres with regenerating clusters (*Jordanova et al., 2003; Abe et al., 2009*). Some individuals have giant axons containing accumulations of irregularly oriented neurofilaments (*Fabrizi et al., 2004, 2007*). In one child with a homozygous nonsense mutation, sural nerve biopsy showed only small myelinated axons lacking neurofilaments (*Yum et al., 2009*). In occasional subjects demyelinating features such as small onion bulbs and irregular myelin sheaths are seen (*Jordanova et al., 2003; Zuchner et al., 2004*); these may represent secondary demyelinating changes.

Early onset neuropathies due to *GDAP1* mutations

In infancy, recessive *GDAP1* mutations are associated with an early onset neuropathy with demyelinating and/or axonal features which has been designated CMT4A (*Baxter et al., 2002*), CMT2H/K (*Cuesta et al., 2002*) and recessive “intermediate” CMT (*Senderek et al., 2003a*). In reality these conditions probably lie on a pathologic spectrum. A later onset autosomal dominant axonal neuropathy (CMT2K), with a milder phenotype, is also caused by *GDAP1* mutations (*Claramunt et al., 2005*).

The clinical phenotype associated with recessive *GDAP1* mutations is fairly homogeneous. Affected individuals present in the first year of life with prominent foot deformities, gait difficulties, and distal weakness (*Nelis et al., 2002; Sevilla et al., 2003*). Some are hypotonic at birth (*Sevilla et al., 2008*) but many have normal early motor development and walk by 2 years of age, although often limited by foot deformity (*Birouk et al., 2003; Senderek et al., 2003a; Sevilla et al., 2008*). Hand weakness develops in the first decade (*Senderek et al., 2003a*). Progression is relatively rapid, leading to severe distal weakness and atrophy of the feet and hands. Many patients develop “claw hands” within the first or second decade, and foot deformities are often severe (*Cuesta et al., 2002; Sevilla et al., 2008*). Progressive proximal weakness renders many subjects wheelchair-dependent by the

end of the second decade (*Sevilla et al., 2003; 2008*). A more slowly progressive course is described in some individuals (*Sevilla et al., 2003*). Vocal cord palsy, manifesting as hoarseness or change in voice quality, is a frequent feature (*Sevilla et al., 2008*). Diaphragmatic dysfunction and restrictive lung disease are also very common (*Sevilla et al., 2008*). Facial weakness has been described (*Boerkoel et al., 2003*) and one patient had optic atrophy (*Claramunt et al., 2005*).

Both axonal and demyelinating features are apparent. MNCVs range from 20 to 60 m/s, with MNCVs in the demyelinating (*Nelis et al., 2002; De Sandre-Giovannoli et al., 2003*), axonal (most commonly) (*Cuesta et al., 2002; Sevilla et al., 2008*) and intermediate range in individual patients (*Senderek et al., 2003a*). CMAPs are low amplitude or unrecordable (*Sevilla et al., 2008*). On nerve biopsy some patients have a predominantly demyelinating process, with a decrease in the number of myelinated fibres, segmental demyelination and frequent onion bulb formations (*Baxter et al., 2002; De Sandre-Giovannoli et al., 2003*). Focal myelin folding is occasionally noted (*Boerkoel et al., 2003*). More commonly, a primarily axonal process is present, with axonal degeneration, regeneration and pseudo-onion bulbs (*Birouk et al., 2003; Sevilla et al., 2008*). In some, a mixed demyelinating-axonal picture is present (*Senderek et al., 2003a*).

GDAP1 mutations are considered to be one of the most frequent causes of recessive CMT, accounting for 15% of European CMT families in one study (*Nelis et al., 2002*). Lower frequencies have been reported by other groups (*Ammar et al., 2003*), and only 1% of infantile neuropathy cases were caused by *GDAP1* in the series reported by Baets *et al.* (2011). A founder mutation has been found in Hispanic populations (*Boerkoel et al., 2003*).

The *GDAP1* protein is expressed in axons, localised to the outer mitochondrial membrane (*Niemann et al., 2005; Pedrola et al., 2005*), and involved in mitochondrial fission and regulation of the mitochondrial network (*Niemann et al., 2005; 2009*). The axonal neuropathy, vocal cord and optic nerve involvement in this neuropathy resemble the early onset axonal neuropathy (CMT2A) due to mutations in *mitofusin 2* (*MFN2*), another mitochondrial protein (*Zuchner et al., 2006*).

Early onset neuropathies due to *MTMR2* mutations (CMT4B1)

Mutations in the *myotubularin-related protein 2* gene (*MTMR2*) are an uncommon cause of recessive CMT (CMT4B1) (*Bolino et al., 2001*). A characteristic feature of CMT4B1 is prominent focally folded myelin sheaths on nerve biopsy. Redundant loops and folds of myelin wrap irregularly around the axon and are

seen as irregular focal thickenings on teased fibre analysis (Quattrone et al., 1996; Houlden et al., 2001). The thickenings are thought to be distinct from the tomacula described in HNPP; they are smaller in diameter and more irregular in contour (Ohnishi et al., 1989; Houlden et al., 2001). Focal myelin folding is not specific to CMT4B1; it has also been observed in neuropathies due to *MTMR13*, *MPZ*, *PRX*, and *FGD4* mutations (Table 2). Other biopsy features of CMT4B1 include a marked decrease in myelinated fibre density, evidence of demyelination-remyelination, and rare onion bulb formations (Quattrone et al., 1996; Houlden et al., 2001).

Onset is usually within the first 2 years of life (Quattrone et al., 1996; Salih et al., 2000). Some patients have normal motor development during infancy (Quattrone et al., 1996). Early complaints are of gait difficulties and proximal leg weakness. Progressive involvement of the upper and lower limbs occurs in the first and second decades, and foot deformities are sometimes severe. By adulthood many are wheelchair-dependent (Quattrone et al., 1996; Houlden et al., 2001). Bilateral facial weakness is common (Salih et al., 2000), and vocal cord paresis and respiratory insufficiency may develop in adulthood (Quattrone et al., 1996; Houlden et al., 2001). MNCVs are in the demyelinating range (9–20 m/s) and CMAPs are usually low amplitude and dispersed. By adulthood upper and lower limb responses are usually unrecordable (Quattrone et al., 1996; Salih et al., 2000).

MTMR2 is a phospholipid phosphatase which dephosphorylates phosphoinositides (such as phosphatidylinositol 3-phosphate; PI(3)P), which are involved in membrane trafficking and homeostasis (Laporte et al., 2003). *MTMR2* and *MTMR13* (a catalytically inactive pseudophosphatase associated with CMT4B2) form heterotetramers and function together (Robinson and Dixon, 2005; Berger et al., 2006); loss of function probably leads to dysregulation of Schwann cell membrane homeostasis and abnormal myelin folding (Bolino et al., 2004; Bolis et al., 2007), and explains the similar pathologic features of CMT4B1 and CMT4B2.

Early onset neuropathies due to *MTMR13* mutations (CMT4B2)

An early onset recessive demyelinating neuropathy with focally folded myelin can also be caused by mutations in *myotubularin-related protein 13* (*MTMR13*), also known as *SET binding factor 2* (*SBF2*) (Azzedine et al., 2003; Senderek et al., 2003c). Some kindreds also have early onset glaucoma, which precedes onset of neuropathy in some individuals (Kiwaki et al., 2000; Azzedine et al., 2003; Hirano et al., 2004). Symptom onset is in infancy or early childhood with delayed motor milestones. CMT4B2 accounted

for 4% of infantile neuropathies in one series (Baets et al., 2011). MNCVs range from 14 to 26 m/s (Azzedine et al., 2003; Baets et al., 2011).

Early onset neuropathies due to *SH3TC2/KIAA1985* mutations (CMT4C)

Mutations in *SH3TC2* (*KIAA1985*) (Senderek et al., 2003b) are a relatively frequent cause of CMT4, accounting for approximately 17% of all cases (Azzedine et al., 2010), and 12% of infantile neuropathies (the highest frequency of all genes tested) (Baets et al., 2011). CMT4C is characterised by early onset severe spinal deformities (affecting over 90% of individuals in some series), which are often the presenting symptom (Kessali et al., 1997; Azzedine et al., 2006). There is significant intra- and inter-familial variability. Symptoms usually begin in childhood or adolescence (Azzedine et al., 2006), but some cases present with hypotonia and scoliosis in the first few months of life, or with delayed motor development (Senderek et al., 2003b; Baets et al., 2011). Most children walk by 24–30 months of age (Senderek et al., 2003b; Colomer et al., 2006), although in rare instances ambulation is never achieved (Gooding et al., 2005; Colomer et al., 2006). Foot deformity is common, often severe, and may precede onset of weakness (Kessali et al., 1997; Azzedine et al., 2006). Some have a normal neurologic examination at presentation despite prominent skeletal deformity (although nerve conduction tests are abnormal) (Kessali et al., 1997). Hearing loss is the most common form of cranial nerve involvement (Azzedine et al., 2006; Gosselin et al., 2008); but internal ophthalmoplegia (Houlden et al., 2009b), facial weakness (Azzedine et al., 2006), nystagmus (Senderek et al., 2003b), and tongue atrophy/fasciculations (Colomer et al., 2006; Houlden et al., 2009b) are also reported.

The clinical course is variable. In some, progression is slow and ambulation maintained past the fifth decade (Senderek et al., 2003b; Gooding et al., 2005). Others are wheelchair-dependent within the first decade (Gosselin et al., 2008). The spinal deformities are also variably progressive, and surgery is required in some patients (Kessali et al., 1997; Gabreels-Festen et al., 1999). Respiratory insufficiency or hypoventilation may also occur (Kessali et al., 1997; Azzedine et al., 2010).

Nerve conduction studies confirm a demyelinating neuropathy, with MNCV ranging from 4 to 37 m/s (mean 23 m/s) (Senderek et al., 2003b; Azzedine et al., 2006). Neuropathological features include loss of myelinated fibres, thinly myelinated fibres, basal lamina onion bulbs, and large cytoplasmic Schwann cell processes surrounding multiple unmyelinated axons; the latter thought to be a distinguishing

feature (Gabreels-Festen et al., 1999; Senderek et al., 2003b). Abnormal organization of the node of Ranvier (Arnaud et al., 2009), and rarely, giant distended axons (Azzedine et al., 2006) and focally folded myelinated fibres are seen (Houlden et al., 2009b).

SH3TC, expressed exclusively in Schwann cells (Arnaud et al., 2009), is thought to play a role in endosomal recycling and membrane trafficking processes required for normal myelin formation (Lupo et al., 2009; Stendel et al., 2010).

Early onset neuropathies due to *PRX* mutations (CMT4F)

Periaxin-related neuropathies are characterised by delayed motor development, prominent sensory involvement and extremely slowed nerve conduction (Delague et al., 2000; Boerkoel et al., 2001b; Marchesi et al., 2010), a phenotype consistent with DSD. The locus was first reported in a large inbred Lebanese family with a recessive demyelinating CMT designated CMT4F (Delague et al., 2000); *periaxin* (*PRX*) was subsequently identified as the responsible gene. All cases demonstrate recessive inheritance (Boerkoel et al., 2001b; Guilbot et al., 2001). In one cohort of 20 unrelated DSD patients, three had *PRX* mutations (four had *MPZ*, three *PMP22*, and two *EGR2* mutations) (Boerkoel et al., 2001b), and *PRX* mutations accounted for 5% of infantile neuropathies in other series (Baets et al., 2011).

Most cases present in infancy with delayed motor development. Affected children may not walk until 4–5 years of age (Takashima et al., 2002; Marchesi et al., 2010). The neuropathy is slowly progressive and weakness generally limited to distal muscles. Ambulation is maintained into late adulthood (Delague et al., 2000; Marchesi et al., 2010). Sensory involvement, including sensory ataxia is common and often out of proportion to the degree of motor involvement (Boerkoel et al., 2001b; Marchesi et al., 2010). Some patients complain of positive sensory symptoms (Delague et al., 2000; Boerkoel et al., 2001b). Scoliosis is common but is usually mild (Takashima et al., 2002; Parman et al., 2004). Hearing loss and tongue fasciculations are reported in some patients (Takashima et al., 2002).

Conduction velocities are extremely low (and often undetectable even in childhood) with MNCV usually less than 10 m/s (range 2–20 m/s) (Boerkoel et al., 2001b; Marchesi et al., 2010). Temporal dispersion is marked in some (Takashima et al., 2002). SNAPs are usually absent (Takashima et al., 2002; Marchesi et al., 2010). Typical neuropathologic features include moderate to severe loss of myelinated fibres, and classic and basal lamina onion bulbs. Focally folded myelin may be seen (Guilbot et al., 2001; Takashima

et al., 2002). Paranodal abnormalities (abnormal paranodal myelin loops and Schmidt–Lantermann incisures) have been reported in three patients (Takashima et al., 2002; Parman et al., 2004). Immunohistochemistry demonstrates absent C-terminal L-periaxin staining (Guilbot et al., 2001; Parman et al., 2004).

PRX encodes periaxin, a cytoskeleton-associated protein expressed exclusively in myelinating Schwann cells as L- or S-periaxin by alternative splicing (Scherer et al., 1995; Dytrych et al., 1998). Periaxin links the basal lamina to the Schwann cell cytoskeleton by interacting with the dystroglycan complex through dystrophin-related protein-2, and is important in elongation of Schwann cells and myelination during development (Scherer et al., 1995; Court et al., 2004). Periaxin-deficient mice display peripheral demyelination and interestingly, prominent sensory involvement (Gillespie et al., 2000).

Early onset neuropathies due to *FGD4* mutations (CMT4H)

Mutations in *FGD4* or *frabin* (FGD1-related F-actin binding protein) cause a recessive demyelinating CMT designated CMT4H (De Sandre-Giovannoli et al., 2005; Delague et al., 2007), and account for 3% of infantile neuropathies (Baets et al., 2011). Age at onset can range from infancy to childhood. Most affected children walk by 2–3 years of age and clinical progression is slow. Scoliosis and foot deformities are common (De Sandre-Giovannoli et al., 2005; Stendel et al., 2007). Nerve conduction velocities are markedly reduced, with MNCV ranging from 5 to 13 m/s (Stendel et al., 2007; Houlden et al., 2009a). On nerve biopsy decreased myelinated fibre density, thin myelin sheaths, demyelination–remyelination, and classic onion bulbs are seen. Focal irregular myelin foldings are prominent, similar to those seen in CMT4B1 and 4B2 (De Sandre-Giovannoli et al., 2005; Fabrizi et al., 2009).

FGD4 is a Rho GDP/GTP nucleotide exchange factor expressed in many tissues including peripheral nerve (Ikeda et al., 2001; Delague et al., 2007). *FGD4* induces changes in Schwann cell shape (Stendel et al., 2007). In addition, pathologic similarities between CMT4H and CMT4B, and the presence of phosphoinositide binding domains in frabin, suggest that altered phosphoinositide metabolism may be a shared mechanism for abnormal myelination in these forms of CMT (Fabrizi et al., 2009).

Early onset neuropathies due to *FIG4* mutations (CMT4J)

Mutations in *FIG4* cause CMT4J, a rare recessive demyelinating neuropathy with variable severity and age of onset ranging from early childhood to mid- to late-adulthood. Some early onset cases have

been diagnosed with DSD; these children had delayed motor milestones or early gait abnormalities and very slow nerve conduction (<12 m/s). CMAP amplitudes were markedly reduced or absent. One child had MNCVs of 29–41 m/s. Nerve biopsies in these early onset cases reflect a primarily demyelinating process with extensive myelinated fibre loss, onion bulbs and segmental demyelination on teased fibre analysis. Unusual features of CMT4J include prominent proximal weakness, asymmetric involvement, and sometimes rapid progression of muscle weakness precipitated by trauma. In those with early onset disease, weakness is progressive and wheelchair dependency occurs by the third decade (Chow *et al.*, 2007; Zhang *et al.*, 2008; Nicholson *et al.*, 2011).

FIG4 is a phosphoinositide phosphatase; CMT4J is thought to be a disorder of phosphoinositide signalling similar to CMT4B1, 4B2, and 4H (Chow *et al.*, 2007).

Early onset neuropathies associated with *GJB1* mutations

Mutations in *gap junction protein beta-1* (*GJB1*, or *connexin 32*) are associated with X-linked CMT (CMTX) type 1, which is classically associated with symptom onset in the first or second decade (Bergoffen *et al.*, 1993). In one paediatric series, however, delayed development in 38% of affected children reflected onset in infancy (Yiu *et al.*, 2011). *GJB1* neuropathy is slowly progressive, and most patients remain ambulant (Dubourg *et al.*, 2001). Sensorineural hearing loss may occur (Dubourg *et al.*, 2001; Yiu *et al.*, 2011). Whilst females generally have a milder course, onset in infancy or a severe phenotype can occur, likely secondary to skewed X-chromosome inactivation (Liang *et al.*, 2005; Yiu *et al.*, 2011). Nerve conduction velocities are in the “intermediate range”, that is, 25–45 m/s, and CMAP amplitudes usually low (Nicholson and Nash, 1993; Yiu *et al.*, 2011). Both demyelinating and axonal features are apparent on nerve biopsies (Birouk *et al.*, 1998; Hahn *et al.*, 2001a), with reduced myelinated fibre density, thinned myelin sheaths, and onion bulb formations in some patients (Yiu *et al.*, 2011). Paranodal abnormalities are also described (Hahn *et al.*, 2001a).

Other forms of CMTX occurring in infancy are associated with mental retardation (CMTX2) (Ionasescu *et al.*, 1992), hearing loss and cognitive deficits (CMTX4) (Cowchock *et al.*, 1985), distal weakness, foot deformities, and significant conduction slowing (Yiu *et al.*, 2011).

Demyelinating Neuropathies of Infancy Associated with Central Nervous System Involvement

Many of these disorders involve the central nervous system (CNS) in addition to peripheral nerve myelin. These can be divided into two groups: those with CNS hypomyelination (i.e., myelin is deficient), and those in which the white matter is abnormal (Schiffmann and van der Knaap, 2009). In patients with these disorders, CNS involvement often masks clinical signs of a peripheral neuropathy.

As this review is focused on disorders in which neuropathy is the prominent feature, detailed descriptions of these conditions should be sought elsewhere. However, we will briefly cover those disorders associated with CNS hypomyelination. Other relevant clinical syndromes are presented in Table 4.

Special mention should also be made of metachromatic leukodystrophy (late-infantile form) and Krabbe disease. Both are consistently associated with an early onset demyelinating sensorimotor peripheral neuropathy (MacFaul *et al.*, 1982; Cameron *et al.*, 2004; Siddiqi *et al.*, 2006). Importantly, both can present in infancy with a neuropathy which appears clinically isolated for several months, without other neurologic manifestations (De Silva and Pearce, 1973; Korn-Lubetzki *et al.*, 2003; Haberlandt *et al.*, 2009). Conduction velocities are usually <30 m/s (Cameron *et al.*, 2004; Siddiqi *et al.*, 2006). Multifocal conduction slowing is sometimes seen in metachromatic leukodystrophy (Cameron *et al.*, 2004). Prompt diagnosis of these conditions is important given the potential benefits of early bone marrow transplantation (Burns *et al.*, 2003).

Demyelinating neuropathies of infancy associated with CNS hypomyelination

Hypomyelination and congenital cataract

Hypomyelination and congenital cataract (HCC) is an autosomal recessive disorder characterised by congenital cataracts, demyelinating neuropathy, slowly progressive neurologic impairment (with spasticity and cerebellar signs), and mild to moderate intellectual disability (Zara *et al.*, 2006; Biancheri *et al.*, 2007). Cataracts are generally noted at birth or within the first month of life. Developmental delay is apparent in the first year. Most children walk with support by 24 months of age but lose ambulation by eight to nine years of age. Seizures and scoliosis may occur (Zara *et al.*, 2006; Biancheri *et al.*, 2007).

MNCVs range between 11 and 39 m/s (Biancheri *et al.*, 2007; Ugur and Tolun, 2008). Loss of myelinated fibres with thinly myelinated or amyelinated axons is seen on nerve biopsy; occasionally small onion bulb formations, uncompacted myelin and irregularly folded

Table 4. Infantile demyelinating neuropathies with CNS involvement.

	Inheritance	Gene	Other features
Associated with CNS hypomyelination			
Hypomyelination with congenital cataracts (HCC)	AR	<i>DRCTNNBIA</i>	Congenital cataracts, pyramidal signs, cerebellar signs, intellectual disability
Peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome and Hirschsprung disease (PCWH)	AD	<i>SOX10</i>	Waardenburg syndrome, Hirschsprung disease, spasticity, ataxia, dysautonomia, intellectual disability
Pelizaeus-Merzbacher disease	X-linked	<i>PLP1*</i>	Early nystagmus and titubation, ataxia, spasticity, movement disorder, intellectual disability
Pelizaeus-Merzbacher like disease	AR	<i>GJA12</i>	Nystagmus, ataxia, delayed development
Cockayne syndrome	AR	<i>ERCC6, ERCC8</i>	Growth failure, photosensitivity, retinopathy, progressive neurologic impairment
Associated with abnormal CNS white matter			
Metachromatic leukodystrophy	AR	<i>ARSA</i>	Psychomotor regression, spasticity, seizures
Krabbe disease	AR	<i>GALC</i>	Extreme irritability, spasticity, psychomotor regression
Niemann–Pick disease type C†	AR	<i>NPC1, NPC2</i>	Hepatomegaly, vertical gaze palsy, progressive ataxia, dystonia, cataplexy
Merosin-deficient congenital muscular dystrophy	AR	<i>LAMA2</i>	Proximal weakness, raised creatine kinase, muscular dystrophy
Navajo neurohepatopathy	AR	<i>MPV17</i>	Liver disease, corneal scarring, recurrent metabolic acidosis, recurrent infections, failure to thrive
Associated with other CNS involvement			
Congenital disorders of glycosylation	AR	<i>Multiple genes</i>	Variable features
Congenital cataracts, facial dysmorphism and neuropathy (CCFDN)	AR	<i>CTDP1</i>	Congenital cataracts, microretina, intellectual disability, facial dysmorphism, short stature, hypogonadism
POLG-related hepatocerebral mtDNA deletion syndromes	AR	<i>POLG1</i>	Encephalopathy, refractory seizures, liver dysfunction
Leigh syndrome	AR, X-linked, mitochondrial	<i>Multiple genes</i>	Psychomotor regression, brainstem and basal ganglia signs, raised lactate levels

AD, autosomal dominant; AR, autosomal recessive.

*Peripheral neuropathy associated with *PLP1* null mutations only.

†Peripheral neuropathy rarely seen in Niemann–Pick disease type.

myelin are also present (*Biancheri et al., 2007*). Brain MRI shows diffuse supratentorial hypomyelination in all patients (*Rossi et al., 2008*).

HCC is caused by mutations in *DRCTNNBIA* (also known as *FAM126A*) which encodes a membrane protein called hyccin, which is of unknown function but clearly essential for proper myelination. The amount of residual hyccin seems to correlate with disease severity (*Zara et al., 2006*).

SOX10 related conditions

Heterozygous mutations in *SOX10* cause Waardenburg syndrome (hearing loss and pigmentary

abnormalities) associated with Hirschsprung disease, also known as Waardenburg–Hirschsprung syndrome, Shah–Waardenburg syndrome, or WS4 (*Pingault et al., 1998*). Some subjects also have central and/or peripheral demyelination, leading to a syndrome called “PCWH” (peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome, and Hirschsprung disease) (*Inoue et al., 1999; 2004*).

Severe cases have hypotonia and weakness, arthrogryposis, and respiratory insufficiency causing death within the first three months of life (*Touraine et al., 2000; Inoue et al., 2002*). Milder cases

have variable hypotonia, spasticity, ataxia, growth retardation, and dysautonomia (Pingault et al., 2000; Inoue et al., 2004).

Nerve conduction studies show MNCV ranging from 2 to 38 m/s (Inoue et al., 2004). Findings on nerve biopsy include absent peripheral myelin (Inoue et al., 2002), micropolyfasciculation with thin myelin sheaths (Pingault et al., 2000), and excessive myelin folding (Inoue et al., 2004). Cerebral MRI shows variable degrees of hypomyelination (Inoue et al., 1999; Verheij et al., 2006), or dysmyelination (Inoue et al., 2004; Verheij et al., 2006). Some subjects have normal cerebral neuroimaging (Pingault et al., 2000; Touraine et al., 2000) or agenesis of the semicircular canals (Pingault et al., 2002).

SOX10 is a transcription factor which plays a crucial role in the early stages of neural crest development, glial cell development, and myelin formation and maintenance (Kuhlbrodt et al., 1998; Britsch et al., 2001). Heterozygous mutations causing haploinsufficiency tend to cause isolated Waardenburg-Hirschsprung syndrome, whilst in PCWH mutant SOX10 protein exerts a dominant-negative effect (Inoue et al., 2004).

Pelizaeus-Merzbacher disease

Classic Pelizaeus-Merzbacher-disease (PMD) due to a duplication of *PLP1* (Inoue et al., 1996) is an X-linked disorder characterised by diffuse CNS dysmyelination and onset in infancy with hypotonia, nystagmus, and titubation, with later development of spasticity, ataxia and a movement disorder (Inoue, 2005). Although *PLP1* is present in compact myelin of the peripheral nervous system (Garbern et al., 1997), individuals with classic PMD do not have peripheral neuropathy (Shy et al., 2003). Those with *PLP1*-null mutations (far less common) however, have a mild to moderate demyelinating neuropathy associated with a milder CNS phenotype. MNCVs range from 20 to 50 m/s (Garbern et al., 1997; Shy et al., 2003).

Pelizaeus-Merzbacher-like disease

Pelizaeus-Merzbacher-like disease (PMLD) due to recessive mutations in gap junction protein *GJA12* (*connexin 47*) shares similar features with PMD: diffuse CNS dysmyelination, early onset nystagmus and hypotonia, delayed development and progressive spasticity and ataxia (Uhlenberg et al., 2004; Bugiani, 2006). Seizures and a mild demyelinating peripheral neuropathy occur in some patients (Uhlenberg et al., 2004; Henneke et al., 2008). A proportion of patients with PMLD do not carry *GJA2* mutations, suggesting genetic heterogeneity (Henneke et al., 2008).

Cockayne syndrome

Cockayne syndrome (CS) is a recessively inherited multisystem disorder characterised by growth failure, early developmental delay with progressive neurologic impairment, CNS hypomyelination and cutaneous photosensitivity. Peripheral neuropathy is frequent. Other typical features include sensorineural hearing loss, dental caries, pigmentary retinopathy, and a characteristic “cachectic dwarfism” appearance (Nance and Berry, 1992; Neilan, 2006). CS encompasses a spectrum of phenotypes. Types I (classic CS) and II (congenital CS, also known as cerebro-oculo-facial syndrome) present in the first two years of life (Neilan, 2006). Overt signs of peripheral neuropathy are uncommon, but nerve conduction studies generally show a demyelinating neuropathy (MNCV 20–38 m/s) (Nance and Berry, 1992). Nerve biopsy findings include segmental demyelination and remyelination, with membrane bound electron-dense inclusions in some Schwann cells (Vos et al., 1983; Schenone et al., 1986).

Congenital cataracts facial dysmorphism neuropathy syndrome

Congenital cataracts facial dysmorphism neuropathy syndrome (CCFDN) has, to date, been reported only in individuals of Balkan Gypsy ethnicity. CCFDN is caused by homozygous founder mutations in the *CTDP1* gene, which encodes the protein phosphatase FCP1 involved in the regulation of RNA polymerase II (Varon et al., 2003).

This disorder is characterised by bilateral cataracts, facial dysmorphism (evident from late childhood), a progressive demyelinating/hypomyelinating neuropathy, mild intellectual disability, short stature and hypogonadotrophic hypogonadism (Tournev et al., 1999a). Congenital cataracts, the first manifestation of the disorder, may be accompanied by other ophthalmologic abnormalities such as microcornea and microphthalmia (Tournev et al., 1999a; Mullner-Eidenbock et al., 2004). Most children do not walk before two to three years. The neuropathy manifests early and is progressive, causing severe disability by the third decade. Skeletal deformities are common (Tournev et al., 1999b; Kalaydjieva et al., 2005). Some individuals with CCFDN have recurrent parainfectious rhabdomyolysis (Mastroianni et al., 2007). CNS involvement is manifest by mild intellectual disability and non-specific brain MRI abnormalities (cerebral atrophy and periventricular white matter changes) (Kalaydjieva et al., 2005).

Nerve conduction studies show conduction slowing (20–30 m/s) after 12 months of age. Sensory responses are often preserved despite the slowed nerve conduction (Tournev et al., 1999b; Kalaydjieva et al., 2005). Nerve biopsy shows thinly myelinated

fibres with mildly reduced density but no onion bulb formations; in older patients superimposed demyelination/remyelination and axonal degeneration may be seen (Tournev *et al.*, 1999a; Shabo *et al.*, 2005).

Conclusion

The infantile-onset demyelinating neuropathies are a genetically heterogeneous group of conditions, and a diagnostic and management challenge for most clinicians. Targeted genetic testing based on clinical, neurophysiologic, and sometimes neuropathologic information enables a definitive diagnosis in some, but not all, children. With the increasing use of advanced techniques such as next-generation sequencing, it seems likely our ability to genetically characterise these conditions will improve rapidly, provided adequate bioinformatics systems exist to manage the explosion in genetic data. Symptomatic management, surveillance and genetic counselling issues are often common to these various conditions regardless of the underlying aetiology. More specific and targeted approaches may become available in the future for some of these inherited conditions, hopefully paralleling our ability to understand their genetic basis.

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