PERIPHERAL NEUROPATHY IN COMPLEX INHERITED DISEASES: AN APPROACH TO DIAGNOSIS

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ABSTRACT

Peripheral neuropathy is a common finding in patients with complex inherited neurological diseases and may be subclinical or a major component of the phenotype. This review aims to provide a clinical approach to the diagnosis of this complex group of patients by addressing key questions including the predominant neurological syndrome associated with the neuropathy e.g. spasticity, the type of neuropathy, and the other neurological and non-neurological features of the syndrome. Priority is given to the diagnosis of treatable conditions. Using this approach, we associated neuropathy with one of three major syndromic categories - 1) ataxia, 2) spasticity, and 3) global neurodevelopmental impairment. Syndromes that do not fall easily into one of these three categories can be grouped according to the predominant system involved in addition to the neuropathy e.g. cardiomyopathy and neuropathy. We also include a separate category of complex inherited relapsing neuropathy syndromes, some of which may mimic Guillain Barré syndrome, as many will have a metabolic aetiology and be potentially treatable.

INTRODUCTION

Inherited peripheral neuropathies can occur as a “pure” neuropathy or as part of a more complex neurological or multi-system disorder. Charcot Marie Tooth disease (CMT) and the related neuropathies, distal hereditary motor neuropathy (HMN) and hereditary sensory neuropathy (HSN) are the classical “pure” neuropathies. They commonly present with a characteristic phenotype of a length-dependant, isolated neuropathy progressing over decades [1].

In the second group of disorders, where neuropathy is part of a more complex disease, the diagnosis is more challenging. In addition to well recognised causes of these complex neuropathies (e.g. Friedreich’s ataxia), next generation sequencing (NGS) has identified an ever expanding number of causative genes. These include genes that were originally thought to cause other neurological syndromes (e.g. Atlastin 1 was originally identified as causing Hereditary Spastic Paraparesis but also causes hereditary sensory neuropathy [2,3]) and complex inherited diseases (such as Krabbe’s disease) which can present with a CMT like neuropathy, and in which the neuropathy may remain as the only manifestation of the disease [4].

This review aims to provide a comprehensive list of the complex inherited neuropathy syndromes and an approach to diagnosis that is based on the major clinical features eg. ataxia plus neuropathy or spasticity plus neuropathy as a pragmatic framework for clinical practice. While aimed at adult neurologists, this review includes some childhood diseases, including *forme frustes* that have adult presentations, such as recessive mutations in *IGHMBP2,* which cause Spinal Muscular Atrophy with Respiratory Distress (usually a fatal childhood disease), but can cause adult onset recessive CMT2 [5].

COMPREHENSIVE DISEASE LIST GENERATION

To identify complex inherited diseases associated with a peripheral neuropathy, we compiled the authors' lists and performed a PUBMED search (in September 2016) for all publications describing a syndromic inherited neuropathy. The following search syntax was used: ("peripheral neuropathy") AND ("inherit*" OR "genetic") NOT ("Charcot Marie Tooth"). All papers which described an inherited neuropathy in conjunction with other clinical features were included. For each condition identified in the search, the presence of a neuropathy was confirmed by reviewing the original clinical description and neurophysiology. Multiple reviews exist, including our recent review, for the "pure" neuropathies [1], i.e. CMT and related disorders so these will not be covered except for selected cases that we feel are more appropriately classified as a complex inherited neuropathy syndrome.

A clinically based approach to the complex inherited neuropathy syndromes

Even knowing where to start in the diagnostic evaluation of a patient with a complex inherited neuropathy syndrome can feel daunting. This is in part due to the large number of potentially causative genes but also to the rarity of these diseases, some of which have are so rare (as small as single families) that even an experienced clinician is unlikely to have encountered them. The situation is further complicated by the fact that the neuropathy can be a major feature of the syndrome or largely masked by other clinical features. In this

review we included all inherited syndromes in which neuropathy has been described even if it is only a minor feature and present in a minority of patients (e.g. SPG3A due to dominant mutations in *Atlastin 1* [2]). This is because the most prominent phenotype of a syndrome may vary for a particular genetic condition. For example, in a patient with Friedreich's ataxia, a sensory neuropathy may be the main presenting feature whereas in others it may be a cerebellar ataxia. Having identified 157 complex inherited diseases with a neuropathy, we addressed the following four questions.

1. What is the predominant neurological phenotype?
2. Is the neuropathy predominantly motor or sensory and is the neuropathy clearly axonal or are the conduction velocities slow?
3. What are the other neurological and non-neurological features of the disease?
4. Is the disease treatable?

This strategy allowed us to develop a diagnostic approach based on the identification of the predominant phenotype (See figure 1). For the majority of conditions this can be divided into the following three major neuropathy associated categories 1) ataxia, 2) spasticity and 3) global neurodevelopmental impairment. For the complex neuropathy syndromes that do not fall easily into one of these three categories we used 11 other phenotypic categories 1) extra pyramidal features 2) ophthalmic disease, 3) cranial neuropathies and deafness, 4) endocrinopathy, 5) musculoskeletal disease / myopathy, 6) cardiomyopathy, 7) hepatic and gastrointestinal disease, 8) renal failure, 9) haematological and immunological diseases and 10) skin and connective tissue features. We also include a separate category of complex inherited relapsing neuropathy syndromes, some of which may mimic Guillain Barre

syndrome. This is an important group of diseases as many have a metabolic aetiology and are often treatable if identified early in the disease course.

The introduction of NGS (either whole genome, whole exome or gene specific panels) into clinical practice offers great promise for diagnosing complex inherited neuropathy syndromes [6]. The ability to sequence all known disease genes (>150 genes can cause a neuropathy as part of a complex inherited syndrome and almost 100 additional genes cause a form of CMT), however, is not a panacea for diagnosing this group of patients. The challenge, therefore, is the interpretation of the large number of novel variants identified in known disease genes for each individual. Knowing the phenotypes of the inherited complex neuropathy syndromes is one key to interpreting these variants. Because the prognosis of rare, treatable complex inherited neuropathy syndromes depends on early diagnosis, we have prioritised early diagnostic screening.

The cost of next generation sequencing in the form of disease specific panels is often cheaper than targeted Sanger sequencing of individual genes. We therefore recommend proceeding to disease specific panels (e.g. ataxia, spasticity, developmental delay) in the first instance. The only exception is for the ataxia and neuropathy syndromes where we recommend targeted testing for repeat expansion diseases first in cases with an appropriate phenotype (e.g. Friedreich's ataxia, FXTAS, SCA1, 2, 3, 10, 12). With advances in next generation sequencing, it is likely that disease specific panels will eventually be able to reliably detect repeat expansions.

Major Complex inherited neuropathy categories

Ataxia and neuropathy syndromes (Table 1a).

In the diagnostic evaluation of patients with neuropathy and cerebellar ataxia, we propose an initial screen for treatable causes followed by categorisation into whether the neuropathy is sensory and motor, predominantly motor, or predominantly sensory as well as those with slow nerve conduction velocities (less than acceptable for axonal loss). Patients without an obvious initial diagnosis and a neuropathy with either normal or slow conduction velocities should have blood levels of phytanic and pristanic acid (Refsum's disease may be treated with dietary modification and plasma exchange [7]) as well as very long chain fatty acids and lysosomal enzymes measured (Allogenic bone marrow transplantation may be effective in some peroxisomal and lysosomal storage diseases (e.g. adrenoleukodystrophy) [8,9]). Vitamins E and B12, including methylmalonic acid and homocysteine (to screen for functional vitamin B12 deficiency) should be measured as deficiencies may cause an ataxia and neuropathy phenotype and may be treatable [10]. Finally, although rare, plasma cholestanol for cerebrotendinous xanthomatosis is an important disease to identify early in the disease course as it is preventable with dietary modification and treatment with chenodeoxycholic acid. Clues to this diagnosis include the combination of diarrhoea, cataracts or infantile jaundice [11].

Most patients with ataxia and a neuropathy will have an axonal neuropathy with normal nerve conduction velocities and reduced distal amplitudes. A motor predominant axonal neuropathy or neuronopathy is rare in the ataxia neuropathy syndromes but is seen in SCA2 and SCA36 [12]. SCA2 is a trinucleotide repeat disease and therefore may not be identified

on NGS. Interestingly, an expansion size of between 30 and 35 repeats are associated with amyotrophic lateral sclerosis [13], whereas larger expansion sizes will cause a combined neuropathy, ataxia syndrome often with slow saccadic eye movements, tremor and occasionally an extrapyramidal disorder that may mimic multiple system atrophy [14]. SCA36 presents as a late adult onset ataxic syndrome with a distal motor neuropathy and bulbar involvement [12]. It is caused by a hexanucleotide expansion.

Ataxia and a sensory axonal neuropathy is the most common combination caused by recessive mutations in a variety of genes, usually with disease onset in the first decade. The sensory neuropathy may contribute to the manifestations of the ataxia. Friedreich's ataxia, due to a trinucleotide repeat expansion in the FDRA gene is the commonest form [15]. Ataxia telangiectasia, early onset ataxia with oculomotor apraxia and hypoalbuminemia (EAOH/aprataxin) and spinocerebellar ataxia, autosomal recessive 1 (SCAR1/senataxin) may also cause a sensory ataxic neuropathy syndrome similar to Friedreich's ataxia often in association with a raised serum alpha fetoprotein level. Distinguishing clinical features include the presence of cardiomyopathy in Friedreich's ataxia, 'oculomotor apraxia' in EAOH and SCAR1 and chorea, conjunctival telangiectasia and the susceptibility to infections and malignancies in ataxia telangiectasia [15].

The autosomal dominant SCAs 1,3,7,10 and 12 may all cause a sensory and motor axonal neuropathy. They are all due to repeat expansions and may therefore require targeted genetic testing. Phenotypic clues to the individual SCAs include extrapyramidal signs and ophthalmoplegia in SCA3 [16], pigmentary macular degeneration in SCA7 and prominent tremor in SCA12 [17,18].

A neuropathy with slow nerve conduction velocities (SNCV) is rare in patients with an ataxia neuropathy syndrome. The most common by far is autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) due to recessive mutations in the *SACS* gene, which encodes the molecular chaperone protein, DNAJC29 [19]. Neuropathy may be the presenting issue and the most prominent clinical finding (see supplementary table 1 for an example of the neurophysiology) [19]. In addition to ataxia and a neuropathy, patients may develop a myelopathy and in rare cases seizures. Ataxia, combined peripheral and cerebellar, with hearing loss and diabetes mellitus (APCHD), due to recessive mutations in another heat shock protein DNAJC3, may also cause a SNCV neuropathy [20]. Finally, PHARC (polyneuropathy, hearing loss, ataxia, retinitis pigmentosa and cataracts) syndrome is also a rare cause [21].

Further diagnostic clues can be obtained by MR imaging of the brain. This may identify white matter changes that are highly suggestive of specific diagnoses for some ataxia neuropathy syndromes - high signal of the deep white matter tracts of the brain and dorsal columns and lateral corticospinal tracts due to recessive *DARS2* mutations [22], T2 high signal of the middle cerebellar peduncles in Fragile X tremor ataxia syndrome [23] and white matter signal abnormalities and bilateral dentate nuclei lesions of the cerebellum in cerebrotendinous xanthomatosis [24] (See Figure 2).

Spasticity and neuropathy syndromes (Table 1b).

The initial diagnostic evaluation of patients with spastic neuropathy syndromes without an obvious cause should include measurement of vitamin B12, methylmalonic acid and folate, phytanic and pristanic acid (alpha-methylacyl-CoA racemase deficiency; AMACR), very long

chain fatty acids and lysosomal enzymes. In addition, one should have a low threshold for performing MR imaging of the spinal cord to find a structural cause of myelopathy.

After screening for treatable spastic neuropathy syndromes, we suggest that the next step is to define the underlying neuropathy. Unlike the neuropathy ataxia syndromes, a motor axonal neuropathy is a feature of some hereditary spastic paraplegias (HSP) which may present as either a HSP or distal hereditary motor neuropathy. In SPG20 (Troyer syndrome), a distal motor neuropathy is seen in combination with spasticity, short stature and learning difficulties [25]. SPG9A and SPG9B are also characterised by spastic paraplegia, learning difficulties and a distal motor neuropathy in addition to cataracts and skeletal abnormalities [26]. SPG17 (Silver syndrome) is an autosomal dominant disorder due to *BSCL2* mutations and is a relatively common cause of HSP and distal motor neuropathy predominantly affecting the upper limbs [27]. Distal spinal muscular atrophy type 2 (DSMA2), due to recessive mutations in SIGMAR1, causes a similar phenotype but preferentially affecting the extensor muscles of the forearm [28]. The combination of motor neuropathy and spastic paraplegia has also been reported in SPG39 [29] and SPG12 (MMR and AMR personal observation in a recessive case).

SPG10 is a more common cause of spasticity and a mixed motor and sensory axonal neuropathy and may be complicated by cognitive decline and parkinsonism [30].

A pure sensory axonal neuropathy and spasticity is less common but in combination with an ulceromutilating phenotype suggests mutations in *CCT5* (HSN with spastic paraplegia) [31], *ARL6IP1* (SPG61) and rarely *ATL1* (SPG3A) [3,32].

A neuropathy with SNCV in association with spasticity is also rare but reported in ARSACS and PHARC syndrome (see ataxia neuropathy section) [21,33]. In addition, SNCV have been described in the neuropathy associated with the peroxisomal disorder, AMACR [34].

Bladder involvement, which is probably not uncommon in many kinds of HSPs may be a prominent feature of adult polyglycosan body disease [35], adrenomyeloneuropathy and SPG5A [36,37].

MRI of the brain can provide important diagnostic clues (See Figure 2). Periventricular white matter lesions suggestive of multiple sclerosis may be seen in adult onset polyglycosan body disease and SPG5A [35,36]. Some cases of neurodegeneration with brain iron accumulation diseases may present as a spasticity neuropathy syndrome (e.g. mutations in *PLA2G6, C19orf12*/SPG43); MRI shows iron deposition in the basal ganglia[38,39]. Finally, a group of recessive spastic paraplegia genes associated with a thin corpus callosum on MRI have recently been identified as a cause of neuropathy spasticity syndromes. SPG11 is the commonest of these syndromes and presents with spastic paraplegia, cognitive decline, sensory and motor axonal neuropathy and often weight gain [40]; patients with SPG15 have a similar phenotype but with pigmentary maculopathy [41]; SPG46 is a similar disease to SPG11 but with cataracts [42].

Global neurodevelopmental impairment and neuropathy syndromes (Table 1c)

Achieving a diagnosis is more difficult in this phenotypic category. Most are rare. Characterising the phenotype may be challenging, as there is a broad range of phenotypes including spasticity, ataxia, cardiomyopathy, endocrine and gastrointestinal dysfunction and

dermatological manifestations, further complicated by developmental delay. Nevertheless, with the advent of NGS, it is likely that milder forms of these diseases will be described and an awareness of the key clinical features may assist in diagnosis. Few are currently treatable, but screening for metachromatic leukodystrophy and Krabbe disease is recommended as both may be treatable disorders. In addition, there are clinical trials for Aicardi-Goutieres syndrome and giant axonal neuropathy. (ClinicalTrials.gov identifier NCT02362453 and NCT02362438).

As for the spastic and ataxic neuropathy syndromes, defining the type of neuropathy can be helpful in achieving a genetic diagnosis. A pure motor axonal neuropathy as part of a complex neurodevelopmental syndrome is seen with mutations in *DYNC1H1* and *BICD2* [43,44]. The two conditions are almost identical and can present as arthrogryposis predominantly affecting the lower limbs. Other causes of a motor neuropathy / neuronopathy in this group include pontocerebellar hypoplasia Type 1 B and hexosaminidase A and B deficiency [45,46].

Global developmental delay is a relatively common finding in several of the congenital insensitivity to pain syndromes (e.g. recessive *CTLCL1* mutations [47]), although in some cases the sensory nerve conduction studies may be normal despite significant ulceromutilation as is seen with recessive loss of function *SCN9A* mutations [48]. Recessive mutations in *TECPR2* are a rare cause of a sensory and autonomic neuropathy with global developmental delay, in which patients also experience chronic respiratory disease, apnoeas and seizures [49].

A peripheral neuropathy with SNCV is a more common finding amongst this group of diseases and includes the lysosomal storage diseases metachromatic leukodystrophy and

Krabbe disease. Other causes include HLD5 (leukodystrophy, hypomyelination and congenital cataracts) [50], congenital disorders of glycosylation (recessive *PMM2* mutations)[51], Andermann's syndrome (agenesis of the corpus callosum and peripheral neuropathy)[52], Cockayne syndrome[53], Leigh' syndrome due to *SURF1* and *MFF* mutations [54,55], the complex infantile onset IMNEPD (complex neurodegeneration in the context of hearing loss and pancreatic insufficiency)[56] and Aicardi Goutières Syndrome which is an inflammatory disease that presents as an inflammatory syndrome and may respond partially to immunosuppression [57].

MRI of the brain can be useful for directing genetic investigations in this group of patients (See Figure 2). The detection of a leukodystrophy is seen in many of the lysosomal storage disorders and in metachromatic leukodystrophy, if characteristic, should prompt further investigations in the face of low normal aryl sulfatase activity to ensure that a suplhatide activator protein deficiency is not missed [58]. Other diseases associated with white matter findings pointing to a possible leukodystrophy include Krabbe disease, congenital disorders of glycosylation, HLD5, giant axonal neuropathy and Aicardi Goutieres syndrome [50,51,59].

Other MRI findings may also provide clues to the genetic aetiology - agenesis of the corpus callosum in Andermann's syndrome (ACPN) [52], cerebral dysgenesis in the severe CEDNIK syndrome [60], pontocerebellar hypoplasia in PCH 1B and 9 (where it is also associated with agenesis of the corpus callosum) [61,62] and iron deposition in NB12A due to *PLA2G6* [38] mutations, and striatal necrosis in Aicardi Goutières syndrome [57].

Other complex inherited neuropathy categories

Extrapyramidal disease and neuropathy syndromes (Table 2a)

Peripheral neuropathy is a rare association with extrapyramidal disease and is most commonly seen in the context of mitochondrial disease due to either nuclear or mitochondrial DNA mutations. The classical SANDO syndrome of sensory axonal neuropathy, dysarthria and ophthalmoplegia can be associated with parkinsonism [63]. Chorea and dystonia in the context of a motor predominant neuropathy is seen with both Chorea acanthocytosis and McLeod's syndrome [64].Finally, recessive mutations in *HSJ1* and both dominant and recessive mutations in *LRSAM1* (proteins involved in the ubiquitin proteosome system), present with late onset CMT2 but may develop Parkinson's disease later in life [65,66].

Ophthalmological and neuropathy syndromes (Table 2b)

Performing a thorough ophthalmological examination to detect external ophthalmoparesis, optic atrophy, retinitis pigmentosa and cataracts can be useful in refining the potential genetic diagnosis of a complex inherited neuropathy syndrome.

The combination of severe optic atrophy and a mild and predominantly sensory axonal neuropathy is suggestive of mutations in either *OPA1* or *OPA3* [67,68]. These patients often have other clinical features including pseudo-obstruction, deafness, extrapyramidal signs and progressive external ophthalmoplegia. Mutations in *MFN2*, the cause of CMT2A may also cause optic atrophy and an axonal neuropathy but in almost all cases the neuropathy predominates [69].

Retinitis pigmentosa is a relatively common feature amongst the complex neuropathy syndromes, particularly disorders of mitochondria (e.g. Kearns Sayer and NARP syndromes) and the peroxisome (Refsum' and related diseases including AMACRD) [7,34,70]. In addition, retinitis pigmentosa is also a feature of several other rare conditions including PHARC syndrome and the congenital disorders of glycosylation [21,51]. Most importantly, it is a feature of a treatable (high doses of B12) genetic B12 deficiency syndrome (MMACHC), in which vitamin B12 plasma levels are normal but the downstream metabolites methylmalonic acid and homocysteine are elevated [71].

Cataracts are common in the general population but are helpful diagnostically if present in young patients. Although present in several conditions, e.g. PHARC, congenital cataracts facial dysmorphism and neuropathy (CCFDN), and HLD5 [21,50,72], most importantly they are a feature of the treatable disease cerebrotendinous xanthomatosis and their presence should prompt testing of plasma cholastenol levels [11].

Cranial neuropathies and deafness (Table 2c)

Bilateral facial weakness and bulbar palsy is an uncommon phenotype in the complex neuropathy syndromes and strongly suggestive of spinal bulbar muscular atrophy (Kennedy's disease) or Brown –Vialetto-Van-Laere (BVVL) syndromes [73,74]. Of these, BVVL is an important diagnosis not to miss. It is due to recessive mutations in one of two riboflavin transporters and both forms appear to respond to riboflavin supplementation [74,75]. BVVL is almost always associated with deafness. In BVVLS2, patients often present with a sensory ataxic neuropathy whereas in BVVLS1 it is predominantly a motor neuronopathy. Some but not all patients with BVVLS2 may have an abnormal plasma acyl carnitine profile [74].

Progressive external ophthalmoplegia is the commonest disorder of cranial musculature and is seen with both nuclear and mitochondrial DNA mutations [76]. The presence of Duane syndrome, a congenital and non-progressive strabismus with a mild sensory and motor axonal neuropathy is seen with dominant mutations in *TUBB3* [77].

Sensory neuronal deafness as part of a complex neuropathy syndrome is commonly, but not exclusively, seen with mitochondrial disorders. The presence of sensory neuronal hearing loss in combination with a myopathy, although most commonly seen with mitochondrial disease, is also a feature of a distal myopathy and neuropathy overlap syndrome caused by mutations in *MYH14*[78]. The combination of ataxia, demyelinating neuropathy and sensory neuronal hearing loss is common to both PHARC syndrome and ACPHD [20,21]. Finally, although classified as a hereditary sensory neuropathy, HSN1E is defined by the presence of sensory neuronal hearing loss in combination with dementia and, in some cases, narcolepsy [79].

Endocrinopathy and neuropathy syndromes (Table 2d)

Although diabetes mellitus is a feature of mitochondrial disease and a number of other complex syndromes including APCHD and Kennedy's disease, its high prevalence in the general population reduces its discriminatory value [20,73]. Adrenal insufficiency, however, is a useful diagnostic clue for adrenomyeloneuropathy but also the achalasia, hypo adrenalism, alacrima syndrome (AAAS) [80]. Ambiguous genitalia in combination with global neurodevelopmental impairment and a mixed sensory and motor axonal neuropathy is seen in the gonadal dysgenesis with minifascicular neuropathy syndrome [81].

Musculoskeletal / myopathy and neuropathy syndromes (Table 2e)

The presence of a myopathy in combination with a leukodystrophy, ataxia, global developmental delay and a sensory and motor peripheral neuropathy with SNCV is almost diagnostic of congenital disorder of glycosylation type 1A [51]. A mild neuropathy with slow conduction velocities is also seen in merosin deficient congenital muscular dystrophy but is not a dominant feature [82]. To date, a sensory and motor axonal peripheral neuropathy with giant axons has been described in myofibrillar myopathy due to recessive mutations in *BAG3,* but the clinical phenotype is dominated by the myopathy and cardiomyopathy [83]. Recessive mutations in lamin A/C are a cause of CMT2 in North Africa, however dominant mutations in the same gene causing a limb girdle muscular dystrophy may rarely be associated with a sensory and motor axonal neuropathy [84].

To date, only a subclinical sensory axonal neuropathy has been described in patients with multiple acyl CoA dehydrogenase deficiency. It is possible that forms of the disease exist in which neuropathy is a more prominent feature. The disease is characterised by episodes of hypoglycaemia, acidosis, and a lipid storage myopathy. Most importantly, it is responsive to riboflavin supplementation [85].

Finally, genes that were originally reported to cause distal hereditary motor neuropathy are now recognised to cause both a myopathy and motor neuropathy [86,87]. This is most pronounced for patients with mutations in *HSPB8* in whom the myofibrillar myopathy dominates the clinical picture [87].

Cardiomyopathy and neuropathy syndromes (Table 2f).

Cardiomyopathy is seen in a number of complex inherited neuropathy syndromes including myofibrillar myopathy due to *BAG3* mutations, mitochondrial disease, Fabry disease, Friedreich's ataxia and McLeod's syndrome.

The presence of an acquired cardiomyopathy in adulthood in combination with a painful sensory and motor axonal neuropathy is highly suggestive of familial amyloid polyneuropathy. Although tissue confirmation of amyloid is important, in the correct clinical context, sequencing of the *TTR* gene is warranted as a number of old (liver transplantation) and new (tafamidis and diflusinal) treatments are available [88]. A significant minority of patients with TTR amyloidosis have been reported with a SNCV neuropathy mimicking CIDP (see supplementary table 2 for example).

Hepatic, gastrointestinal (GI) and neuropathy syndromes (Table 2g).

Recurrent episodes of acute liver failure in combination with a neuropathy is suggestive of mitochondrial disease and has been described with mutations in the nuclear genes *DGUOK* and *MPV17* and can occur in autosomal recessive spinocerebellar ataxia 21 [89,90].

Hirschsprung disease is a developmental disorder of the mesenteric plexus and, in combination with global developmental delay and a neuropathy with SNCV, is seen with dominant mutations in *SOX10* [91]. The association of Hirschprung disease, global neurodevelopmental impairment and an axonal sensory and motor neuropathy is seen in Goldberg-Shprintzen megacolon syndrome due to recessive mutations in *KIAA1279* [92].

Pseudo obstruction is an increasingly recognised complication of mitochondrial disease and can be caused by a number of gene mutations including *POLG, RRM2B* and *TPP* [89]. In its

most severe form, MNGIE (mitochondrial neurogastrointestinal encephalopathy) patients may present with a neuropathy resembling CMT or chronic inflammatory demyelinating polyneuropathy associated with severe GI disturbance and weight loss [93]. It is most commonly due to recessive mutations in the nuclear gene thymidine phosphorylase and can be screened for by testing for elevated levels of thymidine and deoxyuridine in plasma. The disease arises from a deficiency of the enzyme thymidine phosphorylase, which is expressed in platelets. Allogenic bone marrow and liver transplantation have been successfully employed as treatments for this condition [89,94].

The combination of adult onset refractory diarrhoea, sensory axonal neuropathy and dysautonomia is suggestive of familial amyloid polyneuropathy but also rarely mutations in the prion protein gene, *PRNP* [95]. In the latter it is associated with dementia but this often occurs late in the disease.

Renal failure and neuropathy syndromes (Table 2h).

Renal failure is rare in the complex inherited neuropathy syndromes. Nephropathy is a feature of familial amyloid polyneuropathy but it is rare for patients with mutations in *TTR* to develop frank renal failure. Renal failure is also seen in Fabry disease, an X-linked disorder associated with a painful sensory and small fibre neuropathy, angiokeratoma, strokes and a cardiomyopathy.

An intermediate form of CMT due to dominant mutations in *INF2*, a gene expressed in the glomerulus and peripheral nerve, is associated with a focal segmental glomerulosclerosis [96]. In almost all cases the degree of renal failure eventually requires renal replacement therapy. The recently described action myoclonus-renal failure syndrome is characterised by

a progressive myoclonic epilepsy and renal failure beginning in the second decade of life and associated with a sensory and motor neuropathy with slow conduction velocities [97].

Haematological and immunological neuropathy syndromes (Table 2i).

The combination of haematological abnormalities and a peripheral neuropathy is unique to a small number of syndromes. The most important to recognise are the disorders of cobalamin (B12) metabolism that result in functional B12 deficiency. The commonest of this group of diseases is methylmalonic aciduria and homocystinuria, cb1C (MMACHC) which can cause a syndrome similar to sub-acute combined degeneration of the cord but also other haematological abnormalities including a form of vitamin B12 responsive thrombotic thrombocytopenic purpura [71].

Autosomal recessive mutations in *CD59*, a glycoprotein present on the cell surface that prevents formation of the complement mediated membrane attack complex, results in a combination of haemolytic anaemia, strokes and a relapsing remitting demyelinating neuropathy. Eculizumab, an inhibitor of the complement membrane attack complex, has been used successfully in one patient [98].

Chediak-Higashi syndrome is an immunodeficiency syndrome characterised by neutropaenia and an increased risk of lymphoma. It is associated with a sensory and motor axonal peripheral neuropathy and has been treated with allogenic bone marrow transplantation in selected cases [99].

Skin and connective tissue and neuropathy syndromes (Table 2j).

Photosensitivity is a rare symptom but in combination with a peripheral sensory and motor axonal neuropathy is suggestive of xeroderma pigmentosa (XP), a disease which is

associated with developmental delay and an increased risk of cutaneous malignancy [100]. Patient's with Cockayne syndrome also experience skin photosensitivity, but unlike XP, the neuropathy has SNCV and there is no increased risk of malignancy [53].

Skin laxity is an uncommon sign but is seen in combination with a SNCV neuropathy in dominant *FBLN5* mutations, and in combination with a mixed sensory and motor axonal neuropathy with recessive mutations of *PLOD1* and dominant mutations in *EMILIN1* [101,102]. It is important to recognise these two diseases as patients have an increased risk of large vessel injury and aneurysms and may need to enter an aneurysm screening programme.

Relapsing complex inherited neuropathy syndromes (Table 2k).

This group of diseases are important to recognise as they are more likely to have an underlying metabolic defect and are often treatable. The acute porphyrias, including acute intermittent porphyria, coproporphyria and variegate porphyria can present as an acute neuropathy mimicking Guillain Barre Syndrome [103]. In AIP, relapses are associated with abdominal pain and seizures whereas in variegate and coproporphyria there is skin photosensitivity. These diseases can be screened for acutely by testing for porphobilinogen in a light protected sample of urine. Identification of acute porphyria is important as early treatment with glucose and haematin in patients with an acute axonal neuropathy may improve the prognosis.

Tyrosinaemia can present similarly to acute intermittent porphyria. It is diagnosed by the detection of raised levels of succinylacetone in blood and urine. In the acute setting it is treated with plasma exchange. Nitisinone, which prevents the formation of the toxic

products malcylacetoacetic acid and fumarylacetoacetic acid offers a long term treatment [104].

Maple syrup urine disease has been reported as a cause of an acute axonal neuropathy mimicking Guillain Barre Syndrome and is treated with dietary reduction of protein intake [105]. Thiamine metabolism dysfunction syndrome 4 is a condition characterised by a progressive chronic axonal neuropathy superimposed by episodes of acute encephalopathy and paralysis following a febrile illness. Thiamine is an unproven but recognised treatment [106].

CONCLUSION

Although the advent of next generation sequencing means that it is now feasible to sequence all known complex inherited neuropathy genes in a practical timeframe, an overview of the phenotypes is still required to be able to help decide which novel variants are benign, which are pathogenic and which disease genes may not have been comprehensively screened using current NGS platforms. Obtaining an accurate genetic diagnosis in these conditions can be of great benefit to patients and their families especially for genetic counselling and to prevent unnecessary investigations. In this rapidly growing field, the identification of those diseases that may respond to treatment will always be the top priority particularly as the number of treatable conditions increases.

Competing Interests:

There are no competing interests.

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Figure 1. A diagnostic approach for patients with complex inherited neuropathy syndromes. The first step is to decide if the neuropathy is the sole feature of the disease i.e. Charcot Marie Tooth disease (CMT) or the related disorders, hereditary motor neuropathy and hereditary sensory neuropathy or if it is part of a more complex syndrome. In patients in whom there are additional features, the majority will fall into one of the three major categories, ataxia, spasticity or global neurodevelopmental delay. Further classification is based on the features of the neuropathy and the reader is directed to the appropriate table for the list of possible disease genes. A proportion of patients will not fall into one of these three categories ("other") and in this scenario, further classification is based on additional clinical features e.g. extra pyramidal disease and the reader is directed to the appropriate table for a list of disease genes. NCV=nerve conduction velocity.

Figure 2. Examples of central nervous system MR imaging that may assist in the diagnostic evaluation of patients with peripheral neuropathy as part of a complex inherited disease. Ai shows coronal FLAIR and Aii sagittal T1w images from a patient with SPG11 demonstrating a thin corpus callosum and cerebellar hypoplasia. B shows an axial T2w image of a patient with metachromatic leukodystrophy in which there is bilateral confluent white matter signal abnormality with cerebral volume loss. C is an axial T2w image from a patient with fragile X tremor ataxia syndrome and demonstrates bilateral signal change in the cerebellar peduncle (arrows) and pontine, peduncular and cerebellar volume loss. D shows coronal FLAIR (Di) and axial T2w (Dii) images from a patient with adult onset polyglycosan body disease demonstrating multifocal cerebral white matter lesions. E shows axial T2w (Ei) and coronal T1w (Eii) images from a patient with cerebrotendinous xanthomatosis demonstrating

symmetrical signal change involving the peridentate white matter of both cerebellar hemispheres. F shows a selection of images from a patient with leukencephalopathy with brainstem and spinal cord involvement and raised lactate (LBSL). Fi and Fii are sagittal and axial images of the cervical cord demonstrating longitudinally extensive T2 hyperintense signal change involving the dorsal and lateral columns. The characteristic brainstem signal change (red arrows) in an axial T2w image is shown in Fiii. Fiv shows the small lactate peak (red arrow) detected using localised 1H magnetic resonance spectroscopy. G shows axial T2w (Gi and Gii) and coronal FLAIR (Giii) images from a patient with Krabbe disease. The images show signal change involving the long tracts and deep grey matter. H shows axial T2w (Hi) and susceptibility weighted (SWI) (Hii and Hiii) images from a patient with neurodegeneration and brain iron accumulation (NBIA). Although the T2w image looks normal, the SWI images show increased susceptibility from abnormal mineralisation in the superficial and deep cortical grey matter.

Disease (OMIM)	Inheritance	Gene	Clinical description
A. Ataxia and neuropathy syndromes			
Ataxia and sensory predominant axonal neuropathy			
Friedreich ataxia/ FRDA-1 (229300)	AR	*FXN (repeat)*	Early onset ataxia, cardiomyopathy, myelopathy, optic atrophy, sensory axonal neuropathy.
EAOH (208920)	AR	*APTX*	Early onset ataxia, sensory axonal neuropathy, Oculomotor apraxia, Hypoalbuminemia (EAOH)
SCAR1 (606002)	AR	*SETX*	Juvenile onset ataxia, increased α–fetoprotein, nystagmus, cerebellar and pontine atrophy, oculomotor apraxia, sensory axonal neuropathy
Ataxia-telangiectasia (208900)	AR	*ATM*	Childhood onset progressive ataxia, conjunctival telangiectasia, sensory axonal neuropathy, chorea and dystonia, immunodeficiency and increased risk of malignancy, elevated α–fetoprotein
Abetalipoproteinaemia (200100)	AR	*MTP*	Young onset. Hypocholesterloaemia leading to malabsorption of fat soluble vitamins (vitamin E), acanthocytes, retinitis pigmentosa, progressive sensory axonal neuropathy
Ataxia with isolated vitamin E deficiency (277460)	AR	*TTPA*	Early onset ataxia and sensory axonal neuropathy similar to Friedreich ataxia, head titubation, normal fat absorption unlike abetalipoproteinaemia, rarely retinitis pigmentosa
Fragile X tremor ataxia syndrome (300623)	AD	*FXTAS* (repeat)	Late onset tremor, ataxia, parkinsonism, sensory axonal neuropathy, middle cerebellar peduncle changes on MRI
SCA27 (609307)	AD	*FGF14*	Learning difficulties, cerebellar ataxia, sensory axonal neuropathy
Galactosialidosis (256540)	AR	*CTSA*	Coarse facies, dwarfism, hearing loss, cherry red macular spot, global developmental delay, ataxia, haemangiomas, vascular abnormalities, rarely sensory axonal neuropathy
CANVAS (614575)	unknown	*unknown*	Late onset Cerebellar Ataxia, Sensory axonal neuropathy, Vestibular Areflexia Syndrome (CANVAS)
Ataxia and sensory-motor axonal neuropathy			
Leukoencephalopathy with brainstem and spinal cord involvement (LBSL) (611105)	AR	*DARS2*	Slowly progressive spasticity, ataxia and dorsal column dysfunction, sensory-motor axonal neuropathy, characteristic MRI findings
Neuropathy, ataxia, retinitis pigmentosa (NARP) (551500)	m8618insTm8993T>G m8993T>C m9185T>C	*MTATP6*	Ataxia, retinitis pigmentosa, cardiomyopathy, sensory-motor axonal neuropathy
SCAN1 (607250)	AR	*TDP1*	Cerebellar ataxia and sensory-motor axonal neuropathy

Peroxisome biogenesis disorder 6A (214100)	AR	*PEX10*	Failure to thrive, facial dimorphism, agenesis of the corpus callosum, death in first year of life, axonal motor neuropathy, progressive ataxia and sensory-motor axonal neuropathy in adulthood described
Microcephaly, seizures, and developmental delay (MCSZ) (613402)	AR	*PNKP*	Microcephaly, global developmental delay, progressive cerebellar ataxia and atrophy, sensory-motor axonal neuropathy
SCA1 (164400)	AD	*ATXN1 (repeat)*	Adult onset, cerebellar ataxia, spasticity, sensory-motor axonal neuropathy in 40%, occasional choreiform movements
SCA3/MJD (109150)	AD	*ATXN3 (repeat)*	Adult onset, cerebellar ataxia, external ophthalmoplegia, spasticity, extrapyramidal, sensory-motor axonal neuropathy in 50%
SCA7 (164500)	AD	*ATXN7 (repeat)*	Adult onset, cerebellar ataxia, pigmentary macular degeneration, sensory-motor axonal neuropathy
SCA10 (603516)	AD	*ATXN10 (repeat)*	Adult onset cerebellar ataxia, sensory-motor axonal neuropathy
SCA12 (604326)	AD	*PPP2R2B (repeat)*	Adult onset cerebellar ataxia, tremor of head and arms, subclinical sensory-motor axonal neuropathy
SCA23 (610245)	AD	*PDYN*	Cerebellar ataxia, sensory-motor axonal neuropathy
Spinocerebellar ataxia, autosomal recessive 21 (SCAR21) (607982)	AR	*SCYL1*	Early onset ataxia (<1 yr) with recurrent episodes of liver failure, sensory-motor axonal neuropathy, cerebellar atrophy
Ataxia and motor predominant axonal neuropathy			
SCA2 (183090)	AD	*ATXN2 (repeat)*	Adult onset, slow saccades, ataxia, tremor, parkinsonism, motor>sensory axonal neuropathy in 80%
SCA36 (614153)	AD	*NOP56*	Late adult onset gait ataxia, tongue atrophy and fasciculation, distal motor neuropathy
Ataxia and slow nerve conduction velocity (SNCV)			
Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa and cataracts (PHARC) (612674)	AR	*ABHD12*	Onset 2nd decade, neuropathy with SNCV, sensory neuronal hearing loss, retinitis pigmentosa, spastic paraplegia, ataxia
ARSACS (270550)	AR	*SACS*	Complex neurodegenerative disorder characterized by ataxia, spasticity, neuropathy with SNCV
Ataxia, combined cerebellar and peripheral, with hearing loss and	AR	*DNAJC3*	Cerebellar ataxia, neuropathy with SNCV, hearing loss, diabetes mellitus

diabetes mellitus ACPHD (616192)			
Cerebrotendinous xanthomatosis (213700)	AR	*CRP27A1*	Adolescent-onset progressive ataxia, myelopathy and dementia, cataracts, low cholesterol, atherosclerosis, xanthomas, soft palate myoclonus, intractable infantile-onset diarrhoea, cerebral white matter lesions on MRI, sensory>motor axonal neuropathy, SNCV described in a minority of patients
Refsum Disease (266500)	AR	*PHYH*	Sensory-motor neuropathy with normal or SNCV, deafness, retinitis pigmentosa, ichthyosis, heart failure, ataxia, raised CSF protein.
B. Spasticity and neuropathy syndromes			
Spasticity and sensory predominant axonal neuropathy			
HSN with spastic paraplegia (256840)	AR	*CCT5*	Severe mutilating sensory neuropathy with spastic paraplegia
SPG61 (615685)	AR	*ARL6IP1*	Childhood onset spastic paraplegia with mutilating, sensory>motor axonal neuropathy.
Spasticity and sensory-motor axonal neuropathy			
SPOAN (609541)	AR	*KLC2*	Early onset spastic paraplegia, congenital optic atrophy, and axonal sensory-motor neuropathy
SPG3A (182600)	AD	*ATL1*	Early onset spastic paraplegia, axonal sensory-motor neuropathy in some patients
SPG7 (607259)	AR	*PGN*	Spastic paraplegia, optic atrophy, ataxia and sensory-motor axonal neuropathy in some patients
SPG10 (604187)	AD	*KIF5A*	Adult onset; spastic paraplegia, axonal sensory-motor neuropathy, rarely parkinsonism and cognitive decline
SPG11 (604360)	AR	*SPG11*	Onset second decade, spastic paraplegia, intellectual disability and cognitive decline**, thin corpus callosum**, mild cerebellar eye signs, axonal sensory-motor neuropathy, parkinsonism and dystonia, pseudobulbar involvement
SPG15 (270700)	AR	*ZFYVE26*	As SPG11, but with pigmentary maculopathy
SPG26 (609195)	AR	*B4GALNT1*	Spastic paraplegia, intellectual disability, ataxia, dystonia, axonal sensory-motor neuropathy
SPG28 (09340)	AR	*DDHD1*	Spastic paraplegia, occasionally cerebellar eye signs and subclinical axonal neuropathy
SPG43 (615043)	AR	*C19orf12*	Childhood onset spastic paraplegia and sensory-motor axonal neuropathy, NBIA with optic atrophy, extrapyramidal signs
SPG46 (614409)	AR	*GBA2*	Spastic paraplegia, cognitive decline, **thin corpus callosum**, ataxia, cataracts, bulbar dysfunction, axonal sensory-motor neuropathy
SPG55 (615035)	AR	*C12ORF65*	Early onset spastic paraplegia, optic atrophy, intellectual impairment, axonal sensory-motor neuropathy

SPG56 (615030)	AR	*CYP2U1*	Onset 1st decade, spastic paraplegia, rarely dystonia and cognitive impairment, subclinical sensory-motor axonal neuropathy
SPG57 (615658)	AR	*TFG*	Childhood onset spastic paraplegia, sensory-motor axonal neuropathy, optic atrophy
Spastic ataxia 5	AR	*AFG3L2*	Early onset spastic paraplegia, later myoclonic epilepsy, sensory motor axonal neuropathy, ataxia, dystonia
Adult polyglucosan body disease (263570)	AR	*GBE1*	Late onset, cognitive impairment, spasticity, sensory-motor axonal neuropathy, bladder dysfunction, cerebellar and extrapyramidal signs also seen, periventricular white matter abnormalities on MRI
Spasticity and motor predominant axonal neuropathy			
Spinal muscular atrophy, distal (DSMA2) (605726)	AR	*SIGMAR1*	Spastic paraplegia, motor neuronopathy predominantly affecting the extensor muscles of the upper limbs
SPG4 (182601)	AD	*SPAST*	Infantile and adult onset spastic paraplegia, motor axonal neuropathy in some patients
SPG9A (601162) / SPG9B (616586)	AD/AR	*ALDH18A1*	Adolescent and adult onset spastic paraplegia, dysarthria and motor neuronopathy, cataracts, skeletal abnormalities
SPG12 (604805)	AD	*RTN2*	Spastic paraplegia, motor neuropathy seen with homozygous, recessive mutations (MMR, AMR, personal observation)
SPG17 (270685)	AD	*BSCL2*	Silver syndrome, spasticity, motor neuropathy in arms > legs
SPG20/ Troyer syndrome (275900)	AR	*SPG20*	Spasticity, short stature, mental retardation, facial dysmorphism, distal amyotrophy / motor neuropathy
SPG30 (610357)	AR	*KIF1A*	HSP with sensory motor axonal neuropathy +/- cerebellar signs
SPG39 (612020)	AR	*PNPLA6*	Childhood onset of slowly progressive spastic paraplegia; progressive distal motor neuropathy beginning in early through late adolescence
Spasticity and SNCV			
SPG5A (270800)	AR	*CYP7B1*	Childhood to adult onset spastic paraplegia and bladder dysfunction, periventricular white matter abnormalities on MRI, one patient described with SNCV
Adrenoleukodys-trophy (300100)	X-linked	*ABCD1*	Adrenomyeloneuropathy, spastic paraparesis, adrenal insufficiency, axonal sensory-motor neuropathy, sphincter disturbance
Alpha-methylacyl-CoA racemase deficiency (AMACRD) 614307)	AR	*AMACR*	Retinopathy, myelopathy, axonal or SNCV neuropathy, elevated phytanic and pristanic acids
C. Global neurodevelopmental impairment and neuropathy syndromes			

Global neurodevelopmental impairment and sensory predominant axonal neuropathy			
Congenital insensitivity to pain	AR	*CLTCL1*	Congenital insensitivity to pain and severe global developmental delay, dysmorphic, delayed myelination on brain MRI
Familial dysautonomia, hereditary, sensory autonomic neuropathy, with intellectual disability	AR	*TECPR2*	Global developmental delay, sensory axonal neuropathy, autonomic features, central apnoea / chronic respiratory disease, seizures, encephalopathy
MTDPS7 (271245)	AR	*C10ORF2*	Infantile onset ataxia, PEO, encephalopathy, deafness, seizures and sensory axonal neuropathy
Global neurodevelopmental impairment and sensory-motor axonal neuropathy			
Giant axonal neuropathy-1 (256850)	AR	*GAN*	Progressive neurodegenerative disorder characterized by spasticity ataxia and sensory-motor axonal neuropathy, kinky/curly hair
Neurodegeneration with brain iron accumulation 2A (NBI2A)/ infantile neuroaxonal dystrophy (INAD) (256600)	AR	*PLA2G6*	Infantile onset, progressive neurodegeneration (tetraplegia, dementia, visual loss) and axonal sensory-motor neuropathy, globus pallidus iron deposition on MRI
CEDNIK syndrome (609528)	AR	*SNAP29*	Cerebral Dysgenesis and severe psychomotor retardation, axonal sensory-motor Neuropathy, Ichthyosis, palmoplantar Keratoderma, fatal by 2nd decade of life.
Pyruvate dehydrogenase E1-alpha deficiency (PDHAD/312170)	X-linked	*PDHA1*	Episodic lactic acidosis, cerebellar ataxia, neurodevelopmental delay and clinical features resembling Leigh syndrome, neuropathy reported (NCV not reported)
Congenital disorder of deglycosylation (615273)	AR	*NGLY1*	Developmental delay, choreoathetosis, alacrimia, seizures, microcephaly, transaminitis, neuropathy
Hypomyelinating leukodystrophy 6 (HLD6/612438)	AD	*TUBB4A*	Early onset, delayed motor development, extrapyramidal movement disorder, spasticity, ataxia, rarely seizures and sensory-motor axonal neuropathy
Mental retardation 9 (601255)	AD	*KIF1A*	Developmental delay, microcephaly, seizures, extrapyramidal disorder, spasticity, cerebellar atrophy, sensory-motor axonal neuropathy
Harel-Yoon syndrome (HAYOS) (617183)	AD	*ATAD3A*	Global developmental delay, optic atrophy, axonal neuropathy, hypertrophic cardiomyopathy

PBD9B (614879)	AR	*PEX7*	Infantile (more severe) variant of Refsum disease, skeletal and facial dysmorphism, global developmental delay
MTDPS5 (612073)	AR	*SUCLA2*	'Leigh' like syndrome, deafness, progressive dystonia, mild methylmaolic acidaemia.
Global neurodevelopmental impairment and motor predominant axonal neuropathy			
Hexosaminidase A deficiency (272800)	AR	*HEXA*	Usually infantile onset, developmental delay and cognitive decline, visual loss ("cherry red spot"), motor>sensory neuronopathy, hypometric saccades, adult onset (2nd decade) cases described
Sandhoff disease (268800)	AR	*HEXB*	Indistinguishable from HEXA deficiency
Pontocerebellar hypoplasia type 1B (PCH1B) (614678)	AR	*EXOSC3*	Severe disease often with death in first 5 years, developmental delay, pontocerebellar hypoplasia on MRI, motor neuronopathy
Pontocerebellar hypoplasia (PCH9) (615809)	AR	*AMPD2*	Global developmental delay, spasticity, seizures, dysmorphic facies, axonal neuropathy, agenesis of the corpus callosum and cerebellar hypoplasia on MRI
Spinal muscular atrophy, lower extremity predominant (SMALED1) (158600)	AD	*DYNC1H1*	Congenital onset lower limb motor neuronopathy with contractures, global developmental delay and cerebral dysgenesis in some patients
Spinal muscular atrophy, lower extremity predominant (SMALED2) (615290)	AD	*BICD2*	Congenital onset lower limb motor neuronopathy with contractures, global developmental delay and cerebral dysgenesis in some patients
AAAS (231550)	AR	*AAAS*	Achalasia, addisonianism, alacrima, mental retardation, spastic tetraparesis, bulbospinal motor neuropathy, autonomic neuropathy
Spinal muscular atrophy with progressive myoclonic epilepsy (SMAPME) (159950)	AR	*ASAHI*	Onset first and second decade. Neurodevelopmental delay after onset of seizures. Motor neuronopathy.
Global neurodevelopmental impairment and SNCV			
Infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD)	AR	*PTRH2*	Infantile-onset multisystem disease with intellectual disability, microcephaly, progressive ataxia, sensory neuronal hearing loss, hepatomegaly, pancreatic insufficiency, proximal placement of thumb, SNCV neuropathy.

MEDNIK (609313)	AR	*AP1S1*	Congenital onset, Mental retardation, Enteropathy (severe congenital diarrhoea), Deafness, sensory-motor Neuropathy with intermediate conduction velocities, Ichthyosis, Keratoderma
Cockayne syndrome (216400/133540)	AR	*ERCC6/ ERCC8*	Dwarfism, optic atrophy, mental retardation, cutaneous photosensitivity, pigmentary retinopathy, deafness, neuropathy with slow conduction velocities
Leigh syndrome variant (256000)	AR	*SURF1*	Leigh syndrome (early onset progressive neurodegeneration of the brain stem, basal ganglia and spinal cord), neuropathy with SNCV
Encephalopathy due to defective mitochondrial and peroxisomal fission 2 (EMPF2) (617086)	AR	*MFF*	Leigh-like syndrome, developmental delay, optic atrophy, seizures, sensory-motor neuropathy with SNCV, Leigh syndrome-like MRI brain (T2 high signal of basal ganglia and sub thalamic nucleus)
Agenesis of the corpus callosum with peripheral neuropathy (ACCPN) (218000)	AR	*SLC12A6*	Mental retardation and progressive neurodegeneration, dysmorphic facies and facial diplegia, agenesis of the corpus callosum, neuropathy with intermediate conduction velocities
Aicardi-Goutieres syndrome	*TREX1 (606609, AD/AR) RNASEH2A (606034), RNASEH2B (AR, 610326), RNASEH2C (AR, 610330), SAMHD1 (AR, 606754), ADAR1 (AR, 146920), IFH1 (AD, 606951)*		Inflammatory syndrome, encephalopathy and psychomotor regression of utero or infantile onset, bilateral striatal necrosis, leukodystrophy, intracranial calcifications, CSF lymphocytosis, spastic paraparesis, rarely neuropathy with SNCV
Leukodystrophy hypomyelination and congenital cataract (HLD5 HCC) (610532)	AR	*FAM126A*	Congenital cataracts, global developmental delay from 1 year, diffuse cerebral hypomyelination on MRI, neuropathy with SNCV
Congenital disorder of glycosylation type 1A (CDG1A) (212065)	AR	*PMM2*	Neonatal onset, leukodystrophy, abnormal serum glycoproteins, mental retardation, hypotonia, ataxia, retinitis pigmentosa, seizures, slowly progressive neuropathy with SNCV, severe infections, hepatic insufficiency and cardiomyopathy.
Metachromatic leukodystrophy (250100)	AR	*ARSA*	Severe late infantile form with mental retardation and severe course. Regression before 30 months; adult onset, psychiatric symptoms, leukodystrophy on MRI, progressive neuropathy with SNCV, optic atrophy
Globoid cell leukodystrophy/ Krabbe (245200)	AR	*GALC*	Spastic paraplegia, developmental delay, optic atrophy; adult onset has spastic paraplegia and sensory-motor axonal neuropathy with slow or normal conduction velocities, MRI shows leukodystrophy

Pelizaeus-Merzbacher disease (PMD) (312080) SPG2 (312920)	X-linked	*PLP1*	Infantile onset, nystagmus, cognitive impairment, spasticity and ataxia, leukodystrophy on MRI, mild multifocal SNCV neuropathy seen with null mutations and more mild phenotype of mild spasticity and ataxia.

Table 1. A summary of the complex inherited neuropathy syndromes with one of the three major core clinical phenotypes of ataxia, spasticity or global neurodevelopmental impairment. For the sake of brevity, some conditions e.g. ARSACS, that could be classified in more than one major phenotypic category, only appear once in this table with the additional core features outlined in the clinical description. Number in parenthesis is the OMIM phenotype number. AR=autosomal recessive, AD=autosomal dominant. SNCV=slow nerve conduction velocities. SCAR1=spinocerebellar ataxia autosomal recessive 1, SCAN1= spinocerebellar ataxia autosomal recessive with axonal neuropathy, MTDPS=mitochondrial DNA depletion syndrome, CEDNIK=cerebral dysgenesis, neuropathy, ichthyosis and palmoplantar keratoderma syndrome, MEDNIK=mental retardation, enteropathy, deafness, peripheral neuropathy, ichthyosis and keratoderma, PEO=progressive external ophthalmoplegia, NBIA=neurodegeneration with brain iron accumulation

Disease (OMIM)	Inheritance	Gene	Clinical description
A. Extrapyramidal disease and neuropathy syndromes			
Leukoencephalopathy with dystonia and motor neuropathy (613724)	AR	*SCP2*	Dystonia, hyposmia, azoospermia, motor predominant axonal neuropathy, bilateral thalamic T2 high signal on MRI
MTDPS4B (613662)	AR	*POLG*	SANDO: Sensory Axonal Neuropathy, Dysarthria, Ophthalmoplegia, also parkinsonism and deafness. Also caused by recessive C10orf2 mutations.
Chorea acanthocytosis (200150)	AR	*VPS13A*	Onset 3rd to 5th decade, red cell acanthocytosis and progressive neurodegeneration, seizures, dysarthria, chorea, orofacial dyskinesia, psychiatric disturbance, axonal sensory-motor neuropathy, raised CK
McLeod syndrome (300842)	XL	*XK*	Onset 25-60, acanthocytes and Huntington-like syndrome, also epilepsy, cardiomyopathy, axonal motor neuropathy
CMT2P (614436)	AD/AR	*LRSAM1*	Onset 3rd to 8th decade. Late onset parkinsonism described
DSMA 5 (614881)	AR	*HSJ1*	Onset 2nd decade, motor predominant axonal neuropathy, rarely late onset parkinsonism
Mitochondrial disease	m1095T>C	*MTRNR1 (561000)*	Parkinsonism, deafness, and sensory-motor axonal neuropathy
SPG10 (604187)	AD	*KIF5A*	See table 1B
MTDPS5 (612073)	AR	*SUCLA2*	See table 1C
B. Ophthalmological and neuropathy syndromes			
Optic atrophy and neuropathy syndromes			
Syndromic optic atrophy (125250)	AD	*OPA1*	Optic neuropathy, PEO, deafness, myelopathy, sensory-motor axonal neuropathy
Costeff syndrome or OPA3-related 3-methylglutaconic aciduria (258501) Optic atrophy and cataracts (165300)	AR/AD	*OPA3*	Infantile optic atrophy, additionally, extra pyramidal disorder (chorea), ataxia, cognitive defects, axonal sensory neuropathy, autonomic neuropathy, pseudo-obstruction

Leber optic atrophy (53500)	Mitochondrial	MT-ND1, ND4, ND6	Optic atrophy, rarely neuropathy, spasticity, ataxia and extrapyramidal signs.
HMSN6B (616505)	AR	*SLC25A46*	Optic atrophy and progressive visual loss in the 1st decade, then spasticity, cerebellar ataxia, sensory-motor axonal neuropathy
CMTX5 (311070)	X-linked	*PRPS1*	Hearing loss, optic atrophy, sensory-motor axonal neuropathy
BVVLS2 (614707)	AR	*SLC52A2*	Facial and bulbar weakness, sensory ataxia, sensory-motor axonal neuropathy, optic atrophy, sensory neuronal hearing loss
SPOAN (609541)	AR	*KLC2*	See table 1B
SPG7 (607259)	AR	*PGN*	See table 1B
SPG43 (615043)	AR	*C19orf12*	See table 1B
SPG55 (615035)	AR	*C12ORF6*5	See table 1B
SPG57 (615658)	AR	*TFG*	See table 1B
Metachromatic leukodystrophy (250100)	AR	*ARSA*	See table 1C
Krabbe disease (245200)	AR	*GALC*	See table 1C
EMPF2 (617086)	AR	*MFF*	Leigh-like syndrome, see table 1C
Cockayne syndrome (216400/133540)	AR	*ERCC6/ERCC8*	See table 1C
Hexosaminidase A deficiency (272800)	AR	*HEXA*	See table 1C
Sandhoff disease (268800)	AR	*HEXB*	See table 1C
HAYOS (617183)	AD	*ATAD3A*	See table 1C.
Retinitis pigmentosa and neuropathy syndromes			
Methylmalonic aciduria and homocystinuria type Cb1c (MMACHC) (277400)	AR	*MMACHC*	Onset infancy to adulthood; thrombotic thrombocytopenia with encephalopathy, myelopathy, renal and pulmonary complications (can be life threatening), retinitis pigmentosa, axonal motor neuropathy; treat with high dose B12
Kearns-Sayre syndrome (530000)	mitochondrial		Ophthalmoplegia, retinitis pigmentosa, heart block, ptosis
Posterior column ataxia & Retinitis pigmentosa (PCARP / 609033)	AR	*FLVCR1*	Retinitis pigmentosa, sensory ganglionopathy and abnormal posterior columns on MRI
NARP (551500)	mitochondrial	*MTATP6*	See table 1A

Refsum Disease (266500)	AR	*PHYH*	See table 1A
PHARC syndrome (612674)	AR	*ABHD12*	See table 1A
AMACRD (614307)	AR	*AMACR*	See table 1B
SPG15 (270700)	AR	*ZFYVE26*	See table 1B
Cockayne syndrome (216400/133540)	AR	*ERCC6/ERCC8*	See table 1C
PBD9B (Refsum variant) (614879)	AR	*PEX7*	See table 1C
Congenital disorder of glycosylation type 1A (212065)	AR	*PMM2*	See table 1C
Cataracts and neuropathy syndromes			
Congenital cataracts, facial dysmorphism and neuropathy (CCFDN) (604168)	AR	*CTDP1*	Rudari Gypsies, congenital cataracts and microcornea, facial dysmorphism, mild cognitive impairment, neuropathy with SNCV
CMTD1B or CMT2M (606482)	AR	*DNM2*	Intermediate CMT or CMT2, cataracts, ophthalmoplegia, ptosis
Cerebrotendinous xanthomatosis (213700)	AR	*CRP27A1*	See table 1A
SPG9A (601162) / SPG9B (616586)	AD/AR	*ALDH18A1*	See table 1B
SPG46 (614409)	AR	*GBA2*	See table 1B
HLD5 / HCC (610532)	AR	*FAM126A*	See table 1C
C. Cranial and peripheral neuropathy syndromes			
FAP-4 (105120)	AD	*GSN*	Corneal lattice dystrophy, cranial neuropathies, cutix laxa
Kearns-Sayre syndrome (530000)	mDNA deletions		Ophthalmoplegia, retinitis pigmentosa, heart block, ptosis
MTDPS8B (612075)	AR	*RRM2B*	PEO, MNGIE, minimal neuropathy
CFEOMA3 (600638)	AD	*TUBB3*	Congenital strabismus, rarely isolated axonal sensory-motor neuropathy, dysgenesis of the corpus callosum, finger and wrist contractures, developmental delay, Kallmann syndrome
SBMA (313200)	XL	*AR*	Motor neuropathy, facial fasciculations, tremor, androgen insensitivity
BVVLS2 (614707)	AR	*SLC52A2*	Facial and bulbar weakness, sensory ataxia, sensory-motor axonal neuropathy, optic atrophy, sensory neuronal hearing loss
BVVLS1 (211530)	AR	*SLC52A3*	Sensory neuronal hearing loss, facial and bulbar weakness, upper limb predominant motor neuropathy

PNMHH (614369)	AR	*MYH14*	Distal myopathy, motor axonal neuropathy, hoarseness, hearing loss
Cowchock syndrome (310490)	X-linked	*AIFM1*	Mental retardation (60%), deafness, slowly progressive sensory and axonal neuropathy from childhood
MELAS (540000)	mitochondrial	*MTTL1* m3243A>G	Myopathy, deafness, ophthalmoplegia, diabetes, stroke like episodes, predominantly sensory axonal neuropathy
NF2 (101000)	AD	*NF2*	Bilateral acoustic schwannomas. Axonal sensory-motor neuropathy.
Kanzaki disease (609242)	AR	*NAGA*	Adult onset – diffuse angiokeratoma, sensory-neural hearing loss, recurrent episodes of vertigo, sensory-motor axonal neuropathy. Periventricular white matter abnormalities on MRI.
HSN1E (614116)	AD	*DNMT1*	Dementia, deafness and sensory neuropathy
ACPHD (616192)	AR	*DNAJC3*	Deafness. See table 1A
PHARC syndrome (612674)	AR	*ABHD12*	Deafness. See table 1A
Refsum Disease (266500)	AR	*PHYH*	Deafness. See table 1A
PBD9B (Refsum variant) (614879)	AR	*PEX7*	Deafness. See table 1C
MEDNIK (609313)	AR	*AP1S1*	Deafness. See table 1C
MTDPS5 (612073)	AR	*SUCLA2*	Deafness. See table 1C
MTDPS4B (613662)	AR	*POLG*	Deafness. See table 2A
CMTX5 (311070)	X-linked	*PRPS1*	Deafness. See table 2B
D. Endocrinopathy and neuropathy syndromes			
Gonadal dysgenesis with minifascicular neuropathy (607080)	AR	*DHH*	Gonadal dysgenesis, sensory-motor axonal neuropathy
Adrenoleukodystrophy (300100)	XL	*ABCD1*	Adrenal failure, see table 1B
AAAS (231550)	AR	*AAAS*	Adrenal failure, see table 1C
Infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD) (616263)	AR	*PTRH2*	See table 1C
SBMA (313200)	X-linked	*AR*	Androgen insensitivity, see table 2 C
E. Musculoskeletal / myopathy and neuropathy syndromes			
Merosin deficient congenital muscular dystrophy (MDC1A)	AR	*LAMA2*	Congenital muscular dystrophy, mildly slowed PNS conduction,

(607855)			abnormal T2 MRI signal white matter
MFM6 (612954)	AR	*BAG3*	Giant axons on nerve biopsy, myofibrillar myopathy, cardiomyopathy, scoliosis, sensory-motor axonal neuropathy.
Limb girdle muscular dystrophy and neuropathy (181350)	AD	*LMNA*	Limb girdle muscular dystrophy, cardiomyopathy, sensory-motor axonal neuropathy
MERRF (545000)	m8313G>A m8344A>G	*MTTK*	Myoclonic epilepsy, myopathy, lipoma, sensory axonal neuropathy
Multiple acyl-CoA dehydrogenase deficiency (MADD) (231680)	AR	*ETFDH*	Neonatal and late onset forms. hypoglycaemia, metabolic acidosis, and hepatomegaly often preceded by metabolic stress. Muscle involvement in the form of pain, weakness, and lipid storage myopathy also occur. Riboflavin responsive.
HMN2A (158590)	AD	*HSPB8*	Distal hereditary motor neuropathy and proximal myopathy
HMN2B (608634)	AD	*HSPB1*	Distal hereditary motor neuropathy. Myopathic changes on muscle biopsy
Lethal congenital contracture syndrome 7 (602346)	AR	*CNTNAP1*	Congenital severe arthrogryposis multiplex congenital, demyelinating neuropathy
PNMHH (614369)	AR	*MYH14*	See table 2C
F. Cardiomyopathy and neuropathy syndromes			
FAP-1 (105210)	AD	*TTR*	Dysautonomia, cardiac disease carpel tunnel syndrome, painful sensory-motor axonal neuropathy, SNCV may mimic CIDP.
Fabry disease (301500)	X-linked	*GLA*	Angiokeratoma, painful sensory axonal and small fibre neuropathy, cardiomyopathy, renal failure
Mitochondrial complex V deficiency (516070)	m8529G>A	*MTATP8*	Hypertrophic cardiomyopathy, ataxia, PEO, dysarthria, sensory-motor axonal neuropathy
NARP (551500)	mitochondrial	*MTATP6*	See table 1A
Friedreich ataxia (229300)	AR	*FXN*	See table 1A
HAYOS (617183)	AD	*ATAD3A*	See table 1C
McLeod syndrome (300842)	XL	*XK*	See table 2A

Kearns-Sayre syndrome (530000)	mitochondrial		See table 2B
MFM6 (612954)	AR	*BAG3*	See table 2E
G. Hepatic, gastrointestinal and neuropathy syndromes			
Hepatic			
MTDPS3 (251880)	AR	*DGUOK*	Neonatal liver failure, myopathy, sensory-motor axonal neuropathy
MTDPS6 (256810)	AR	*MPV17*	Corneal opacification, neonatal liver failure, acromutilation, sensory axonal neuropathy
SCAR21 (607982)	AR	*SCYL1*	See table 1A
Tyrosinemia type 1 (276700)	AR	*FAH*	See table 2H
Gastrointestinal			
MTDPS1 (603041)	AR	*TYMP*	MNGIE: Chronic pseudo-obstruction, Sensory-motor neuropathy with slow conduction (may mimic CIDP), myopathic weakness, cachexia. Leukodystrophy on MRI.
MTDPS4B (613662)	AR	*POLG*	MNGIE: Chronic pseudo-obstruction, axonal sensory ataxic neuropathy, myopathic weakness, cachexia. Normal brain MRI
MTDPS8B (612075)	AR	*RRM2B*	PEO, MNGIE, minimal neuropathy
familial visceral amyloidosis (105200)	AD	*B2M*	Adult onset chronic diarrhoea. Autonomic and sensory-motor axonal neuropathy.
Somatic and autonomic neuropathy	AD	*PRNP*	Autonomic and sensory axonal neuropathy preceding cognitive decline, Chronic diarrhoea.
Goldberg-Shprintzen megacolon syndrome with associated sensory motor axonal neuropathy. (609460)	AR	*KIAA1279*	Intellectual disability, microcephaly, dysmorphic facies, Hirschprung disease, pachygyria, cerebellar hypoplasia (defect in neural crest migration)
Waardenburg syndrome type 2E (611584) / PWCH (609136)	AD	*SOX10*	Hypopigmentation of the hair and skin, sensory hearing loss, demyelinating neuropathy, dysmyelinating leukodystrophy, developmental delay, spasticity, ataxia, Hirschsprung disease.
AAAS (231550)	AR	*AAAS*	Achalasia. See table 1C
MEDNIK (609313)	AR	*AP1S1*	Congenital diarrhoea. See table 1C
Cerebrotendinous xanthomaosis (213700)	AR	*CRP27A1*	Congenital diarrhoea. See table 1C
FAP-1 (105210)	AD	*TTR*	See table 2F

H. Renal failure and neuropathy syndromes			
FAP-3 (105200)	AD	*APOA1*	Axonal sensory-motor neuropathy similar to TTR FAP, amyloid nephropathy
Action myoclonus-renal failure syndrome (AMRF) (254900)	AR	*SCARB2*	Progressive myoclonic epilepsy with preserved cognition, onset 2nd decade, renal impairment, rarely demyelinating sensory-motor neuropathy (without renal failure)
CMTDIE (614455)	AD	*INF2*	Focal segmental glomerulonephritis and sensory-motor neuropathy with intermediate conduction velocities.
Fabry disease (301500)	X-Linked	*GLA*	See table 2F
MMACHC (277400)	AR	*MMACHC*	Thrombotic microangiopathy of kidneys (See table 2I below)
I. Haematological and immunological neuropathy syndromes			
Methylmalonic aciduria and homocystinuria type Cb1c (MMACHC) (277400)	AR	*MMACHC*	Onset infancy to adulthood; thrombotic thrombocytopenia with encephalopathy, myelopathy, renal and pulmonary complications (can be life threatening), retinitis pigmentosa, axonal motor neuropathy. Treated with high dose vitamin B12.
Chediak-Higashi syndrome (214500)	AR	*LYST*	Partial albinism, immunodeficiency, cerebellar atrophy, sensory-motor axonal neuropathy.
Early-onset chronic axonal neuropathy, strokes, and haemolysis: inherited CD59 deficiency (612300)	AR	*CD59*	Onset 1st and 2nd decade. Haemolytic anaemia, strokes and relapsing immune-mediated demyelinating neuropathy
McLeod Syndrome (300842)	X-Linked	*XK*	See table 2A
J. Skin and connective tissue and neuropathy syndromes			
Xeroderma pigmentosum (278700)	AR	*XPA*	Photosensitivity and increased risk of cutaneous malignancy, global developmental delay, deafness, sensory-motor axonal peripheral neuropathy.
HNARMD (608895)	AD	*FBLN5*	Age related macular degeneration, hyperelastic skin, demyelinating neuropathy also described.
EDS6 (225400)	AR	*PLOD1*	Congenital hypotonia, joint laxity, scleral fragility,

			susceptibility to large vessel injury, mild sensory-motor axonal neuropathy.
Connective tissue disorder and peripheral neuropathy (130660)	AD	*EMILIN1*	Aortic aneurysm, skin laxity and sensory-motor axonal neuropathy (single family reported)
Refsum disease (266500)	AR	*PHYH*	Ichthyosis. See table 1A
PBD9B (Refsum variant) (614879)	AR	*PEX7*	Ichthyosis. See table 1A
Cerebrotendinous xanthomaosis (213700)	AR	*CRP27A1*	Xanthoma. See table 1A
CEDNIK syndrome (609528)	AR	*SNAP29*	Icthyosis and palmoplantar keratoderma. See table 1C.
MEDNIK (609313)	AR	*AP1S1*	Icthyosis and palmoplantar keratoderma. See table 1C.
Cockayne syndrome (216400/133540)	AR	*ERCC6/ERCC8*	Cutaneous photosensitivity. See table 1C
FAP-4 (105120)	AD	*GSN*	Cutis laxa. See table 2C
Kanzaki disease (609242)	AR	*NAGA*	Angiokeratoma. See table 2C
Fabry disease (301500)	X-linked	*GLA*	Angiokeratoma. See table 2C
K. Relapsing complex inherited neuropathy syndromes			
Porphyria, acute intermittent (AIP) (176000)	AD	*HMBS*	Abdominal pain, psychosis, depression, seizures, axonal predominantly motor neuropathy
Coproporphyria (121300)	AD	*CPOX*	Skin photosensitivity and haemolytic anaemia. Can present acutely similar to AIP
Porphyria, variegata (176200)	AD	*PPOX*	Skin photosensitivity. Acute episodes similar to AIP.
Tyrosinemia type 1 (276700)	AR	*FAH*	Infantile or adolescent onset liver disease, renal tubular dysfunction and hypophosphatemic rickets. Acute episodes of neuropathy similar to AIP.
Trifunctional protein deficiency with myopathy and neuropathy (609015)	AR	*HADHA* *HADHB*	Disorder of mitochondrial beta oxidation of fatty acids. Severe neonatal, infantile and late adolescent onset described, the latter characterised by a progressive myopathy with recurrent rhabdomyloysis and a sensory-motor axonal neuropathy. Abnormal urine organic acids.
Maple syrup urine disease Ib (248600)	AR	*BCKDHB*	Metabolic encephalopathy, elevated branched chain amino

			acids in urine, acute axonal neuropathy
Thiamine metabolism dysfunction syndrome 4 THMD4 (613710)	AR	*SLC25A19*	Acute encephalopathic episodes and paralysis following febrile illness with almost complete recovery. Absent sensory-motor action potential during illness. Bilateral striatal necrosis on MRI. Additional chronic progressive axonal neuropathy
Tangier disease (205400)	AR	*ABC1*	Multifocal relapsing mononeuropathies. Orange tonsils, organomegaly; pain, paresthesias, anaesthesia.
Inherited CD59 deficiency (612300)	AR	*CD59*	See table 2I

Table 2. A summary of the complex inherited neuropathy syndromes with one of the minor 10 clinical phenotypes associated with neuropathy. Number in parenthesis is the OMIM phenotype number. AR=autosomal recessive, AD=autosomal dominant. SNCV=slow nerve conduction velocities. PEO=progressive external ophthalmoplegia, MNGIE=mitochondrial neuro gastrointestinal encephalopathy, CFEOMA3=fibrosis of extraocular muscles, congenital, 3A, with or without extraocular involvement, SBMA=spinal bulbar muscular atrophy, BVVL=Brown-Vialetto-Van Laere syndrome, HMN=hereditary motor neuropathy, MFM=myofibrillar myopathy, PWCH=peripheral demyelinating neuropathy, central demyelination, Waardenburg syndrome, HNRAMD=neuropathy, hereditary, with or without age-related macular degeneration, FAP=familial amyloid polyneuropathy, EDS=Ehlers Danlos syndrome, MTDPS=mitochondrial DNA depletion syndrome, PNMHH=peripheral neuropathy, myopathy, hoarseness and hearing loss, MELAS=mitochondrial myopathy, encephalopathy, lactic acidosis and stroke like episodes, MERFF=myoclonic epilepsy associated with ragged red fibres, NARP=neuropathy, ataxia, retinitis pigmentosa, NF2=neurofibromatosis type 2.