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Diagnosis of hereditary neuropathies in adult patients

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Abstract This paper reviews the clinical diagnostic approach to hereditary neuropathies in adults by analysing: elements that point to a neuropathy of inherited origin, different modalities of presentation, laboratory and instrumental diagnostic tests, including molecular tests, symptoms and signs of involvement of other organs. Different phenotypes may be identified according to: disease course; involvement of motor, sensory, autonomic fibres; site of lesion (neuropathy versus neuronopathy); calibre of involved fibres (small-fibre versus large-fibre neuropathy); presence of distinctive symptoms (neuropathic pain); involvement of other organs or apparatus. Charcot-Marie-Tooth disease, Familial Amyloid Polyneuropathy, Hereditary Sensory and Autonomic Neuropathy, Fabry disease, Tangier disease, Porphyric Neuropathies, Refsum disease, Hereditary Neuropathy with liability to Pressure Palsies, Hereditary Neuralgic Amyotrophy, and other rare disorders involving the peripheral nervous system are reviewed.

Key words Charcot-Marie-Tooth disease · amyloid neuropathies · Fabry disease · porphyria · hereditary neuropathy with liability to pressure palsies

Introduction

Adult patients with peripheral neuropathy of a possible inherited nature are commonly encountered in clinical practice. Although there are a number of signs pointing to a hereditary neuropathy, some patients are not properly diagnosed and the full potential of molecular diagnosis is not completely exploited. This paper reviews the clinical diagnostic approach to these patients by analysing: elements that point to a diagnosis of a hereditary neuropathy, different modalities of presentation, laboratory and instrumental diagnostic tests (including molecular tests), symptoms and signs of involvement of other organs that may accompany some inherited neuropathies.

Clues pointing to hereditary neuropathy

Family history

This obviously needs to be thoroughly investigated, and when other family members are affected by a peripheral neuropathy the diagnosis of hereditary neuropathy is very likely. The greatest difficulties arise when dealing with sporadic cases due to de novo mutations. Moreover, there are diseases, such as Charcot-Marie-Tooth disease (CMT) and hereditary neuropathy with liability to pressure palsies (HNPP), which present considerable expression variability and may go unrecognised in mildly affected family members. Apparently sporadic cases indeed often turn out to be familial when at-risk family members are carefully examined both clinically and electrophysiologically [88]. In acute porphyrias, the attacks occur only in a minority of disease carriers, while

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the disease remains latent in the vast majority [111, 125]. In other cases, the parents and ascendants of the patient have died and may be reported to have had heart disease but no clear neurological disorder, or, if one is present, it has been neglected (e. g. carpal tunnel syndrome): this may happen in familial amyloid neuropathy (FAP). On the other hand, diabetic and alcoholic neuropathies are frequent and the significance of a mild neuropathy in family members must be carefully weighed.

Age at onset

Although most hereditary neuropathies have early onset, in CMT for instance, only a minority of patients seeks medical advice during childhood and many are diagnosed later in life. In other neuropathies, onset occurs during adulthood, as in some cases of CMT (more frequently for the axonal variety CMT2), and in FAP, where disease onset may be delayed until the 7th decade of life [104].

Skeletal deformities

Pes cavus and scoliosis are stigmata of hereditary neuropathies, and they are present in most hereditary neuropathies when onset occurs early, but they may be absent when onset is late (even in CMT). Furthermore, patients with early-onset acquired neuropathies, such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), may have pes cavus.

Disease course

Although slowly progressive course should always raise the hypothesis of an inherited neuropathy, there are several examples of hereditary diseases with an acute and/or relapsing course: typically HNPP, porphyric neuropathy, and also Tangier and Refsum diseases.

Therefore, there is no single issue that is specific and pathognomonic of inherited as opposed to acquired neuropathy, but the diagnostic hypothesis requires evaluation of the entire clinical picture.

Phenotypes of hereditary neuropathies

The main phenotypes of hereditary neuropathies will be analysed and the clinical approach for each discussed. Different phenotypes may be identified (Table 1) according to: a) disease course (chronic, acute, relapsing-remitting), b) involvement of motor and/or sensory fibres, and of the autonomic system (sensori-motor, sensory, motor, plus autonomic); c) site of lesion (neuropathy versus neuronopathy); d) calibre of involved fibres (small-fibre versus large-fibre neuropathy); e) evidence of distinctive symptoms (neuropathic pain); d) involvement of other organs or apparatus.

Chronic sensory-motor polyneuropathy

This is the most common phenotype in both hereditary and acquired neuropathies. It is the typical presentation of CMT: an adult patient coming to the neurologist because of a slowly progressive distal symmetrical sensori-motor neuropathy. CMT is characterised by wasting and weakness of distal limb muscles (especially in the peroneal compartment), usually accompanied by distal sensory loss, decrease or absence of tendon reflexes, and skeletal deformities. Pes cavus is present in the vast majority of cases, while scoliosis is less common. Severity is highly variable even within the same kinship, only rarely leading to severe impairment [34]. Subclassification of CMT into demyelinating (CMT1, accounting for about $^{2}/_{3}$ of cases) and axonal (CMT2, about $^{1}/_{3}$) varieties is based on nerve conduction velocities (NCV), while further subdivision depends on molecular genetics [27, 48, 88, 99] (Table 2).

For such patients, diagnosis proceeds according to the following steps: identification of inheritance pattern, electrophysiological examination, molecular analyses, and, for selected cases, nerve biopsy [2].

a) Inheritance pattern is assessed by analysis of family pedigree and, whenever possible, by direct clinical examination of at-risk family members; in some, electrophysiologic examination may be warranted. CMT is usually transmitted as an autosomal dominant trait (CMT1 and CMT2). However, an X-linked form exists (CMTX, associated with mutations of the connexin-32 gene – Cx32) and appears to be rather common. CMTX might represent up to 10 % of all CMT cases; it is characterised by absence of male-to-male transmission, and is more severe in affected males than in females both clinically and electrophysiologically [10, 14, 32, 45]. The autosomal recessive forms of CMT, grouped under the term of CMT4, almost invariably have early onset and are more severe than the dominant types [27, 88].

b) Electrophysiological examination is the next diagnostic step and is extremely important for orienting DNA analyses. The presence, degree, and pattern of nerve conduction slowing should be assessed. In the demyelinating variety CMT1, NCV is diffusely and homogeneously slowed, and by definition motor conduction velocity (MCV) is slowed below the limit of 38 m/s; in contrast, in the axonal variety CMT2, MCV is preserved or only mildly decreased, above 38 m/s in upper limb nerves [34]. Therefore, homogeneous nerve conduction slowing below 38 m/s in upper limb nerves points to CMT1. CMTX has a peculiar behaviour, as conduction slowing is greater in males than females; although NCV may vary between 18 and 60 m/s, conduction velocities are often intermediate between CMT1 and CMT2 in males (30–45 m/s in upper limbs), and in the lower range

Table 1 Main phenotypes of hereditary neuropathies in adulthood

Phenotype	Disease	Inheritance	Neurologic involvement	Extranervous involvement
Chronic sensori-motor polyneuropathy	Charcot-Marie-Tooth disease (also: Refsum disease, HNPP, Tangier disease)	AD, X-linked, AR	Distal, symmetric, sensori-motor. Skeletal deformities.	
Chronic Motor Neuronopathy	Distal HMN	AD, AR	Distal, symmetric, motor.	
Early small-fibre involvement	Familial Amyloid Polyneuropathy	AD	Early: autonomic, algo-thermal anaesthesia, pain and paraesthesiae; later: other sensory modalities; motor; carpal tunnel sy; rare CNS involvement.	Weight loss. Heart, kidney, vitreous body.
Pure sensory (and autonomic) neuropathy	HSAN I	AD	Early algo-thermal anaesthesia; recurrent ulcers, acromutilation, Charcot joints.	
Painful neuropathy	Fabry disease (also HSAN, FAP)	X-linked (Females may be symptomatic)	Episodic lancinating pain, acroparaesthesiae, autonomic involvement. Cerebrovascular disease.	Skin (angiokeratomas), heart, kidney, respiratory tract, cornea and lens, brain vessels.
Pseudo-syringomyelic	Tangier disease	AR	Dissociated algo-thermal sensory loss, cranial, cervical and brachial preference; facial diplegia; motor upper limb, hands. Recurrent or progressive.	Tonsils, liver and spleen. Cornea, heart (coronaries).
Acute generalised polyneuropathy	Porphyria (AIP, HC, VP)	AD	Acute paralysis. Motor > > sensory. Cranial nerves. Autonomic. Abdominal pain. Psychosis, seizures, coma, SIADH.	Photosensitivity (HC, VP)
Relapsing (-progressive) generalised polyneuropathy	Refsum disease	AR	Distal symmetric sensori-motor, deep sensation. Episodic, relapses, progressive. Cerebellar ataxia. Cranial nerves (hearing loss, anosmia, pupillary abnormalities).	Retinitis pigmentosa. Heart. Bones. Skin.
Acute focal neuropathies	HNPP	AD	Acute painless mononeuropathy and brachial plexopathy. Generalised polyneuropathy.	
	HNA	AD	Recurrent brachial plexopathy, pain, weakness.	Dysmorphic features

AD Autosomal dominant; *AR* Autosomal recessive; *AIP* Acute Intermittent Porphyria; *FAP* Familial Amyloid Neuropathy; *HC* Hereditary Coproporphyria; *HMN* Hereditary Motor Neuronopathy; *HNA* Hereditary Neuralgic Amyotrophy; *HNPP* Hereditary Neuropathy with liability to Pressure Palsies; *HSAN* Hereditary Sensory and Autonomic Neuropathy; *VP* Variegate Porphyria

of CMT2 in females [32, 45, 62]. A certain degree of asymmetry in nerve conduction abnormalities has been reported in CMTX, as the median nerve is often more affected than the ulnar nerve, conduction slowing may be nonuniform along nerve trunks, and sometimes excessive temporal dispersion and even conduction blocks are found [32, 44, 62].

c) Molecular analyses. All of the clinical, inheritance, and electrophysiological data are usually sufficient to define the diagnostic hypothesis and select the molecular tests to be performed [2, 31, 88].

The genetic subdivision of CMT according to gene mutations and to identified loci is shown in Table 2. The majority of CMT1 cases (60–90 %) carry a duplication on chromosome 17p11.2, encompassing the peripheral myelin protein 22 (PMP22) gene (CMT1A); in other CMT1 patients, micromutations involving the PMP22 gene (1 %) or the myelin protein zero gene (P0, MPZ) (CMT1B, 4–5 %) are rarely found [14, 31, 78]. Mutations in the early-growth-response-2 gene (EGR2) have been demonstrated in very few CMT1 families [90, 119]. The above-mentioned and more common CMTX is associated with Cx32 mutations. In other cases, no mutation is detected. Consequently, the steps in molecular diagnosis reflect frequency of mutations. In autosomal dominant or sporadic CMT with electrophysiological evidence of demyelination (CMT1), the 17p11.2 duplication should first be investigated. If absent, diagnosis of CMTX needs to be considered (no male-to-male transmission, more severe disease in affected males) and Cx32 mutations looked for; if CMTX is ruled out, P0, PMP22, and EGR2 mutations should be looked for in this order.

The axonal type CMT2 is also genetically heterogeneous and it is now possible to search for mutations in the gene coding for the neurofilament light gene (NF-L) [29, 71]; recently another gene (Kinesin family member 1B beta, KIF1Bβ, on chromosome 1p) has been associated with CMT2 [128]. Furthermore, mutations in the Cx32 and P0 genes have been found in families with a CMT2 phenotype [14, 22, 28, 31, 67, 89]. To further complicate the matter, other so-called intermediate forms of

Table 2 Hereditary neuropathy in adulthood: genetic and biochemical abnormalities

Disease	Locus	Involved gene	Metabolic abnormalities
Charcot-Marie-Tooth disease (CMT)			
CMT1			
CMT1A	17p11.2	PMP22 (duplication, point mutations)	
CMT1B	1q22-q23	P0	
CMT1C	16p13.1-p12.3	?	(Ref. 108)
CMT1D	10q21-q22	EGR2	
CMTX	Xq13-q22	Cx32	
CMT2			
CMT2A	1p35-p36	KIF1Bbeta	
CMT2B	3q13-q22	?	
CMT2C	?	?	(Vocal cord and respiratory involvement)
CMT2D	7p14	?	
CMT2E	8p21	NF-L	
CMT2F	7q11-q21	?	(Ref. 52)
CMT intermediate	10q24-q25	?	
	19p12-p13.2	?	
Distal HMN II	12q24-q25	?	
Distal HMN V	7p	?	
Distal HMN VII	2q14	?	
HNPP	17p11.2	PMP22 (deletion, nonsense mutations)	
HNA	17q24-q25	?	
	?	?	
HSAN I	9q22	Serin Palmitoyltransferase, Long Chain Base Subunit-1 (SPTCL1)	Increased synthesis of glucosyl ceramide
Refsum disease	10pter-p11.2	Phytanoil-CoA α-hydroxylase	Increased phytanic acid in tissues and body fluids
	6q22-q24	Peroxisome biogenesis factor 7 (PEX7)	
Fabry disease	Xq22	α-Galactosidase A	Glycosphyngolipid accumulation
Tangier disease	9q22-q31	ATP-binding cassette transporter 1 gene (ABC1)	Cholesteryl esters accumulation, low serum colestherol & HDL
Familial Amyloid Neuropathy (FAP)	18q11.2-q12.1	Transthyretin (TTR)	Amyloid deposits
	9q34	Gelsolin (Finnish type)	
Porphyrias			
AIP	11q24.1-q24.2	porphobilinogen deaminase	Increased urinary and faecal porphyrins
HC	3q12	coproporphyrinogen oxidase	
VP	1q22	protoporphyrinogen oxidase	

AD Autosomal dominant; *AR* Autosomal recessive; *AIP* Acute Intermittent Porphyria; *FAP* Familial Amyloid Neuropathy; *HC* Hereditary Coproporphyria; *HMN* Hereditary Motor Neuronopathy; *HNA* Hereditary Neuralgic Amyotrophy; *HNPP* Hereditary Neuropathy with liability to Pressure Palsies; *HSAN* Hereditary Sensory and Autonomic Neuropathy; *VP* Variegate Porphyria

CMT have been mapped, by linkage studies performed in families with conduction velocities between CMT1 and CMT2 [58, 117].

In the highly heterogeneous recessive forms (CMT4), mutations in five genes have so far been identified: periaxin (PRX), reported in CMT4 and also in Dejerine-Sottas disease patients with severe neuropathy and relevant sensory involvement [13, 43, 109]; ganglioside-induced differentiation-associated protein 1 (GDAP1) in a few families with early-onset axonal CMT [7, 25]; myotubularin related protein-2 (MTMR2), associated with the peculiar form CMT4B, characterised by the presence of myelin outfoldings in peripheral nerves [15]; n-myc down-regulated gene-1 (NDRG1), associated with HMSN-L, a severe recessive neuropathy with deafness in a gypsy community in Bulgaria [55]; and Lamin A/C Nuclear-Envelope Protein (LMNA), in families with recessive axonal CMT [30].

d) Neuropathology. The presence of several well-formed onion bulbs is typical of CMT1A. However, nerve biopsy should be performed only after the main genetic tests have been performed. There is still room for neuropathology in selected cases, and it may be useful in differentiating CMT from acquired neuropathies (mainly inflammatory ones) and other hereditary disorders (FAP, late-onset leukodystrophy, etc.). Moreover, it may demonstrate the presence of some myelin figures that, although not specific, might orient the molecular investigations. In CMT1B, for instance, besides onion-bulb

formations, the presence of some tomacula and myelin foldings or, in other cases, of myelin uncompaction has been reported with some frequency [40]. However, myelin uncompaction may also be encountered in CMT1A [36]. The presence of several myelin outfoldings in the majority of fibres is characteristic of the rare CMT4B, prompting the search for MTMR2 mutations [15]. Predominance of axonal changes in spite of nerve conduction slowing is frequently observed in CMTX, and is attributed to the localisation of Cx32 at the paranodal region and its possible role in Schwann cell-axon interactions [10, 62, 88].

Special CMT phenotypes. There are a number of additional features that may be associated with CMT. Postural and action tremor is relatively common in many CMT forms and is sometimes particularly prominent (Roussy-Levy syndrome, RLS); the original RLS family has been shown to carry a P0 gene mutation [93]. Hearing loss is not rare (up to 5 % in CMT1A patients) and is probably caused by a dysfunction of the acoustic nerve [9, 85]. Involvement of other cranial nerves is occasionally seen, particularly of the VII, V (exceptionally with trigeminal neuralgia), IX and X [88, 113]. CMT2C is characterised by vocal cord paresis and diaphragmatic weakness and is exceedingly rare [34]. Ophthalmoparesis is also exceptional and has been reported in patients with EGR2 mutations [90]. The Thr124Met mutation in the P0 gene has been identified in several families with late onset CMT2 and peculiar features, namely pupillary abnormalities, pain, hearing loss, and dysphagia [22, 28]. Pyramidal involvement or optic atrophy are sometimes seen in otherwise typical CMT patients and correspond to Hereditary Motor and Sensory Neuropathy type V and VII in the HMSN classification [34]. Recently, transient symptoms related to central nervous system (CNS) involvement have been described in a few CMTX patients [83, 91]; subclinical CNS involvement is known to occur in CMTX, as revealed by abnormalities of evoked potentials, particularly of brainstem auditory evoked potentials [62, 80], and is explained by the expression of Cx32 not only in Schwann cells, but also in oligodendrocytes [62, 88].

Differential diagnosis. Many neuropathies of different aetiologies need to be differentiated from CMT. Differential diagnosis may be difficult in sporadic cases or whenever the familial nature of the disease is not evident. It may be particularly difficult to differentiate sporadic CMT1 and CMTX from CIDP and demyelinating neuropathies associated with monoclonal gammopathy. Genetic tests and serum immunofixation are of help in the diagnosis. Fluctuating course, inflammatory infiltrates at nerve biopsy, and very high levels of CSF proteins favour the diagnosis of acquired demyelinating neuropathy. It is very difficult to differentiate sporadic CMT2 from chronic axonal neuropathies, as clinical course and instrumental examination may be similar [110]. Early onset and the presence of pes cavus make the diagnosis of CMT2 more likely. Genetic tests for some CMT2 subtypes have recently become available. HNPP may have a polyneuropathic presentation mimicking CMT (see below) [86, 87]. Friedreich's ataxia in the early stages may be mistaken for CMT, but signs of CNS and extraneurological involvement should prompt the appropriate search for the intronic GAA expansion in the frataxin gene [84]. Distal myopathies may be misdiagnosed as CMT; EMG examination and muscle biopsy can help by demonstrating myopathic changes [101].

Management. In spite of the great advances in diagnosing and understanding pathophysiology, little improvement has been made in treating these neuropathies. There is no drug therapy. Physiotherapy is important in preventing skeletal deformities (pes cavus and scoliosis) and tendon tightening. Once they occur, however, surgery may be useful, but care is needed in selecting patients and in choosing the surgical technique. Genetic counselling is important, particularly for the most severe forms. Prenatal diagnosis is feasible when the mutation is known [57]. Gene therapy will be hopefully available in a not too distant future [46, 127].

Chronic motor neuronopathy

This is a rare phenotype. Usually the presentation is entirely similar to CMT but there is no involvement of sensory nerves at the clinical, electrophysiologic, and neuropathological levels. Inheritance is autosomal dominant or recessive, disease severity is variable. Electroneuronography (ENG) shows evidence of a motor neuronopathy with distal predominance. However, examination of sensory nerves must be very carefully performed, as it is not uncommon to overlook mild sensory abnormalities that would cause a shift of diagnosis to CMT2. These forms are currently classified among the motor neuron disorders as distal hereditary motor neuro(no)pathy (distal HMN) [47]. One adult form (distal HMN II) has been mapped to chromosome 12q24, distal HMN type V with upper limb predominance is linked to chromosome 7p, and HMN VII with vocal cord paralysis to chromosome 2q14 (see Table 2) [23, 69, 114].

Chronic sensory (or predominantly sensory) neuropathy

This phenotype is less frequently encountered than sensory-motor polyneuropathy, and is heterogeneous. It can be further subdivided according to the clinical presentation, which reflects the type of fibres involved: pref-

erential and early involvement of small fibres, pure sensory neuropathy or neuronopathy, painful neuropathies.

Chronic polyneuropathy with early small-fibre involvement

In CMT, motor involvement almost invariably dominates the clinical picture, and sensory symptoms are usually much less prominent. When the opposite occurs, at least in the early phases of the disease, and patients show loss of thermal and pain sensation, other diagnoses should be considered.

Familial Amyloid Polyneuropathy (FAP) typically presents with these symptoms, which are due to a small-fibre neuropathy [3, 50, 51, 60, 94]. Unmyelinated and small myelinated fibres are first involved. Other early symptoms of FAP that reflect autonomic system dysfunction with impotence, postural hypotension, pupillary abnormalities may be present. Patients may also complain of positive sensory symptoms such as paraesthesiae and neuropathic pain. A carpal tunnel syndrome may be superimposed. Loss of weight, gastrointestinal abnormalities with alternating constipation and diarrhoea are other typical features as the disease worsens. Motor involvement soon becomes evident and disabling with muscle weakness spreading from distal to proximal segments. Dysphagia and dysarthria due to bulbar involvement may occur late. Age of onset is highly variable. Progression is much faster than in CMT and disease duration until death usually ranges between 7 and 15 years. The disease is transmitted as an autosomal dominant trait; however, penetrance is incomplete and, as mentioned before, family history is sometimes misleading. Several different disease-causing mutations in the transthyretin (TTR) gene on chromosome 18q11.2-q12.1 have been described [3, 51, 102]. The most common FAP mutation is Val30Met. Transthyretin is a transporter protein carrying thyroxine and retinol and is one of the proteins constituting the pre-albumin electrophoretic peak. In its mutated form, it becomes unstable and precipitates as amyloid at different sites, accounting both for the neuropathy and for the involvement of other organs [3, 50, 51, 60]. It may accumulate: a) in the heart, giving rise to a cardiomyopathy with arrhythmia, congestive heart failure, hypertrophy of interventricular septum, sudden death; b) in the vitreous body (vitreous opacities); c) in the kidney, sometimes causing a nephrotic syndrome; d) rarely in the leptomeninges, causing subarachnoid haemorrhage, seizures, and hydrocephalus [19, 51]. It is of interest that although TTR is produced by the liver, a small amount is synthesised by the epithelial cells of the choroid plexus and by the retinal epithelium. Orthotopic liver transplantation (LT) is the only currently available therapy [3, 50, 51]. LT stops or even improves autonomic dysfunction and sensory neuropathy, and levels of abnormal TTR decrease after LT [3, 6, 50, 51]. However, the procedure still carries significant mortality and morbidity and careful selection of candidates is needed. Prognosis is better when LT is performed in younger patients or early in the course of the disease. There is also evidence that prognosis after LT differs depending on TTR mutation [50, 51].

Molecular analysis of TTR mutations has greatly simplified the diagnostic process. However, FAP diagnosis may be difficult when family history is negative and in the early stages. Autonomic signs may be overlooked and erroneous diagnosis of idiopathic chronic axonal neuropathy is frequently made. Electrophysiological examination shows aspecific features of an axonal neuropathy. Demonstration of tissue amyloid deposits is a straightforward way of making the diagnosis. However, specific staining for amyloid needs to be performed. The highest probability of finding amyloid is obtained with biopsy specimens of nerve, abdominal fat pad, rectal mucosa, and skin [3, 50, 51, 60]. Amyloid deposits may be specifically labelled with anti-TTR antibodies [51]. Nerve biopsy also shows early loss of small fibres, but as the disease progresses all fibre types are involved [3, 60]. Amyloid accumulates preferentially around vessels in the endoneurium.

Evidence of extranervous involvement can help the diagnosis. Slit lamp examination for vitreous opacities, EKG and echocardiography for rhythm abnormalities and enlargement of interventricular septum, and renal function assessment are all complementary tests.

Amyloid deposition may also cause lattice corneal dystrophy leading to corneal clouding, often followed by a cranial neuropathy with facial weakness, bulbar signs, a mild generalised neuropathy, and skin changes [70]. This is a different and rare disorder due to mutations in the gelsolin gene on chromosome 9q34 and has been reported in Finnish families [68, 70]. A mutation in the apolipoprotein A-I protein has been shown to be responsible for amyloid neuropathy in the family reported by Van Allen et al. in 1968 [79, 116].

Chronic sensory neuropathy – neuronopathy

The phenotype of pure sensory neuropathy is rare in hereditary neuropathy and is more frequently associated with involvement of other nervous system fibres, such as in Friedreich's ataxia, spinocerebellar diseases, vitamin E deficiency, abetalipoproteinaemia, the syndrome of neuropathy ataxia and retinitis pigmentosa (NARP) [34, 76, 124, 126]. In these cases, it usually reflects the involvement of dorsal root ganglia (DRG) and is therefore a sensory ganglionopathy. Magnetic resonance imaging (MRI) of the cervical spinal cord may help in localising the disease process to the DRG by demonstrating hyperintensity of the posterior columns

in T2-weighted images, which is due to central sensory projection degeneration [61].

An adult patient with a familial pure sensory neuropathy is most likely to suffer from a hereditary sensory and autonomic neuropathy (HSAN). HSANs are a group of rare disorders classified according to inheritance pattern, age of onset and class of involved fibres [33, 99].

HSAN type I is transmitted as an autosomal dominant trait, and is characterised by a severe and progressive sensory loss of all modalities, particularly of temperature and pain sensation, leading to recurrent perforating plantar ulcers, acromutilations, stress fractures, and Charcot-type arthropathy [33, 99]. Patients often complain of shooting pains. Pes cavus is commonly present, and mild motor involvement may be seen. Hearing loss has also been reported. Electrophysiology demonstrates an absence of sensory action potentials. Disease onset occurs at juvenile or adult age, and the course is very slowly progressive. Nerve biopsy reveals loss of fibres of all calibres. DRG neurons are the likely site of degeneration. HSAN I is associated with mutations of the SPTLC1 gene (Serin Palmitoyltransferase, Long Chain Base Subunit-1) on chromosome 9q22: there is in vitro evidence that the deficit of the beta subunit 1 of this enzyme causes an increased synthesis of glucosyl ceramide which, in turn, is supposed to activate apoptosis and neuronal death [8, 26].

HSAN type II, which is characterised by a more generalised loss of superficial and deep sensations, with ulcers, acromutilation, and decreased sweating, is transmitted as an autosomal recessive trait and has infantile onset [33, 99]. Like HSAN II, the other HSAN subtypes have early onset and are diseases of the paediatric age.

Painful neuropathy

Positive sensory symptoms are rarely seen in CMT. Paraesthesiae and pain are common in amyloid neuropathy, and in HSAN I. Shooting and lancinating pain is typically seen in another hereditary neuropathy: *Fabry disease*. This is an X-linked disease due to mutations in the α-galactosidase A (GLA) gene on chromosome Xq22; deficit of the enzymatic activity leads to accumulation of incompletely metabolised glycosphingolipids in different tissues [16, 17]. Accumulation in DRG and autonomic gangliar cells is responsible for a sensory and autonomic neuronopathy characterised by: episodes of excruciating distal limb pain and acroparaesthesiae (which can be exercise-related and accompanied by fever), visceral pain, hypohydrosis, decreased lacrimation and salivation, impaired enteric motility. Hemizygous male patients usually develop the full clinical picture due to massive deposition of glycosphingolipids (mainly in endothelial and smooth muscle cells of blood vessels) with involvement of several organs [16, 17, 65]: a) the skin, with angiokeratoma corporis diffusum; b) the heart, with electrocardiographic changes, exercise intolerance, angina, hypertrophic cardiomyopathy; c) the kidney, with proteinuria progressing to renal failure; d) the respiratory tract, with airway obstruction that is likely to result from narrowing by accumulated glycosphingolipids [21]; e) the eye, with corneal opacities and posterior capsular cataract; f) the brain, with cerebrovascular disease. Nerve biopsy specimens show loss of small myelinated and unmyelinated fibres; glycosphingolipid deposits appear as lysosomal inclusions with a concentric lamellar configuration when seen on electron microscopy [16]. Diagnosis is not difficult when the full-blown clinical picture is evident. However, diagnosis is difficult in the early stages and in symptomatic heterozygous females, who may manifest the disease with a painful neuropathy, variably associated with other mild signs, such as cardiac and renal dysfunction, corneal opacities (usually present), sometimes cerebrovascular disease, that may be overlooked or considered not to be linked to the disease [16, 17, 121]. Diagnosis is based on the demonstration of decrease of alpha-galactosidase A activity in leukocytes or fibroblasts, but this is not always evident in female carriers [11, 16, 17, 41]. Skin biopsy may demonstrate the typical inclusions; brain MRI may show hyperintense focal lesions linked to vascular disease [24]. Currently, diagnosis relies also on screening for GLA gene mutations [11, 41]. Enzyme replacement therapy (with intravenously-administered alpha-galactosidase A) has recently become available and appears to be safe and efficacious for affected males [17, 18, 35]. Gene therapy and agents for the treatment of glycosphingolipid storage disorders are being developed [1, 98].

Pseudo-syringomyelic neuropathy

Progressive or recurrent neuropathy with dissociated loss of temperature and pain sensations which spares the distal part of the limbs (resembling syringomyelia) is seen in the very rare *Tangier disease* [37, 42, 92, 95, 103, 126]. The cranial, cervical and brachial dermatomes are preferentially involved. Facial diplegia, wasting and weakness of upper limb muscles, particularly hand muscles, may be associated. In other cases, Tangier disease presents with a slowly progressive sensori-motor polyneuropathy [126]. Onset may occur during childhood or adulthood. Transmission is autosomal recessive. Homozygous patients show accumulation of cholesteryl esters in macrophages, which causes enlargement of the liver, spleen, lymph nodes, and tonsils. The latter are characteristically orange and very enlarged, and this may be a clue to diagnosis. Corneal clouding may cause visual impairment. Early coronary artery disease is another feature of Tangier disease. Lab-

oratory screening shows reduced total cholesterol level, and very low HDL concentration. Nerve biopsy reveals lipid storage in Schwann cells and interstitial cells, and preferential loss of small myelinated and unmyelinated fibres [37, 42, 92, 95, 103, 126]. The disease has been shown to be due to mutations in the ATP-binding cassette transporter 1 gene (ABC1) on chromosome 9q22-q31, which is involved in cholesterol and phospholipid cellular trafficking [12, 20, 100].

Acute generalised neuropathy

Acute polyneuropathy rapidly progressing to tetraplegia and cranial nerve involvement is usually due to the dysimmune Guillain-Barré syndrome (GBS). However, the diagnosis of *porphyric neuropathy* should always be considered, particularly when the electrophysiological examination shows an axonal rather than a demyelinating neuropathy and if abdominal pain and evidence of encephalopathy precede or accompany the neuropathy. Although the porphyrias are rare disorders, they should be borne in mind since they are potentially life-threatening diseases which can be treated and prevented. Neurological manifestations are seen almost exclusively in the hepatic porphyrias, particularly in acute intermittent porphyria (AIP) with defective porphobilinogen deaminase, and less commonly hereditary coproporphyria (HC) with defective coproporphyrinogen oxidase, Variegate Porphyria (VP) with defective protoporphyrinogen oxidase), and Doss Porphyria (aminolaevulinic acid dehydrase deficiency) [82, 97, 111, 125]. Porphyrias are usually transmitted as autosomal dominant traits and are latent until an acute attack (which occurs only in a minority of disease carriers) is precipitated by environmental factors such as infections, surgery, drugs, or by metabolic (low-caloric diet, starvation) or hormonal (menstrual luteal phase, pregnancy) changes. Attacks occur after puberty and are more common in females.

Colicky abdominal pain, constipation and tachycardia are the first symptoms, often leading to inappropriate treatment with sedatives and even abdominal surgery which can further worsen the attack. Central nervous system involvement causes agitation, which may progress to frank psychosis, seizures, and even coma. Hyponatraemia due to inappropriate secretion of ADH, or to electrolyte depletion, is another possible complication. Neuropathy develops within a few days and closely resembles GBS because of back pain, rapidly progressive proximal and distal motor weakness, mild sensory symptoms, frequent cranial nerve involvement with facial and bulbar weakness (and even oculomotor paresis); respiratory palsy may occur. Autonomic sympathetic overactivity produces also mydriasis, hypertension, and micturition dysfunction.

The following elements are of help in distinguishing porphyric neuropathy from GBS: ascending paralysis, early loss of deep tendon reflexes, and marked CSF protein elevation are rarely seen in porphyrias; electroneurography evidence of axonal neuropathy, history of urine colour changes (due to polymerisation of porphobilinogen to porphyrins and other pigments), photosensitivity (seen in HC and VP and due to porphyrin accumulation in the skin) suggest porphyria. Differential diagnosis includes metal poisoning (thallium and arsenic). Diagnosis is based on the demonstration of increased levels of urinary aminolaevulinic acid, and of urinary and faecal porphyrins during the acute attacks; in the latent phases, however, urinary and faecal porphyrin levels may be normal. Each porphyria type shows a specific excretion pattern of haem metabolites. Demonstration of decreased enzymatic activity (e. g., of porphobilinogen deaminase in erythrocytes for AIP patients) makes it possible to reach the right diagnosis [82, 111, 125]. Several different mutations in the porphobilinogen deaminase gene have been reported in AIP [97, 111]. Prevention requires avoiding several drugs (including most anti-epileptic drugs), following a proper caloric diet and, in women with menstrual-related attacks, administering analogues of luteinizing hormone-releasing hormone [4]. During acute attacks, intravenous glucose (up to 300 g/day) and haem arginate (usually 3 mg/Kg/day for 4 days) revert the biochemical abnormalities and, if administered early, the symptoms [82, 111, 125].

Relapsing (-progressive) generalised polyneuropathy

A generalised sensori-motor polyneuropathy with a relapsing-remitting or progressive course is a feature of *Refsum disease*, a rare recessive disorder associated with mutations in the phytanoil-CoA α-hydroxylase gene on chromosome 10pter-p11.2, which cause impaired degradation of branched chain fatty acids and tissue accumulation of phytanic acid [53, 74, 105, 118, 122]. The neuropathy is demyelinating as shown by NCV studies and nerve biopsy evidence of hypertrophic neuropathy with onion-bulb formations [105]. Sudden worsening may occur and the neuropathy may be episodic in the early stages; nerve conduction slowing may be nonuniform [62, 118]. On the whole, the course of this polyneuropathy is progressive, pes cavus is usually present and CSF examination shows increased protein concentration [105]. Therefore, it may be confused with either CMT1 and CIDP. However, Refsum disease is always characterised by the presence of salt-and-pepper retinitis pigmentosa with hemeralopia, and cerebellar ataxia is present, particularly in the late stages. Other features may be found [105, 118] and include: 1) cranial nerve involvement with sensorineural hearing loss, anosmia,

pupillary abnormalities; 2) cardiopathy with EKG abnormalities, cardiomegaly; 3) other skeletal malformations, i.e. symmetrical shortening or elongation of metatarsal (particularly III and IV), metacarpal, finger or toe bones; 4) skin changes, from dry skin to overt ichthyosis; 5) cataract. Diagnosis is based on the demonstration of increased plasma level of phytanic acid. Therapy calls for a diet limiting the intake of phytanic acid and free phytol, which are contained mainly in dairy products and ruminant meat and fat [105, 118, 122]. Plasmapheresis, which is able to lower phytanic acid levels, can also be used as a long-term treatment and is particularly helpful during acute relapses, which may occur spontaneously or after stress, weight loss, concurrent illnesses, pregnancy [105, 118]. Currently, research is focused on the possibility of rescuing the mutated enzyme via dietary supplementation with appropriate amino acids [118]. Recently, genetic heterogeneity of Refsum disease has become evident and mutations in the peroxisome biogenesis factor-7 gene (PEX7) in a subset of patients have been demonstrated [118, 122].

Acute-relapsing focal neuropathy

Acute painless mononeuropathy or brachial plexopathy is the usual presentation of *hereditary neuropathy with liability to pressure palsies (HNPP, tomaculous neuropathy)*, an autosomal dominant disorder characterised by abnormal sensitivity of nerves to compression. Episodes of focal neuropathies are typically painless and transient, may be recurrent, occur after mild trauma or pressure, or with no evident triggering factor [123]. Ulnar, radial, and peroneal nerves, and brachial plexus are the most frequently affected segments. Compression paraesthesiae are a typical complaint. Pes cavus is seen in more than one third of the cases. Disease expression varies considerably: some subjects are asymptomatic and show only minimal signs at clinical examination, whereas older patients may develop a generalised neuropathy mimicking CMT disease [75, 86, 115]. Electrophysiological studies demonstrate nerve conduction abnormalities which may be mild or diffuse but typically are non-homogeneous, asymmetric, and always more evident at common entrapment sites [5, 63, 75, 86]. Nerve biopsy reveals the characteristic focal myelin thickenings (tomacula) in several fibres [123].

HNPP is associated with the deletion of the same 17p11.2 chromosomal region that is duplicated in CMT1A and encompasses the PMP22 gene [27, 48, 87]. Rarely is the deletion not found and in a few HNPP cases PMP22 micromutations have been demonstrated [73, 87].

Patients with acute painless mononeuropathy, brachial plexopathy, multiple mononeuropathy, and even those with chronic asymmetric polyneuropathy of unknown aetiology, especially if young, should be considered potentially affected by HNPP. Therefore, they should undergo electrophysiological examination to look for evidence of multiple entrapments, and, if they are found, the patients must be submitted to DNA analysis. Like CMT, a family history of HNPP patients may often be apparently unremarkable, and thorough clinical, electrophysiological, and molecular examination of at-risk family members is warranted to disclose the familial nature of the disease.

Another familial form of recurrent focal neuropathy is *Hereditary Neuralgic Amyotrophy (HNA),* characterised by repeated episodes of acute brachial plexopathy with muscle weakness and atrophy, sometimes with sensory changes, preceded by severe pain [107, 123]. Like the sporadic Parsonage-Turner syndrome, the episodes may be triggered by pregnancy, delivery, infections or immunisation. In very few patients the acute episodes may selectively involve cranial nerves, distal segments of the upper limb, or a lower limb [123]. Recovery is usually complete but requires several weeks or months. Dysmorphic features have been reported in affected patients, mainly orbital hypotelorism, and unusual skin folds and creases in the neck [54]. EMG examination and nerve biopsy findings are not consistent with a generalised neuropathy. HNA is an autosomal dominant disorder and in some families it has been linked to chromosome 17q24-q25, whereas in others linkage to 17q has been excluded [59, 72, 106, 107, 120].

Rare inherited neuropathy

Peripheral neuropathy may be a feature of a number of rare diseases or sometimes may be the onset manifestation of more complex neurological diseases. Peripheral neuropathy has been reported as the presenting feature of late-onset Krabbe leukodystrophy [66]; peripheral neuropathy is a feature of other leukodystrophy (LD) (metachromatic LD, adrenoleukodystrophy-adrenomyeloneuropathy) [112] and also of some cases of Pelizaeus-Merzbacher disease associated with certain mutations of the proteolipid protein (particularly null mutations which involve also its DM20 isoform) [39, 62]. An adult-onset sensori-motor neuropathy with increased levels of pristanic acid has been associated with mutations of the gene encoding peroxisomal alpha-methylacyl-CoA racemase [38]. Among the mitochondrial cytopathies, NARP is characterised by a sensory neuropathy [76], and the MNGIE (MyoNeuroGastroIntestinal Encephalopathy) syndrome by a peripheral neuropathy with frequent enteric pseudo-obstructions (together with a diffuse leukoencephalopathy, and a myopathy) [49, 76, 81]. Madelung disease combines multiple symmetrical lipomatosis with peripheral neuropathy [96]; other neurological signs may be present and in

some cases mtDNA mutations have been identified [76, 77].

Adult onset polyglucosan body disease is characterised by involvement of central and peripheral nervous systems, with pyramidal signs, cognitive impairment, urinary disturbances and polyneuropathy: nerve biopsy may be particularly useful by demonstrating polyglucosan bodies [64]. Chedjack-Higashi is a rare and lethal disease characterised by severe immunologic defects, reduced pigmentation, and lymphoproliferative disorders; a proportion of patients have a milder phenotype and in adult life develop progressive neurological dysfunction including peripheral neuropathy [56].

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