NEUROLOGICAL INVESTIGATIONS

Investigation of peripheral neuropathy

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Peripheral neuropathy is a common condition that is associated with many systemic diseases. Its exact prevalence in the community is not known although epidemiological studies have established the frequency of certain subtypes—for example, Guillain-Barré syndrome,¹ diabetic neuropathy,² and Charcot-Marie-Tooth disease.³ Because of the numerous causes (well over 100) of peripheral neuropathy and the likelihood of finding an underlying treatable condition, it is important to take a systematic approach to the diagnosis. Diagnostic algorithms for evaluation of neuropathies have been published.^{4,5} Although it used to be believed that in more than half the cases a cause was not found,⁶ several large series have shown that after intensive investigation only about 20% of cases remain undiagnosed and these tend to have a relatively good prognosis.⁷⁻⁹

Pathological types of peripheral neuropathy

There are three major pathological processes that affect the peripheral nervous system: axonal degeneration, segmental demyelination, and neuronopathy. It is important in the investigation of a peripheral neuropathy to be able to recognise the underlying pathological nature of the condition as it influences subsequent management. *Axonal degeneration* is the most common pathology seen in systemic, metabolic, toxic, and nutritional disorders. It characteristically has a predilection for large diameter and long fibres—distal axonopathy or dying back neuropathy. *Segmental demyelination* is primary destruction of the myelin sheath leaving the axon intact, although axonal degeneration may also be present in demyelinating neuropathies and secondary segmental demyelination may be seen in axonal degeneration. Electrophysiological studies are helpful in differentiating primary demyelination from axonal degeneration. *Neuronopathies* are those conditions in which the cell bodies of axons—anterior horn cells or dorsal root ganglia—are primarily affected.

Clinical evaluation

The most important parts of the investigation of suspected peripheral neuropathy are the taking of an accurate history and the performance of a careful clinical examination.

Sensory symptoms are usually the presenting features of neuropathy and include numbness, tingling, pins and needles in the hands and feet, burning sensations, pain in the extremities, sensations of walking on cotton wool, band like sensations around the wrists or ankles, unsteadiness on the feet, or stumbling. Motor symptoms are usually those of weakness and patients may find it difficult to turn keys in locks, unfasten buttons, and remove the tops of bottles and jars. In the early stages of peripheral neuropathy, weakness is usually distal; however, early proximal weakness is a feature of inflammatory neuropathies and porphyric neuropathy. Autonomic symptoms, particularly postural hypotension, impotence, sphincter disturbances, diarrhoea, constipation, and dryness or excessive sweating of the extremities point to damage of small myelinated and unmyelinated fibres. In the history, attention should be paid to recent upper respiratory tract or other infections, alcohol and drug intake, diet, possible exposure to industrial and environmental toxins, family history, and symptoms of systemic diseases. It is important to note the tempo of the disease—acute, subacute or insidious onset; rapid or slow progression; progressive, stepwise or relapsing and remitting course. Table 1 shows some of the more common causes of peripheral neuropathy with acute onset.

Signs are usually those of distal muscle wasting and weakness, and sensory impairment, predominantly over distal regions and often in a glove and stocking distribution. In distal axonopathies, particularly in diabetes, there may be loss of sensation over the ventral regions of the trunk due to distal degeneration of the intercostal nerves. A truncal neuropathy, with a dermatomal distribution of dysaesthesia and sensory loss, may also be seen in diabetes¹⁰ as well as in Lyme disease¹¹ and Sjögren's syndrome¹² (table 1). In conditions that affect predominantly small fibres (amyloid neuropathy, Tangier disease, and some cases of diabetic neuropathy) there may be dissociated loss of sensation with loss of pain and temperature sensation and preservation of tactile sensation. Reflexes are usually depressed or absent but in mild cases, in small fibre neuropathies, and when peripheral neuropathy is associated with pyramidal tract lesions, reflexes may be preserved. Careful general examination should seek evidence of

Table 1 Clinical types of peripheral neuropathy

Acute onset:
Guillain-Barré syndrome
Porphyria
Toxic (for example, arsenic, nitrofurantoin)
Serum sickness (postimmunisation)
Diphtheria
Malignancy
Critical illness polyneuropathy
Diabetes, uraemia (rarely)
Predominantly motor:
Guillain-Barré syndrome
Porphyria
Diphtheria
Lead
Charcot-Marie-Tooth disease
Diabetes (diabetic amyotrophy)
Predominantly sensory:
Leprosy
Diabetes (distal sensory polyneuropathy)
Vitamin B12 or thiamine deficiency
Malignancy
Hereditary sensory and autonomic neuropathy
Primary of familial amyloidosis
Uraemia
Lyme disease
Sjögren's syndrome
Radicular:
Diabetic truncal neuropathy
Lyme disease
Sjögren's syndrome
Painful neuropathies:
Alcohol, nutritional deficiencies
Diabetes (acute painful neuropathy)
Hereditary sensory and autonomic neuropathy (HSAN type 1)
Arsenic
Cryoglobulinaemia
Lyme disease
Paraneoplastic sensory neuropathy
Vasculitic neuropathies

pes cavus or other skeletal deformities, enlarged nerves, skin lesions, arthritis, dry mucous membranes, and enlargement of liver, spleen, and lymph glands.

The clinical features of the neuropathy may indicate the underlying cause and enable the most appropriate investigations to be undertaken (table 1). Mononeuropathy is usually due to direct compression or entrapment but may be the first manifestation of diabetic or vasculitic neuropathy. Mononeuritis multiplex (multiple mononeuropathy) is caused by vasculitis, leprosy, sarcoidosis, and some other conditions (table 2).

Laboratory investigations

General laboratory tests and nerve conduction studies will be performed as the first stage of investigation in all patients unless the diagnosis is clinically obvious—for example, diabetic or alcoholic neuropathy; subsequent

investigation will depend on the results of these initial studies.

GENERAL LABORATORY TESTS

Basic laboratory investigations that should be performed on all patients with peripheral neuropathy of undetermined aetiology include urinalysis, haemoglobin, white cell count, platelets, erythrocyte sedimentation rate, fasting blood glucose, serum electrolytes, serum proteins, serum protein electrophoresis and immunoelectrophoresis, serum creatinine, liver function tests, chest radiographs, and electrophysiological studies (see later). If these do not provide a diagnosis, other special investigations may include thyroid function tests, serum vitamin E concentrations, serum cholesterol and triglycerides, cryoglobulins, urinary heavy metals and porphyrins, antinuclear antibodies, rheumatoid factor, Sjögren's syndrome (SS) antibodies, (SS-A (anti-Ro) and SS-B (anti-La)), serology for Lyme disease and HIV, antiganglioside GM1 antibodies, Schirmer's test, and screening for occult malignancy with endoscopic and radiological examinations including skeletal surveys (table 3).

NERVE CONDUCTION STUDIES

Nerve conduction studies play a key part in confirming the presence of peripheral neuropathy and in establishing its cause. They assist in determining whether the patient has a mononeuropathy, mononeuritis multiplex, or a generalised peripheral neuropathy, and if so, whether it is symmetric or asymmetric, whether both sensory and motor fibres are affected, and whether the underlying pathology is that of axonal degeneration or segmental demyelination as there is a correlation between the conduction velocity and the underlying pathological process.¹³⁻¹⁷ Table 4 shows the causes of segmental demyelination and conduction velocities in the demyelinating range.

Nerve conduction studies should be performed on nerves that are clinically unaffected as well as those that are clinically affected. In general, several nerves should be studied in upper and lower limbs—for example, motor and sensory conduction in median and ulnar nerves, motor conduction in common peroneal and posterior tibial nerves, and sensory conduction in sural nerves. In some cases it may be appropriate to perform sensory conduction on radial, tibial, and saphenous nerves and to record mixed nerve action potentials in ulnar and common peroneal nerves. Every clinical neurophysiology laboratory should have established its own control values. The age of the patient needs to be taken into account because nerve conduction velocities in full term infants are about half the adult values but increase to the adult range at 3 to 5 years of age; there is also a reduction in conduction velocity after the age of 40. Temperature of the limbs must be controlled or a temperature correction applied because the conduction velocity changes by 2.4 m/s/°C from 29 to 38°C.¹⁸⁻¹⁹

Table 2 Causes of mononeuritis multiplex

Vascular:
Diabetes
Polyarteritis nodosa
Rheumatoid arthritis
Systemic lupus erythematosus
Wegener's granulomatosis
Sjögren's syndrome
Non-systemic vasculitis
Inflammatory:
Leprosy
Sarcoidosis
Lyme disease
Infiltrations:
Malignancy
Amyloidosis
Immune reactions:
Immunisation, foreign serum and proteins
Trauma:
Multiple nerve injuries

Table 3 General laboratory investigations

Condition	Investigations
Metabolic:	
Diabetes	Urinalysis, fasting blood glucose, glucose tolerance test
Hypoglycaemia	Fasting blood glucose, serum insulin, or C peptide concentrations
Uraemia	Blood urea, serum creatine, urinalysis
Porphyria	Urinary porphyrins, ALA, porphobilinogen. Total faecal porphyrins. Erythrocyte porphobilinogen deaminase
Hypothyroidism	Serum free thyroxine, serum TSH
Acromegaly	Serum growth hormone concentrations
Deficiencies:	
B1 (thiamine)	Erythrocyte transketolase activity + enhancement with thiamine pyrophosphate
Vitamin B6 (pyridoxine)	Erythrocyte aspartate amino transferase + enhancement with pyridoxal-5-phosphate
Vitamin B12	Serum B12, Schilling test
Vitamin E	Serum vitamin E
Toxic:	
Arsenic, lead, mercury, thallium	24 hour urinary heavy metals
Paraproteinaemias, dysproteinaemias:	
Multiple myeloma, Waldenström's macroglobulinaemia, cryoglobulinaemia, monoclonal gammopathy of uncertain significance	Hb, WCC, platelets, ESR, plasma immunoelectrophoresis, urinary Bence-Jones protein, radiological skeletal survey, bone marrow biopsy, plasma cryoglobulins
Connective tissue disorders:	
Systemic lupus erythematosus, mixed connective tissue disease, scleroderma, rheumatoid arthritis, polyarteritis nodosa, Sjögren's syndrome, Wegener's granulomatosis	Hb, WCC, platelets, ESR, serum immunoelectrophoresis, antinuclear antibodies, antidouble stranded DNA antibodies, rheumatoid factor, serum complement (C3, C4, CH50), antineutrophil cytoplasmic antibodies
Sjögren's syndrome	All above + anti-Sjögren's syndrome antibodies, Schirmer's test, lip biopsy
Inflammatory neuropathies:	
Acute inflammatory neuropathy	HIV, blood glucose, urinary porphyrins, Epstein-Barr virus, Campylobacter infections, cytomegalovirus, mycoplasma ESR, serum immunoelectrophoresis, anti-ganglioside GM1 antibodies, antinuclear antibodies, antineutrophil cytoplasmic antibodies
Chronic inflammatory demyelinating polyradiculoneuropathy	
Infections:	
HIV	HIV serology
Lyme disease	Lyme serology
Leprosy	Lepromin tests; skin, nasal scrapings; skin, nerve biopsy
Hereditary neuropathies with known biochemical abnormalities:	
Primary amyloid neuropathy	Rectal, liver, renal, abdominal fat, nerve biopsy; serum immunoelectrophoresis; urinary Bence-Jones protein
Familial amyloid polyneuropathy	Serum, tissue transthyretin
Metachromatic leukodystrophy	Blood leucocyte, skin fibroblast arylsulphatase
Krabbe's disease (globoid cell leukodystrophy)	Blood leucocyte, skin fibroblast galactosylceramide β galactosidase
A β lipoproteinaemia (Bassen-Kornzweig disease)	Acanthocytes in blood, serum cholesterol, plasma low density and very low density lipoproteins
An α lipoproteinaemia (Tangier disease)	Serum cholesterol
Refsum's disease	Plasma high density lipoproteins
	Serum phytanic acid. α oxidation of phytanic acid in skin fibroblasts

Hb = haemoglobin; WCC = white cell count; ESR = erythrocyte sedimentation rate.

Motor conduction velocities should be recorded from surface electrodes to measure the amplitudes of the muscle action potential after stimulation at distal and proximal sites; reduced amplitude of the muscle action potential at distal stimulation sites is indicative of axonal degeneration, or, rarely, demyelination in distal motor fibres. A significant reduction in the amplitude of the muscle action potential on moving the stimulating electrode from a distal to a more proximal site is supportive evidence of conduction block.²⁰ Conduction block is suspected if there is greater than 20% reduction in amplitude (provided there is less than a 15% change in duration of the muscle action potential between proximal and distal sites of stimulation²¹ as dispersion and polyphasic action potentials can cause phase cancella-

Table 4 Demyelinating neuropathies

Inflammatory neuropathies:
Guillain-Barré Syndrome
Chronic inflammatory demyelinating polyradiculoneuropathy
Motor neuropathy with multifocal conduction block
Chronic inflammatory neuropathy associated with paraproteinaemia
Inflammatory neuropathy associated with HIV infection
Hereditary neuropathies:
HMSN type I
HMSN type III
Refsum's syndrome
Metachromatic leukodystrophy
Krabbe's disease
Metabolic neuropathies:
Diabetes (sometimes)
Uraemia (sometimes)
Toxic neuropathies:
Perhexiline maleate
Amiodorone
Hexacarbons
Infections:
Diphtheria
Malignancy
Some acute or subacute neuropathies associated with lymphoma, carcinoma

tion).²² Abrupt change in area, or amplitude, or both over a short segment of nerve, rather than a gradual reduction over a longer distance, is strong evidence of conduction block.²² Further evidence of demyelination is temporal dispersion (increased duration of the muscle action potential), prolonged distal latencies, and reduction in conduction velocity to less than 80% of the lower limit of normal in two or more motor nerves.^{21 23}

In axonal degeneration there is normal or only mild slowing of conduction due to fall out of the damaged large diameter fibres, the remaining intact fibres having normal conduction velocities. Other evidence of axonal degeneration is a reduced muscle action potential and electromyographic evidence of denervation. It should be noted that mild degrees of slowing of conduction do not exclude the possibility of underlying segmental demyelination in peripheral nerves.^{15 17} Sensory conduction is usually impaired, with reduced amplitudes of action potentials in both axonal degeneration and segmental demyelination. Although sensory action potentials are difficult to record over long distances in diseased nerves, slowed conduction and dispersion of the action potentials can be recorded in segmental demyelination with appropriate techniques. Because motor and sensory conduction are routinely measured only in large diameter fibres with standard nerve conduction techniques, they may be normal in small fibre neuropathies.

F waves

F waves are late waves that can be recorded from muscles after supramaximal stimulation of the nerve and result from antidromic nerve impulses causing anterior horn cells to back-fire.²⁴ They provide a measure of conduction over the whole length of the motor nerve and are therefore a useful way of recording conduction in proximal segments.¹⁹

H reflex

The H reflex measures the conduction through afferent and efferent fibres in the

monosynaptic reflex arc. It is most easily recorded from the calf muscles. It is usually absent when the F wave and other nerve conduction studies are abnormal.¹⁹

Needle electromyography

When muscles are denervated, spontaneous fibrillation, positive sharp waves, and a reduced interference pattern are recorded on needle electromyography. Electromyography is useful in confirming the presence of axonal degeneration in the Guillain-Barré syndrome.²⁵ It should be borne in mind that denervation potentials may not appear until three weeks after the onset of axonal degeneration.

Somatosensory evoked potentials

Somatosensory potentials may be useful in detecting abnormalities of conduction in proximal segments when conventional nerve conduction studies are normal.²⁵ Walsh *et al*²⁶ found them more useful than the F waves in the Guillain-Barré syndrome although others have had a different experience.²⁷

EXAMINATION OF CSF

A lumbar puncture with examination of CSF is unrewarding in most cases of axonal neuropathy but should be performed in demyelinating neuropathies. In the Guillain-Barré syndrome the CSF protein rises during the first week. The white cell count varies with the time of lumbar puncture and is raised in about 10% of cases.^{28,29} An increased white cell count raises the possibility of HIV infection or Lyme disease.^{28,30} CSF protein is also raised in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and may help to distinguish this condition from hereditary demyelinating neuropathies. A high CSF protein suggests inflammatory causes and demyelination of spinal roots or both. In my experience, oligoclonal IgG bands are present in the CSF of about 6% of cases of Guillain-Barré syndrome, and 16% of cases of CIDP.

QUANTITATIVE SENSORY TESTING

Quantitative sensory testing is the use of psychophysical methods for measuring abnormalities of the different modalities of sensation. With these techniques, quantitative values for thresholds of vibration, touch—pressure, and warm and cold sensation may be obtained on individual patients and compared with control values. These investigations are not routinely employed in the investigation of peripheral neuropathy but are

useful in detecting early sensory abnormalities in people exposed to occupational and environmental toxins, in controlled clinical trials, and in epidemiological studies.³¹

AUTONOMIC FUNCTION STUDIES

Autonomic dysfunction is a common complication of peripheral neuropathies although often it is mild and of little relevance. In some conditions, however, there may be profound disturbance of autonomic function including orthostatic hypotension, impairment of blood pressure, heart rate and bladder control, and impotence. Diseases that primarily affect small fibres in peripheral nerves or cause acute demyelination of small myelinated fibres are those most likely to cause autonomic dysfunction. These include acute dysautonomia, familial and primary amyloidosis, Guillain-Barré syndrome, diabetes, porphyria, Chagas' disease, and some hereditary sensory and autonomic neuropathies.^{32–35} There are many available tests from which to select; tests of both sympathetic and parasympathetic function should be included and it is generally necessary to find abnormalities in two or more of these tests to confirm the presence of autonomic dysfunction.³³ Tests of autonomic function that can be readily undertaken in the clinical neurophysiology laboratory are heart rate variation with respiration, Valsalva ratio, heart rate response to standing or tilting, blood pressure response to sustained hand grip, and the sympathetic skin response.³⁴ Autonomic function studies, together with quantitative sensory testing and sural nerve biopsy, are the most useful ways of confirming a diagnosis of small fibre neuropathy.³⁶

MOLECULAR GENETICS

There are now several hereditary neuropathies in which the gene locus has been identified and the number is rapidly increasing with advances in recombinant DNA technology. The types of genetic analysis available to the clinician fall into two groups: linkage studies for conditions in which the region of the gene on the chromosome has been identified but the defective gene has not been cloned, and mutation analysis or positional cloning in those conditions in which the gene has been cloned.^{37–39}

Table 5 shows the hereditary peripheral neuropathies in which the gene has been identified.

SURAL NERVE BIOPSY

Nerve biopsy is a valuable method for establishing a cause of peripheral neuropathy in specific circumstances.^{5,40,41} It should not be performed simply to establish the presence of peripheral neuropathy as clinical evaluation and nerve conduction studies are nearly always adequate for this purpose. It should only be undertaken where the biopsy can be evaluated by a laboratory experienced in the techniques of light and electron microscopy, teased fibre studies, and the use of immunohistochemical methods of staining. Biopsies

Table 5 Genetic tests for hereditary neuropathies

Disease	Chromosome location	Gene product	Genetic defect
CMT Ia (HMSN Isa)	17p11.2–12	PMP22	Duplication
CMT Ib (HMSN Ib)	1q21.2, 23	Po	Point mutation
CMT X (HMSN-X)	Xq13	Connexin-32	Point mutation
Hereditary liability to pressure palsies (Tomaculous neuropathy)	17p.11.2,12	PMP22	Point mutation
Familial amyloid polyneuropathy (most types)	18q11.2,12.1	Transthyretin, Apo A1 + 2 unidentified genes on chromosomes 9 and 11	Point mutations

should only be undertaken after full clinical and electrophysiological assessment and when other laboratory investigations have been completed. It is usually performed on the sural nerve but sometimes the radial sensory nerve is more appropriate. Whole nerve or fascicular biopsies are undertaken in different centres. Although not required in those cases where the diagnosis is certain from family history or from other investigations, nerve biopsy may confirm a diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP),⁴²⁻⁴³ hereditary motor and sensory neuropathy (HMSN),⁴⁴⁻⁴⁸ hereditary sensory and autonomic neuropathy (HSAN),⁴⁹ primary and familial amyloid neuropathy,⁵⁰⁻⁵³ vasculitis,⁵⁴⁻⁵⁷ sarcoidosis,⁵⁸ giant axonal neuropathy,⁵⁹⁻⁶⁰ hereditary liability to pressure palsies (tomaculous neuropathy),⁶¹ and hexacarbon (n-hexane and methyl n-butyl ketone) neuropathy.⁶² Specific appearances may be seen in the nerve biopsy in IgM κ paraproteinaemic neuropathy,⁶³ metachromatic leukodystrophy,⁶⁴⁻⁶⁶ Krabbe's disease,⁶⁶⁻⁶⁷ Fabry's disease,⁶⁸⁻⁶⁹ and Friedreich's ataxia.⁷⁰ In some cases of vasculitis, sarcoidosis, amyloidosis, sensory perineuritis, and chronic inflammatory neuropathy, the biopsy is essential for diagnosis.

In general, nerve biopsy is of little diagnostic value in metabolic disorders and alcoholic and nutritional neuropathies, in which the appearances are non-specific. There is a case for performing biopsies in patients with chronic neuropathies of undetermined cause when all other investigations have been completed. The morphometry of peripheral nerves is related to age and every laboratory should have its own established control values for different age groups.

Application of investigations to specific types of peripheral neuropathy

HEREDITARY NEUROPATHIES

Charcot-Marie-Tooth disease (hereditary motor and sensory neuropathy, peroneal muscular atrophy)

Charcot-Marie-Tooth disease (CMT) is a genetically heterogeneous disorder. There are four major types: HMSN I (CMT 1a and 1b), HMSN II (CMT 2), X linked (CMT-X), and HMSN III (Déjérine-Sottas disease).³ HMSN I and II are usually dominant although some autosomal recessive cases have been described. Déjérine-Sottas disease (HMSN III) is autosomal recessive.

Nerve conduction studies—Nerve conduction studies are of considerable value in the initial categorisation of Charcot-Marie-Tooth disease into different subtypes. Although there is some overlap, motor conduction velocities in both HMSN Ia and b are greatly slowed (median motor conduction velocity < 38 m/s) and sensory conduction is impaired. By contrast, there is only mildly impaired or normal motor conduction velocity in HMSN II.^{3 44-46 71-74} Bradley *et al*⁴⁵ suggested that there was also an intermediate type of Charcot-Marie-Tooth disease with intermediate conduction velocities

(25–45 m/s) and intermediate changes on nerve biopsy. It is likely that some of these cases were CMT-X as slow conduction velocities are found in affected males with CMT-X (< 40 m/s) and intermediate range motor conduction velocities (> 40 m/s) in affected or obligate female carriers.⁷⁵ In HMSN III (Déjérine-Sottas disease) motor conduction velocities are typically grossly slowed (< 12 m/s).^{47 48 71} It may be a genetically heterogeneous condition.⁷⁶

Sural nerve biopsy—Sural nerve biopsy is helpful in distinguishing the different types of HMSN when they are not clearly separated on the basis of electrophysiological studies.^{44-48 71} In HMSN Ia and b there is a reduction in the density of fibres, evidence of segmental demyelination on light and electron microscopy and teased nerve fibres, and in most myelinated fibres the myelin sheath is of appropriate diameter for the axon. In HMSN II there is a reduction in the density of myelinated fibres but no evidence of demyelination. In HMSN III onion bulbs are prominent and the myelin sheath is abnormally thin relative to the axon diameter.

Genetic studies—Most cases of HMSN I are type 1a, which is linked to chromosome 17.⁷⁷⁻⁷⁹ There is usually a duplication on 17p11.2–12⁷⁹⁻⁸¹ in which region the PMP22 gene is located. In some cases of the disease, a point mutation of the coding region of PMP22 has been demonstrated where an identical mutation also occurs in the trembler mouse.⁸¹⁻⁸⁴ Duplication in this region has also been shown in nine out of 10 sporadic cases that had been considered to be recessive.⁸⁵ It has been suggested that overdosage of PMP22 caused by the DNA duplication is the mechanism for producing the HMSN Ia phenotype. A deletion in the same region that is duplicated in HMSN Ia is found in hereditary neuropathy with liability to pressure palsies.^{86 87} It has been shown that the gene involved is also PMP22. A frame shift or null mutation was found, indicating that underdosage of PMP22 is the cause of this condition.⁸⁸

The gene mutation in HMSN 1b has been located near the Duffy locus on chromosome 1 where HMSN Ib was originally mapped by linkage analysis.^{89 90} A point mutation in the gene for Po (1q21.2q23) was subsequently found when Po was mapped to this region.⁹¹

HMSN type II is genetically heterogeneous; the gene for one of the forms of autosomal dominant HMSN II (CMT 2) has been localised to chromosome 1p36.⁹²

The gap junction protein connexin-32 has been identified for the gene mutation in CMT X (Xq13).⁹³

Déjérine-Sottas disease (HMSN III) now seems to be a heterogeneous disorder. Cases have been reported with mutations of PMP22 and Po genes.^{94 95}

Amyloid neuropathy

Peripheral neuropathy is a feature of primary amyloidosis and several types of familial amyloid polyneuropathy. Dysaesthesiae, loss of pain and temperature sensation in the

extremities, and autonomic dysfunction (postural hypotension, impotence, impaired sweating, bladder disturbance) are characteristic features. Distal sensory loss, predominantly of pain and temperature sense, are found on examination. Nerve conduction studies and electromyography are consistent with axonal neuropathy. Autonomic function studies are abnormal. Sural nerve biopsy is usually diagnostic and shows amyloid deposits in blood vessels and endoneurium on Congo red staining and there is selective loss of small myelinated and unmyelinated fibres. The diagnosis of amyloidosis may also be established by abdominal fat, rectum, kidney, and liver biopsy.⁵⁰⁻⁵³ A high proportion of patients with primary amyloidosis have monoclonal proteins on immunoelectrophoresis of urine and blood, and some have multiple myeloma. Immunohistochemical staining of tissue amyloid identifies protein specific types—AL in primary amyloidosis and AF in familial types. The amyloid in familial polyneuropathy is not derived from immunoglobulin and therefore abnormal immunoglobulins are not present in the serum. In most, but not all, types of familial polyneuropathy (Portuguese, Indian, German and Jewish, and Appalachian types), there is a prealbumin (transthyretin) fraction in the serum and a point mutation in the transthyretin gene (chromosome 18q.11.2, q12.1). The Finnish type of amyloidosis has been located on 9q33 and the Iowa type on 11q33-q24. The Van Allen type is due to a genetic defect of apolipoprotein A1.³⁷⁻⁵³

Hereditary disorders of lipid metabolism

Metachromatic leukodystrophy—Metachromatic leukodystrophy is associated with peripheral neuropathy that may sometimes be a presenting feature in adult cases. Nerve conduction studies are consistent with the segmental demyelination that is seen on sural nerve biopsy together with metachromatic granular inclusions in Schwann cells.⁶⁴⁻⁶⁶ Diagnosis may be established in the laboratory by determination of reduced arylsulphatase concentrations in blood leucocytes and skin fibroblasts, and by the finding of intracellular deposits of metachromatic material on microscopic examination of urinary sediment.⁶⁶ There is a mutation of the gene encoding for arylsulphatase A on chromosome 22q-13qter.³⁸

Krabbe's disease (globoid cell leukodystrophy)—Krabbe's disease is autosomal recessive, affects children in the first year of life, and is associated with peripheral neuropathy. Nerve biopsy shows loss of myelinated fibres, and inclusions in Schwann cells and macrophages that are diagnostic.⁶⁶⁻⁶⁷ Assay of the enzyme galactosylceramide β galactosidase in leucocytes, serum, or cultured fibroblasts will establish the diagnosis without the need for biopsy.⁶⁶

A- β lipoproteinaemia (Bassen-Kornzweig disease)—Peripheral neuropathy is associated with a progressive ataxia resembling Friedreich's ataxia.^{4,5} There is moderate slow-

ing of motor conduction, and nerve biopsy shows segmental demyelination and loss of large diameter fibres. The diagnosis can be confirmed by laboratory investigations which show acanthocytes in the peripheral blood, low serum cholesterol and low density and very low density lipoproteins. Genetic testing is not available.

An- α lipoproteinaemia (Tangier disease)—Peripheral neuropathy is usually present. The presence of large orange tonsils is characteristic. Sural nerve biopsy shows reduced numbers of myelinated and unmyelinated fibres and lipid droplets may be seen in Schwann cells.⁹⁶ Plasma high density lipoproteins are greatly reduced.

Fabry's disease—This is associated with a painful neuropathy and a selective loss of small myelinated and unmyelinated fibres may be seen in the sural nerve biopsy.⁶⁸⁻⁶⁹ It is an X linked recessive disorder. Glycolipid granules may be seen in perineurial and endothelial cells in peripheral nerve.⁶⁸ There is a deficiency of the enzyme ceramidetrihexosidase that results in the accumulation of ceramidetrihexoside in tissues. Diagnosis may be established by enzyme assay of α galactosidase which is reduced on leucocyte and skin fibroblast preparations.⁹⁷

Refsum's disease—Refsum's disease is a rare autosomal recessive disorder characterised by demyelinating hypertrophic neuropathy, retinitis pigmentosa, ataxia, ichthyosis, and deafness. Motor nerve conduction is very slow due to demyelination; with onion bulb formation that may be seen on sural nerve biopsies. There is impaired α -oxidation of phytanic acid causing an accumulation of phytanic acid in the tissues.⁹⁸ Diagnosis is made from the clinical picture and by increased serum phytanic acid and defective α oxidation of phytanic acid by skin fibroblasts.

Friedreich's ataxia—Friedreich's ataxia is associated with a sensory neuropathy. Electrophysiological studies typically show small or absent sensory potentials and normal motor conduction and on sural nerve biopsy there is a selective loss of large diameter fibres.⁷⁰ Other spinocerebellar degenerations may be associated with a mild neuropathy affecting myelinated fibres of all diameters.⁹⁹

INFLAMMATORY NEUROPATHIES

Guillain-Barré syndrome

In the first instance, a clinical diagnosis of peripheral neuropathy must be established and other conditions such as transverse myelitis, spinal cord compression, botulism (pure motor features), and myasthenia gravis (pure motor features) must be excluded. Other causes of acute neuropathy (toxins, drugs, nutritional deficiencies, porphyria, Lyme disease, acute neuropathy of the critically ill, vasculitis, and malignancy) are eliminated by clinical evaluation and appropriate tests. Antecedent precipitating factors (for example, immunisation, *Campylobacter*, Epstein-Barr virus, and mycoplasma infections) should be sought. The CSF may show

the typical abnormalities of increased protein and low white cell count; a high white cell count raises the suspicion of HIV, Lyme disease, and other infections.^{28 30 100} Nerve conduction studies are essential for diagnosis but may be normal in the early stages in which case recording of F waves and somatosensory evoked potentials should be undertaken to seek evidence of impairment of proximal conduction. Three or more nerves should be studied in upper and lower limbs as the peripheral nerve demyelination may be asymmetric and patchy.²⁵ Serial studies should be undertaken if the diagnosis is in doubt. Electromyography should be performed after two or three weeks if recovery is slow, or muscle wasting has developed, to ascertain the extent of axonal degeneration. Nerve conduction studies should be repeated if recovery is delayed; persistent slowing of conduction, conduction block, and dispersion should raise the suspicion of chronic inflammatory demyelinating polyneuropathy with acute onset but it should be borne in mind that electrophysiological evidence of demyelination may persist in typical Guillain-Barré syndrome for many weeks.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Typically the onset is subacute, the peak of disability being reached later than four weeks; however, it may have a more rapid onset. The diagnosis is confirmed by evidence of demyelination from nerve conduction studies.^{42 43 101} These may help differentiate it from the demyelination seen in hereditary demyelinating neuropathies HMSN types I and III and Refsum's syndrome in which the conduction velocities are uniformly slow in all nerves and conduction block and dispersion of the action potential are uncommon.¹⁰² Protein in CSF is usually increased.^{42 43 101} Other types of demyelinating neuropathy (paraproteinemic, vasculitic, leprosy, Lyme disease, HIV infections) must be excluded by appropriate investigations. If there is doubt about the diagnosis, confirmation should be obtained from sural nerve biopsy as the patient is likely to be committed to a long course of immunotherapy with its attendant risks.¹⁰³ The progress can be monitored by nerve conduction studies although the changes of improvement or deterioration will lag behind those of the clinical features.

Paraproteinemic neuropathies

Paraproteins may be found on immunoelectrophoresis during the investigation of patients with peripheral neuropathy, and the finding should arouse suspicion of multiple myeloma, Waldenstrom macroglobulinaemia, cryoglobulinaemia, primary amyloidosis, and other dysproteinemias. Bone marrow aspiration, examination for urinary Bence-Jones protein, and radiological skeletal survey should be performed; if these investigations are normal it is likely that the patient has a benign monoclonal gammopathy, or monoclonal gammopathy of undetermined significance.¹⁰⁴

Benign monoclonal gammopathy—There is an association between benign monoclonal paraproteins in the blood and peripheral neuropathy.¹⁰⁵ IgM paraproteins are particularly associated with a chronic demyelinating sensorimotor neuropathy, tending to occur in older people and being accompanied by a postural tremor.⁶² Sural nerve biopsy often shows demyelination with widely spaced myelin lamellae being seen on electron microscopy, particularly in the presence of IgM κ .⁶² IgA and IgG proteins may also be associated with demyelinating neuropathies. The relation between paraproteinemia and CIDP is uncertain.^{106 107}

Multifocal motor neuropathy with persistent conduction block

This is a rare condition in which there is an asymmetric chronic demyelinating neuropathy affecting predominantly motor nerves and clear electrical evidence of conduction block. It presents with asymmetric weakness and wasting with a motor neuron disease-like picture and increased antiganglioside GM1 antibodies in about 80% of cases.^{108 109} Motor nerve conduction studies show conduction block and slowing localised to sharply circumscribed areas in nerve trunks.¹¹⁰ Sensory conduction is normal, at least in the early stages of the disease, and sural nerve biopsy shows only minor changes.^{108 111 112} Biopsy of affected segments of nerves show subperineurial oedema, onion bulb formations, and demyelinated and remyelinated axons.¹¹³ The relation of this condition to CIDP is unclear.

Vasculitic neuropathy

Vasculitic neuropathies (polyarteritis nodosa, Churg-Strauss syndrome, Waldenstrom's macroglobulinaemia, rheumatoid arthritis, mixed connective tissue diseases, Sjögren's syndrome, non-systemic vasculitis, systemic lupus erythematosus) classically present as mononeuritis multiplex although about half the patients have a clinical picture of asymmetric or symmetric generalised sensorimotor polyneuropathy.⁵⁴ In most cases there will be evidence of systemic disease and raised erythrocyte sedimentation rate; the presence of increased titres of antinuclear antibodies and rheumatoid factor will confirm the diagnosis. Nerve conduction studies are consistent with an axonal neuropathy. Nerve biopsy usually shows pathological changes of vasculitis in small vessels in the endoneurium and perineurium and acute severe axonal degeneration. Non-systemic vasculitic neuropathy is being increasingly recognised; up to 30% of all vasculitic neuropathies fall into this group.⁵⁴⁻⁵⁷ Some cases may have increased erythrocyte sedimentation rate and antinuclear antibodies titres but in most there are no serological markers and diagnosis can be made only on sural nerve biopsy.

Sjögren's syndrome

Sjögren's syndrome is often difficult to diagnose in the early stages as it may present as a symmetric or asymmetric predominantly

sensory neuropathy in which there is evidence of vasculitis on sural biopsy^{57 114 115} before systemic symptoms of dry eyes, arthritis, and other manifestations of the disease become obvious and before titres of autoantibodies to Ro(SS-A) and La(SSB) become raised. Another manifestation of Sjögren's syndrome may be an ataxic sensory neuronopathy in which the primary pathology is dorsal root ganglionitis.^{115 116}

INFECTIONS

HIV infections

Symptomatic neuropathy affects about 5% to 10% of patients infected with HIV. Acute inflammatory polyneuropathy of the Guillain-Barré type most often occurs at the time of seroconversion.^{100 117} The CSF cell count may be raised.^{100 117} Subacute multifocal neuropathy of a demyelinating type with inflammatory pathology is the most common pattern of neuropathy before the onset of cellular immunosuppression.¹¹⁷ The CSF may be normal or show increased protein or white cell count. At the late stage of HIV infections an acute lumbosacral polyradiculopathy or multifocal neuropathy may be caused by cytomegalovirus infection. It is important to diagnose cytomegalovirus neuropathy as it is treatable.^{117 118}

Leprosy

Leprosy should be considered in mononeuropathy or multiple mononeuropathy with predominantly sensory symptoms in patients who live or have lived in endemic regions. Nerve biopsy is useful in the diagnosis and nerve conduction studies are helpful in identifying affected nerves.^{117 119}

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NEUROLOGICAL STAMP

Atropa belladonna (deadly nightshade)

Atropa belladonna is a member of the nightshade family solanaceae. Its botanical name is derived from Atropos who, in Greek mythology, cut the thread of life. The red sap enlarges the pupils of the eye. The plant was named at the time of the Italian Renaissance in the days of the infamous Borgia family, when the ready availability of poison was popular. The ladies of the court used one of these poisons, belladonna, not to kill their rivals but to beautify and enlarge their pupils.

The solanaceous alkaloids are among the earliest effective treatments for parkinsonism. Belladonna contains atropine, scopolamine, and hyoscyamine. The ripe berries are sweet tasting and poisonous and attractive to children.

A medicinal plant series published and produced by Yugoslavia in 1965 shows the belladonna flower (Stanley Gibbons 1161, Scott 775).

L F HAAS