MANAGEMENT OF CHRONIC PERIPHERAL NEUROPATHY*

R. A. C. Hughes, Professor of Neurology, Guy's, Kings and St Thomas' School of Medicine, King's College, London

In 1831 William Henderson directed his trustees to administer a fund for 'the advancement and diffusion of the science of phrenology'. His trustees have interpreted this task imaginatively and over the years have solicited lectures by a series of distinguished, mostly surgical, speakers on aspects of the brain and brain damage, such as Professor Douglas Miller in 1993 on *Function, Dysfunction and Damage in the Brain*. When lectures have descended to explore territory below the foramen magnum, it has been to visit the spinal canal, such as in 1986 when Professor Giles Brindley spoke on *The control of micturition, erection and seminal emission by surgical implanted stimulators of nerves or spinal roots*. This lecture will stoop even lower and consider diseases of the peripheral nerves whose manifestations – but not necessarily their pathology – lie outside the spinal canal. For this conference *Neurology 2000 and beyond*, I shall offer guidelines for the management of chronic peripheral neuropathy, based where possible on evidence and not just on that most maligned source, clinical experience.

RECOGNITION

The classical picture of advanced polyneuropathy with distal muscular wasting and weakness, absent tendon reflexes, and glove and stocking distribution of sensory loss is easy to recognise. However, the clinical features of peripheral neuropathy overlap with other conditions, especially myelopathy, radiculopathy, primary muscle disease, and hyperventilation syndrome. Consequently, recognising the presence of peripheral neuropathy is not always straightforward. Apportioning the blame for symptoms to peripheral neuropathy when this is combined with other coexisting problems can also be difficult. Furthermore neurophysiological tests may detect surprising degrees of abnormality of nerve conduction in asymptomatic patients and be disconcertingly normal in patients with small fibre neuropathy.

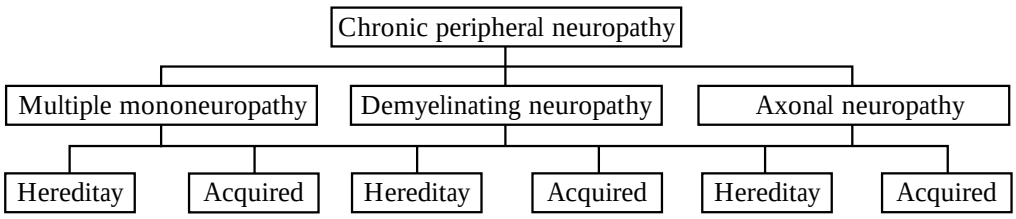

FIGURE 1
Diagnosis of chronic peripheral neuropathy

EPIDEMIOLOGY

Chronic peripheral neuropathy can certainly be a serious problem. In South-east Asia, Central and South America, and Africa, leprosy is still the commonest cause of neuropathy, and causes disabling and disfiguring mutilation of the hands and feet. In Europe the commonest cause is diabetes mellitus which causes foot ulcers, Charcot joints, and autonomic neuropathy, the latter contributing to sudden death.

The few available studies suggest a population prevalence of peripheral neuropathy of 2,400 per 100,000,[1] which rises with age to 8,000 per 100,000.[2] In a population-based study of 100,230 patients from London general practices, MacDonald *et al*. reported an annual incidence per 100,000 of 54 for diabetic neuropathy (95% CI 33 to 83), of 49 (95% CI 39 – 61) for compressive neuropathy (even excluding carpal tunnel syndrome) and of 15 for peripheral neuropathy (95% CI 9 to 23).[3] In their study peripheral nerve disorders collectively were almost as common as stroke. Therefore, peripheral nerve disorders are a neglected but common and potentially serious public health problem, and an appropriate topic for a Henderson Trust lecture.

Innumerable causes of peripheral neuropathy are known. Planning investigations requires a robust triage of investigations based on the clinical history, examination and results of neurophysiological investigations. The initial triage should divide patients into two groups, multiple mononeuropathy and polyneuropathy. Neuro-physiological testing should then determine whether the pathological process is axonal or demyelinating (Figure 1).

MULTIPLE MONONEUROPATHY

Multiple mononeuropathy may be due to multifocal compression, vasculitis or, very rarely, neural infiltration (Table 1). Nerve damage from compression is more likely to occur in patients with a predisposing metabolic abnormality, especially diabetes mellitus or alcohol abuse. It also occurs in patients with a genetic predisposition, especially hereditary liability to pressure palsies arising from the autosomal dominant inheritance of deletion of the gene for the peripheral myelin protein 22.[4] Infiltration occurs occasionally with carcinoma, lymphoma, sarcoidosis, amyloid and, of course, leprosy.

Sometimes it is difficult to distinguish the clinical picture

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TABLE 1
Causes of acquired multiple mononeuropathy

Multiple compression palsies associated with metabolic or toxic neuropathy
Vasculitis
Primary systemic vasculitis
Polyarteritis nodosa
Churg-Strauss syndrome
Systemic vasculitis associated with connective tissue diseases
Rheumatoid arthritis
Sjögren's syndrome
Vasculitis confined to peripheral nerves
Sarcoidosis
Lymphoma
Carcinoma
Amyloidosis
Leprosy

TABLE 2
Genes responsible for demyelinating and hypomyelinating forms of hereditary motor and sensory neuropathy[66]

CMT1a	PMP22[1] gene duplication
HNPP[2] (60 – 90%)	PMP22 gene deletion
CMTX (20%)	Connexin 32 gene mutation
CMT1b(5%)	P0 gene mutation
CMT1 (1%)	PMP22 gene mutation
CMT1	Early Growth Response (EGR) gene 2 mutation
CMT1	others
Dejerine-Sottas disease[3]	PMP22, P0, or EGR2 gene mutations

[1] Peripheral myelin protein 22
[2] Hereditary neuropathy with liability to pressure palsies
[3] Severe infantile-onset neuropathy first described in siblings with unaffected parents[67] and considered to be autosomal recessive; autosomal dominant inheritance also occurs.

of a multiple mononeuropathy from an asymmetrical inflammatory demyelinating polyradiculoneuropathy. This distinction is made the more difficult because re-perfusion following ischaemic lesions of nerves can induce focal inflammatory demyelination;[5, 6] this probably explains the focal conduction block, which sometimes occurs in multiple mononeuropathy due to vasculitis.[7]

In the absence of a predisposing cause, vasculitis must be investigated as a likely and treatable cause. In most cases vasculitis is associated with systemic symptoms of a classical vasculitic syndrome, such as polyarteritis nodosa, Churg-Strauss syndrome, or essential mixed cryoglobulinaemia,[8] or a connective tissue disease such as rheumatoid arthritis or Sjögren's syndrome, or systemic lupus erythematosus. However, peripheral neuropathy may be the presenting feature of vasculitic disorders.[7] Furthermore, there is an uncommon condition in which the vasculitis is confined in its clinical manifestations to the peripheral nerves.[9] If the symptoms of neuropathy are sufficient to merit treatment with steroids, the possibility of vasculitis warrants a nerve biopsy.

The painful condition of diabetic amyotrophy has an acute onset with pain in the thigh, and wasting and weakness of the quadriceps; it usually progresses to become bilateral with distal pain and weakness as well. Although at first considered to be due to a bland ischaemic process, there is now convincing histological evidence that the underlying pathology is vasculitic, and it results in a mixture of axonal degeneration and demyelination.[10] These findings raise the question whether diabetic amyotrophy would respond to treatment with immunotherapy. Steroids would exacerbate the difficulty of controlling the diabetes, which is not usually at fault in diabetic amyotrophy, but intravenous immunoglobulin is now being tested in a randomised trial.

CHRONIC DEMYELINATING NEUROPATHY

Hereditary motor and sensory neuropathy (HMSN)

The population prevalence of HMSN lies between 17 and 41 per 100,000 in European countries:[11] this condition is thus common enough to demand taking an extended family history in all individuals with chronic peripheral neuropathy. Two-thirds of patients with HMSN have a demyelinating neuropathy with an upper limb conduction velocity less than 39 m/s. Affected individuals may be asymptomatic. Clinical and neurophysiological examination of first-degree relatives may be needed to identify affected individuals and clinch the diagnosis.[12]

Demyelinating hereditary motor and sensory neuropathy is genetically heterogeneous (Table 2). Most of these have a duplication of the gene for PMP22, a 22kD trans-membrane protein on chromosome 17p11.2. Testing for this gene duplication is relatively simple and should now be included in the investigation of an undiagnosed demyelinating neuropathy. The next most common cause is a mutation in the gene encoding P0, the major peripheral nerve glycoprotein though this and other genetic causes are rare: molecular genetic diagnosis should therefore be best reserved for special cases where the information will be helpful in genetic counselling.

Chronic inflammatory demyelinating polyradiculoneuropathy

The diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) depends on the identification of an acquired demyelinating neuropathy, usually with a pattern of proximal as well distal weakness, reflecting marked involvement of spinal roots, and the absence of alternative causes.

The CSF protein concentration is almost always increased and its level is often taken as indicating the activity or the severity of the neuropathy, although little formal evidence exists to support this statement.[13] Research diagnostic criteria were laid down by a NINCDS committee and depend on criteria for the presence of demyelination: these are acknowledged as being too strict.[14]

Proof of the diagnosis may be achieved by detection of macrophage-associated demyelination in a nerve biopsy. However, the sural nerve is usually the peripheral nerve that is frequently biopsied and is relatively unaffected in this predominantly motor neuropathy in which the bulk of the pathology is proximal. The diagnosis usually rests on the neurophysiological findings and a favourable response to immunoregulatory treatment.

The minimum population prevalence of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) has recently been estimated at 1–2 per 100,000.[15, 16] About half of a large series of patients pursue a relapsing course and half a progressive one. A progressive phase of more

TABLE 3
Features of Multifocal Motor Neuropathy (MMN)[38]

Progressive - usually distal - upper limb weakness in individual nerve territories
Progression usually smooth, occasionally stepwise, rarely remitting
Male 80%
Onset usually 20–50, rarely 15–70 years
Fasciculation or cramp in 70% of patients
Reduced tendon reflexes patchily (in 50%) or diffusely (in 25%)
Multifocal partial conduction block in motor nerves
Normal sensory nerve conduction
CSF protein normal in 90% of patients
IgM antibodies to ganglioside GM1 present in 20 – 80% of patients

than eight weeks is taken as the cut-off point from subacute or acute inflammatory demyelinating polyradiculoneuropathy with which it shares similarities.

While CIDP is generally assumed to be an autoimmune disease, the supportive evidence stems merely from the inflammatory pathology in the nerves and apparent response to immunoregulatory treatment. No target antigen has been identified. In a cross-sectional population study 13% of 46 patients required aid to walk, 54% were still receiving treatment and 22% were receiving more than one treatment, one of the treatments usually being plasma exchange or intravenous immunoglobulin.[15] Since these treatments are expensive and have to be repeated frequently, sometimes every two weeks, these patients consume an exceptional amount of healthcare resource.

Treatment of CIDP can only be based to a limited extent on evidence from randomised trials and systematic reviews. The short-term benefits of oral steroids, suspected from clinical experience, were shown in the one and only randomised trial.[17] The long-term risks, most appropriate regimen, measures to avoid osteoporosis, and value of added immunosuppressive agents are currently based solely on clinical experience.

Historically, plasma exchange was the next immunomodulatory treatment to have its short-term efficacy proved by randomised trials,[18, 19] which led Dyck to recommend plasma exchange as the treatment of first choice.[13] Subsequent randomised trials demonstrated the short-term efficacy of intravenous immunoglobulin (IVIg).[20-22] In the published randomised trials only 70% of patients responded to treatment and about 20% responded to placebo. Consequently, each individual has to be looked at very carefully and the value of continued treatment may need careful individual assessment with n of 1 trials.[23] Patients need to be re-treated every 2-12 weeks.

The underlying relapsing and remitting nature of the disease further complicates the situation. There may be periods when the inflammatory process is active and treatment-responsive, and other times when it is inactive and the residual deficit is due to the underlying fixed neurological deficit resulting from axonal loss.[24] The short-term benefit of plasma exchange was similar to that of IVIg in a comparative controlled trial.[25] Because of convenience most centres and patients prefer IVIg. Whether it is better to start treatment with IVIg or steroids is still debatable, but the results of a randomised trial being conducted by the European Inflammatory Neuropathy Cause and Treatment Group should become available by September 2000.

The number of different immunomodulatory agents tried in CIDP is a sure sign that that there is no panacea. The most popular treatment is azathioprine. The single randomised trial failed to demonstrate any benefit from 2 mg/kg, admittedly a lower dose than that usually recommended.[26] We encountered a dramatic response to beta-interferon 1a in a patient with treatment-resistant CIDP.[27] Others have also reported favourable responses,[28,29,30] but we were unable to confirm a treatment response in a small randomised crossover trial.[31] Others have reported the successful treatment of some patients with cyclosporin A[32-34] or cyclophosphamide.[35,36] In the renal transplant field the purine synthesis inhibitor, mycophenolate mofetil, is supplanting azathioprine and would be worth testing in CIDP.[37] Determining which agents offer real benefit will require large multicentre trials because CIDP is heterogeneous, variable in outcome and uncommon. Establishing an international 'neuropathy trial centre' would facilitate this.

My own preference is to treat such patients with IVIg as the initial treatment and to replace this with steroids if it appears to be ineffective. If steroids are prescribed I measure bone density and start the patients on a biphosphonate to prevent osteoporosis since it is likely that prolonged high-dose steroids will be needed and bone loss is greatest during the first three months of steroid treatment. If steroids were ineffective then I would try plasma exchange. As a last resort I would try an immunosuppresive drug.

Multifocal motor neuropathy

One variant of CIDP, multifocal motor neuropathy (MMN), deserves special mention because in some centres it appears to be as common as CIDP and its response to treatment is different (Table 3).[38] The typical patient with MMN has a purely motor disorder characterised electrophysiologically by multiple partial conduction blocks in motor nerves which persist at the same sites but spare sensory nerve fibres in the same nerve segments.[39-41] Similar patients with sensory as well as motor deficits were described slightly earlier,[42] and the argument continues as to whether they represent the same condition. I consider that MMN represents one end of a spectrum which has typical sensory and motor CIDP in the middle and pure sensory CIDP[43] at its other end.

The main reason for recognising MMN as different from the usual case of CIDP is that steroids rarely benefit and may worsen MMN whereas they are usually beneficial in CIDP.[38] Several open studies, and now some small randomised trials, testify to the short-term benefit of IVIg.[44-50] Unfortunately IVIg usually only gives short-term benefit and resort is often had to immunosuppressive treatment. Oral cyclophosphamide is the drug which is most favoured in the literature. No randomised trials are available to support the use of cyclophosphamide or of any other agent.[38] A European group is preparing a trial of azathioprine.

Paraprotein-associated demyelinating neuropathy

About 10% of patients with otherwise undiagnosed neuropathy have a paraprotein[51] in their body fluids; in many cases an important and often causal connection can be demonstrated between the paraprotein and the underlying neuropathy (Table 4).

One of the commonest of these syndromes is the demyelinating neuropathy associated with IgM paraprotein

TABLE 4 Paraprotein-associated neuropathies
Multiple myeloma Radiculopathy Axonal neuropathy (rare)
Waldenstrom's macroglobulinaemia Demyelinating neuropathy
Monoclonal paraprotein of undetermined significance Demyelinating neuropathy with IgM paraprotein and anti-myelin associated glycoprotein antibodies Demyelinating neuropathy with IgG or IgA paraprotein and CIDP-like clinical picture
Solitary myeloma, osteosclerotic myeloma or Castleman's disease Demyelinating neuropathy (POEMS syndrome)[1]
Amyloidosis Amyloid neuropathy

[1] Polyneuropathy, organomegaly, endocrinopathy, monoclonal paraprotein and skin changes.

and antibodies to myelin-associated glycoprotein (MAG). It usually causes a very slowly progressive sensory-predominant neuropathy in elderly men, often with a postural tremor. Nerve conduction is characteristically markedly and, by contrast with CIDP, uniformly, slowed with some accentuation of slowing in the distal nerve segments.[52] Nerve biopsies show characteristic widely spaced myelin lamellae, with deposition of IgM paraprotein and complement components at the sites of the widening. The serum contains antibodies, which recognise carbohydrate epitopes on several myelin proteins, including myelin associated glycoprotein, and two peripheral nerve lipids, sulphated glucuronic acid paragloboside and sulphated glucuronic acid lactosaminosylparagloboside. There is experimental evidence that these antibodies will induce demyelination.[53-55]

Treatment of the underlying plasma cell dyscrasia will often be rewarded by improvement in the neuropathy, especially when the cause is a solitary myeloma or plasmacytoma. This in itself justifies a diligent search for a paraprotein in demyelinating neuropathy; this search should be repeated annually since the neuropathy may precede the detection of the paraprotein by several years. For those patients with a so-called 'benign' paraprotein, the neuropathy usually pursues a very indolent course: reassurance and supportive treatment may be the best treatment policy in these patients. It is advisable to monitor the blood count and paraprotein level at least every 12 months so as to detect conversion into a malignant plasma cell dyscrasia at an early stage. When treatment is deemed appropriate, chlorambucil has been most commonly used for IgM associated paraproteins. We have had success with fludarabine.[56]

There is anecdotal support for the use of plasma exchange, but in a randomised trial benefit was only obtained in patients with IgG or IgA paraproteins and not in those with IgM paraproteins.[57] Anecdotal support for the use of IVIg also exists. However, in a randomised trial in patients with IgM paraproteins, benefit was only found in 2 of 12 patients.[58] An European trial of IVIg in paraproteinaemic neuropathy is in progress. More trials are needed to demonstrate the value of different cytotoxic regimens in the management of paraproteinaemic demyelinating neuropathy.

CHRONIC AXONAL NEUROPATHY

Hereditary

Symptoms of hereditary neuropathy commonly appear in childhood but may be overlooked until middle or old age. History-taking should include enquiry about motor development, mobility in childhood and adolescence, and neurological illness in all first degree family members. Clinical examination should include an inspection for pes cavus.

It is not uncommon to diagnose hereditary motor and sensory neuropathy type 2 for the first time in middle-aged or elderly people because mild pes cavus and absent ankle reflexes had gone unnoticed over the years. Some hereditary neuropathies, such as familial amyloid polyneuropathy, do not present until their third or forth decade or even later. The familial amyloid polyneuropathies are due to mutations, most commonly in transthyretin but also other proteins. The clinical picture of transthyretin-related familial amyloid polyneuropathy is a characteristic painful sensory and autonomic neuropathy with later motor involvement. It is particularly common in Portuguese, Swedish, Japanese and Greeks. A transthyretin mutation can readily be detected in the blood when the diagnosis is suspected and thus avoids the need for nerve biopsy.

Axonal neuropathy may form part of many multi-system hereditary disorders in which the predominant impairments affect the central nervous system. Examples include the spinocerebellar atrophies, a-betalipoproteinaemia, Fabry's disease and ataxia telangiectasia. Their diagnoses should be evident from the clinical picture, genetic or metabolic diagnostic tests and will not be considered further.

Acquired

Most patients with chronic peripheral neuropathy have an acquired axonal polyneuropathy, which may be sensory or both sensory and motor. Acquired chronic purely motor neuropathies are rare. Many acquired axonal neuropathies begin with sensory symptoms and only develop motor symptoms at a later stage.

The list of possible causes would include most of a textbook of medicine. Investigation should follow any leads

TABLE 5 Initial investigation of acquired axonal neuropathy (Stage 1)	
Urine	Glucose, protein
Haematology	Full blood picture Erythrocyte sedimentation rate B_{12} Folate
Biochemistry	Random glucose Renal function tests Liver function tests TSH Serum protein electrophoresis
Immunology	Anti-nuclear factor
Other	Chest radiograph

TABLE 6 Further investigation of unexplained acquired axonal neuropathy	
Stage 2 Urine	Bence-Jones protein Porphobilinogen
Biochemistry	Glycosylated haemoglobin Fasting glucose/glucose tolerance test Serum angiotensin converting enzyme
Immunology	Anti-extractable nuclear antigen antibodies (anti-Ro, anti-La) Anti-neutrophil cytoplasmic antigen antibodies Anti-neuronal antibodies (Hu, Yo) Anti-ganglioside antibodies Anti-Myelin Associated Glycoprotein antibodies
Stage 3 Cerebrospinal fluid	Cells, protein, immunoglobulins
Tests for Sjögren's syndrome	Salivary flow rate Schirmer's test, Rose Bengal test
Search for carcinoma or lymphoma	Pelvic ultrasound, abdominal CT scan, chest CT scan or PET scan
Stage 4	Nerve biopsy

in the history and examination which suggest systemic disease, such as diabetes mellitus, alcohol abuse, connective tissue disease or carcinoma. The history should include symptoms not always included in a systemic review, dryness or grittiness of the eyes, dryness of the mouth, and a detailed drug history including the use of complementary medicines, drug abuse, and possible environmental toxin exposure. This will then be followed with a set of relatively inexpensive outpatient investigations, which are designed to identify any potentially relevant general medical condition, and the commonest or most important treatable causes of axonal neuropathy (Table 5). If the initial investigations do not reveal a cause, and the severity or rate of progression of the symptoms warrant it, then a more extensive set of investigations should be considered, aimed at excluding with certainty such common causes as diabetes mellitus, and detecting uncommon causes (Table 6).

Nerve biopsy

Nerve biopsy should only be considered as a last resort and only in a specialist centre which is in a position to perform electron microscopy and immunohistochemistry as well as provide a report on the basis of a large experience of peripheral nerve pathology.[59] Although the actual procedure of nerve biopsy under local anaesthesia is not uncomfortable, personal experience confirms that numbness and lancinating pain in the territory of the biopsied nerve do occur; some people find these symptoms very distressing. In our recent prospective study of 50 consecutive nerve biopsies, the procedure confirmed the diagnosis in 70%, affected management in 60%, and changed the diagnosis in 14%. The biopsy thought by the patients to have caused increased pain in 33%. Despite this 63% of patients were 'very' or 'fairly' pleased that they had had the biopsy.[60] Consequently in my practice, I reserve nerve biopsy for patients in whom the diagnosis cannot be achieved in any other way, who have dense pain loss in the territory of the nerve biopsied (usually the sural), and in whom the neuropathy is severe enough to demand treatment if relevant pathology is identified. The principal diagnosis which the biopsy might reveal is that of vasculitic neuropathy. If the neuropathy is so mild or so indolent in its progress that steroids would be inappropriate, then there is no point in doing the biopsy. Similarly, if the systemic clinical picture is typical of a vasculitic neuropathy (e.g. Churg-Strauss syndrome or temporal arteritis), then a nerve biopsy which does not show vasculitis may just have missed an affected vessel, would not alter management and is not worth doing.

Idiopathic axonal neuropathy

Even after extensive investigation, published case series have left 74%,[61] 24%[12] and 13% of patients[62] without a satisfactory explanation of their neuropathy. Notermans *et al.*[63] studied the clinical features of 75 such patients. More men (46) than women (29) were represented, a sex difference which is characteristic of autoimmune peripheral nerve disease; the average age was 56.5 years. My own experience suggests that this is an age-related disorder, becoming more frequent in old age, another feature shared with GBS and CIDP. Most patients had sensory and motor neuropathy, but some only experienced sensory symptoms. Sensory impairment and paraesthesiae are often the initial symptoms, and weakness only develops later. The symptoms gradually worsen. After five years all but two of 35 patients in the Notermans series with initial minor symptoms (modified Rankin score 1) had developed moderately disabling symptoms (modified Rankin score 2).

Treatment

Preventive and palliative treatments are important in all forms of neuropathy. Most patients have or are at risk of developing impairment of pain in the feet, and need to be advised to take appropriate care, as would a diabetic. In practice, foot care means wearing sensible shoes, inspecting the feet each night for abrasions or infections and consulting a podiatrist to help with treatment of callosities, nail care and provision of inserts to protect bony prominences; support stockings should be prescribed to control oedema. Weak ankles may need support with ankle boots, and foot-drop correction with ankle-foot orthoses. An orthotist needs to tailor these to the individual and review their fit to ensure that they do not themselves cause pressure sores; they are best prescribed in consultation with a physiotherapist who can train the patient to use them. Severe leg weakness may demand a stick or sticks, crutch or crutches or frame: again the physiotherapist is the key person in prescribing these aids, which may need to be adapted on account of weakness of the hands. Weak wrist extension can be helped by simple Futura wrist splints; more complex splints for weak fingers and hands are usually cumbersome and rarely used. Disabled patients require help from a multidisciplinary team including an occupational therapist who may help with the provision of special utensils and home adaptations.

The physician has a few drugs which help. The commonest autonomic manifestation of peripheral neuropathy is erectile impotence, which may be corrected

by sildenafil - the NHS will indeed pay for such medication if the neuropathy is due to diabetes mellitus. Restless legs syndrome is common in peripheral neuropathy, and randomised trials have demonstrated benefit from dopamine agonists, while anecdotal reports suggest benefit from L-dopa itself. Pain is unfortunately a common and sometimes the principal symptom of peripheral neuropathy of most types. Systematic reviews suggest benefit from tricyclic antidepressants, the anti-epileptic drugs carbamazepine and gabapentin, dextromethorphan, tramadol, L-dopa, and to a lesser extent from the sodium channel blocking drug, mexiletine.[64] Randomised trials indicate benefit from the weak opioid analgesic tramadol.[65]

Except for subclinical cases chronic peripheral neuropathy is always a nuisance to the patient, and can be quite distressing and disabling. Confident diagnosis, careful explanation and considerate treatment help the patient, and are worthwhile goals for the physician.

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