PAPER

Additional causes for distal sensory polyneuropathy in diabetic patients

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Objective: To assess the frequency of additional causes of distal sensory polyneuropathy (DSP) in patients with diabetes mellitus (DM).
Methods: Retrospective review of patients with DM and DSP during a 5 year period. A quantitative sensory score (QSS) was determined at the initial evaluation and extensive laboratory and EMG studies were performed. Patients with one or more potential causes for DSP were compared to those with DM alone.
Results: Fifty five patients (53%) had potential additional causes for DSP. These included: neurotoxic medications (seven), alcohol abuse (six), and B12 deficiency and renal disease (four each). The most common laboratory abnormalities were: abnormally low levels of vitamin B6 (11) or B1 (10), monoclonal gammopathy (eight), and hypertriglyceridaemia (eight). Twenty six (25%) subjects had more than one additional cause. Nine (9%) had three or more demyelinating features on EMG. There was a trend toward a lower QSS score ($p=0.05$) and reduced mean amplitude of the sensory potentials in those with additional causes. Those with additional causes more often had upper limb sensory symptoms ($p=0.001$) and sensory findings ($p=0.003$).
Conclusion: There was a high frequency of additional sources of DSP in patients with DM. These patients more often had sensory symptoms and findings in the hands. Tests that may be useful in the evaluation of DSP in diabetic patients include measures of vitamins B1, B6, B12, serum triglycerides, and immunofixation.

Distal sensory polyneuropathy (DSP) is probably the most common type of neuropathy associated with diabetes mellitus (DM) and is characterised by symmetric, slowly progressive or static, toe and distal foot numbness, paraesthesias, with or without neuropathic pain, absent Achilles tendon reflexes, and little or no weakness.[1–4] One study found that 10% of diabetic patients with DSP had other possible causes of neuropathy,[3] and other investigators have found that one third of DM patients had a neuropathy unrelated to diabetes.[5] Some have suggested that extensive evaluation of patients with diabetes and DSP yields few additional causes.[1 6 7] We determined the frequency of potential alternative or additional causes of DSP after extensive clinical, laboratory, and electrodiagnostic evaluation in a homogeneous group of patients with DM.

METHODS

Patient selection

We reviewed clinical, laboratory, and electrophysiological data from 103 consecutive DM patients with DSP who were referred between 1999 and 2004 and met the following criteria. Diabetic patients were classified with DSP if they had: (i) established DM with fasting serum glucose >126 mg/dl or >200 mg/dl after a 2 h oral glucose tolerance test[8]; (ii) symptoms and findings consistent with a distal, symmetric, sensory predominant, polyneuropathy[3 4 9]; and (iii) duration of symptoms for 3 or more months with a static or slowly progressive course. Those with mild weakness of the toe extensors or flexors were included. Patients with MRC grade 4/5 or greater weakness of the legs, any hip or upper limb weakness, mononeuropathy or multiple mononeuropathies, lumbosacral plexopathy, radiculopathy, and prominent asymmetric or multifocal symptoms or findings were excluded.[4 10]

Clinical evaluation

Patients were systematically queried about: (i) the intensity, duration, distribution, and progression of neuropathic symptoms; (ii) medical history, including malignancy, kidney, liver, and bowel diseases, nutritional disorders, and connective tissue and infectious diseases; (iii) medications (including vitamin supplements) and toxin exposure; (iv) alcohol consumption; and (v) family history of other affected individuals.[1 2 5 11] Relatives were examined when possible.

At the initial evaluation a quantitative sensory score (QSS) was determined based upon sensory findings at the bedside, similar to prior studies.[12–14] Vibration, joint position, light touch, and pinprick sensation were graded in the hands and feet bilaterally, as follows: 4 points, normal sensation at the distal toe or fingertip; 3 points, abnormal sensation extending to the metatarsophalangeal (MTP) or distal interphalangeal (DIP) joints; 2 points, abnormal to the ankle or metacarpophalangeal joint; 1 point, abnormal to the mid-calf or wrist crease; 0 points, abnormal above the mid-calf or wrist crease. Joint position was graded as 4 points for 6/6 correct trials at the MTP and DIP joints; 3 points, 4–5/6 correct; 2 points, 3/6 correct; 1 point, 1–2/6 correct; and 0 points, 0/6 correct. Romberg sign was graded as absent (8 points), equivocal (swaying but balance maintained for 5 s; 4 points), or present within 5 s (0 points). Tandem gait was graded as normal if the patient could walk six or more steps heel-to-toe (8 points); impaired if limited to three to five steps (4 points);

Abbreviations: ACE, angiotensin converting enzyme; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; anti-ENA, encapsulated nuclear antibody; DIP, distal interphalangeal; DM, diabetes mellitus; DSP, distal sensory polyneuropathy; ESR, erythrocyte sedimentation rate; MAG, myelin associated glycoprotein; MTP, metatarsophalangeal; QSS, quantitative sensory score; RDNS, Rochester Diabetic Neuropathy Study; RPR, rapid plasmin reagin

Table 1 Potential additional factors causing neuropathy in patients with DM and DSP: historical features

Factor	n
Exposure to neurotoxic medications (amiodarone, 3; colchicine, 2; platinum chemotherapy, 2)	7
Alcohol abuse	6
B12 deficiency (documented level <200 mg/dl prior to onset of neuropathic symptoms)	4
End stage renal disease	4
Inflammatory bowel disease (ulcerative colitis in 3, Crohn's disease in 1)	3
Rheumatoid arthritis	1
Total	25 (24%)

and absent if the patient took less than two steps before correction. The maximum possible QSS was 80 points. Upper limb sensory symptoms and findings were defined as involving the fingertips of both hands symmetrically, encompassing regions outside common areas of nerve entrapment.

Laboratory evaluation

The following laboratory tests were performed in all patients[15]: complete blood count, renal, liver and thyroid function tests, lipid screen, C-reactive protein, erythrocyte sedimentation rate (ESR), anti-nuclear antibody (ANA), encapsulated nuclear antibody (anti-ENA), anti-SSA and SSB antibodies, anti-neutrophil cytoplasmic antibody (ANCA), serum immunofixation, cryoglobulins, angiotensin converting enzyme (ACE), hepatitis B and C titres, Lyme titre, HIV titre, rapid plasmin reagin (RPR), and vitamin levels of B1 and B6 (assayed by high pressure liquid chromatography), B12, folate, and vitamin E. Additional laboratory studies performed included: urine immunofixation (99 patients), methylmalonic acid and homocysteine levels (89 patients), and anti-gliadin and tissue transglutaminase antibodies (79 patients).

Anti-neuronal antibody levels were measured in 93 patients and included myelin associated glycoprotein (MAG), SGPG, GD1A, GM2, sulfatide, GM1, asialo-GM1, B-tubulin, chondroitin sulfate, heparin sulfate, GALNAc-GD1a, and Hu.

Electrophysiological assessment

Electrophysiological studies were performed at the initial evaluation according to standardised methods previously described.[16] Motor conduction studies were performed using supramaximal percutaneous stimulation with surface electrode recordings. Sensory nerve action potentials were recorded following antidromic stimulation using ring (median and ulnar) or bar (sural) electrodes, and skin temperature was maintained at 32℃. The median, ulnar, peroneal, and tibial motor nerves and median, ulnar, radial, and sural sensory nerves were sampled in most patients. Partial conduction block was defined as a 40% or more baseline-to-peak amplitude reduction between proximal and distal sites of motor nerve stimulation.[17]

Statistical analysis

We compared those patients with one or more additional possible causes for DSP (multifactor-DSP) to those in whom DM was found to be the only cause (DM-DSP). Fisher's exact test (two sided) was used to compare categorical responses and Wilcoxon matched sign rank test was used to compare non-parametric ordinal and continuous variables. To assess for possible referral bias, we also determined the frequency of patients who were referred from our primary care physician network (primary referrals) and those initially evaluated by a local neurologist and sent for tertiary consultation (tertiary referrals). Because of multiple comparisons, a p value of $\leqslant 0.01$ was considered significant.

Table 2 Additional risk factors for neuropathy in patients with DM and DSP: laboratory evaluation

Abnormal laboratory value	n
Low serum B1 level (nl: 9–44 nmol/l)	10
Low serum B6 level (nl: 5–50 μg/l)	11
Serum immunofixation with monoclonal protein detected	8
Elevated methylmalonic acid level (>0.40 μmol/l)	8
Elevated homocysteine level (>13 μmol/l) (and normal methylmalonic acid level)	7
Hypertriglyceridaemia (>500 mg/dl)	8
ANA >1:160	7
Elevated C-reactive protein (>1.6 mg/dl)	7
ESR >60 mm/h	6
Abnormal renal function studies (creatinine >2.0 mg/dl)	4
Elevated ACE level (>60 U/l)	4
RF >1:160	4
Elevated anti-IgG gliadin antibody (>50 EU)	3*
Elevated anti-MAG antibody (>1:6400)	3†
Elevated anti-DNA antibodies (>31 IU)	2‡
Elevated B6 level (>125 μg/l)	2
Low serum B12 level (<200 mg/dl)	2
Elevated anti-sulfatide antibody (>1:2500)	2¶
Elevated WBC level (>16×10^9/l)	2§
Positive serum ANCA level	1**

*One with elevated tissue transglutaminase at 75 EU, none had jejunal biopsy; †2 of 3 with M-spike; ‡both with normal ANA and no associated diagnosis; ¶1 with IgG M-spike; §both diagnosed with chronic lymphocytic leukaemia; **no associated diagnosis.
nl, normal value.

RESULTS

The cohort comprised 58 men and 45 women with an average age of 64 years (range: 26–92 years) and an average duration of diabetes of 10 years. Eight had type I diabetes. The mean glycosylated haemoglobin was 7.4%.

Fifty five patients (53%) with DSP had one or more additional potential causes of polyneuropathy; 29 had one other cause, 18 had two other causes, 4 had three, and 4 had four additional causes of DSP.

Comprehensive medical history identified additional putative causes of DSP in 25 patients (24%; table 1). Seven patients had chronic exposure to neurotoxic medications: amiodarone for over 3 years in three, daily colchicine ingestion for 22 years in one and 5 years in another, and treatment with platinum based chemotherapy in two patients who had prior breast cancer. All had established diabetes prior to the exposure, but neuropathic sensory symptoms began after platinum therapy in both breast cancer patients. Forty two patients received statin medications, but the dose and duration of treatment were not always recorded and therefore could not be included in the analysis. Alcohol abuse, B12 deficiency (one with ulcerative colitis), and end stage renal disease were also common (table 1). Four patients had inflammatory bowel disease and one had rheumatoid arthritis. None had a family history or clinical stigmata of an inherited neuropathy.

Laboratory abnormalities are provided in table 2. Salient findings included abnormally low serum levels of vitamin B6 (11 patients) and B1 (10 patients, none with a history of alcohol use; one with ulcerative colitis). Elevated methylmalonic acid levels were found in eight patients, all with normal

Table 3 Abnormal B vitamin levels and metabolites in patients with DSP and DM

Patient	Age/gender (years)	B1 level (nl: 9–44 nmol/l)	B6 level (nl: 5–50 μg/l)	B12 level (nl: >200 pg/ml)	MMA level (nl: >0.40 μg/l)	Homocysteine level (nl: 0–13 μmol/l)
LM	74/F	14	12	430	0.98*	ND
RF	81/F	71	128*	>2000	0.48	16*
MO	61/F	8*	10	557	0.27	9
TC	70/M	34	4*	374	0.22	15*
PR	61/M	9	3*	462	0.44*	12
TCC	73/M	3*	9	525	ND	ND
CS	62/F	39	2*	487	0.42*	9
NP	64/M	14	57	364	ND	ND
EB	54/F	7*	30	864	0.39	ND
JA	69/M	8*	19	453	0.36	14*
HK	73/M	12	4*	348	0.54*	9
DN	45/F	38	3*	546	0.15	7
CH	47/F	22	2*	602	ND	ND
CJS	45/F	9	3*	249	0.16	9
WB	78/M	<7*	7	313	ND	ND
PW	68/F	<7*	10	731	0.37	ND
JN	67/F	35	3*	642	0.18	17*
SP	26/F	7*	8	361	0.10	6
MS	72/F	7*	6	498	0.58*	17*
BB	75/M	14	4*	277	0.37	16*
LA	54/F	<7*	13	445	0.35	19*
GK	72/F	<7*	6	221	ND	ND
LC	62/M	25	4*	605	0.48*	ND
WL	66/M	47	17	167*	ND	ND
RS	68/M	39	170*	250	ND	ND
JC	73/F	10	27	671	0.59*	16*
EC	67/M	36	7	361	0.56*	9
CB	36/F	43	3*	109*	0.36	16*

MMA, methylmalonic acid; ND, not done; nl, normal value.
*Abnormal values.

B12 levels. Homocysteine levels were elevated in nine (all but two with normal methylmalonic acid levels; all with normal B12 levels). An alternative cause was considered present only if serum B12 deficiency was documented by a low level (four patients) or both methylmalonic acid and homocysteine levels were elevated when the serum B12 level was normal (two patients, one also had a monoclonal protein). Two had raised B6 levels twice the upper limit of normal (both were taking B6 supplements). Abnormal vitamin B levels are listed in table 3. Serum triglycerides were elevated above 500 mg/dl in eight patients.

A monoclonal protein was detected in eight (IgM in five, IgG in three), and none had a plasma cell dyscrasia after further evaluation. Two had elevated (>1:6400) anti-MAG antibodies, two had raised anti-GD1b antibodies, and one had an elevated anti-sulfatide antibody. One had an elevated anti-MAG antibody titre (1:16 000) and another, a raised anti-sulfatide titre (1:3000), both without a monoclonal protein; these findings were of questionable significance and neither were classified as multifactor-DSP. None had cryoglobulins.

Laboratory tests associated with systemic immune disorders were often abnormal but rarely led to a specific diagnosis (table 2). Tests for connective tissue diseases uncovered a specific diagnosis in only two cases (rheumatoid arthritis in one and Sjögren syndrome in another). Similarly, none had positive titres for HIV, hepatitis B and C infection, or Lyme disease.

In summary, laboratory testing detected additional recognised causes of DSP in 41 diabetic patients (vitamin B1/B6 deficiency, 21; monoclonal gammopathy, 8; hypertriglyceridaemia, 8; connective tissue disorder, 2; B6 excess, 2).

Electrodiagnostic studies showed low or absent sural potentials, normal or mildly reduced peroneal and tibial motor amplitudes, and mild slowing or normal conduction velocities in the majority of patients, consistent with a length dependent, sensory predominant, axonal polyneuropathy. However, nine of 98 (9%) patients had three or more demyelinating features suggestive of a chronic, acquired demyelinating polyneuropathy[16]; six had conduction block. Four of the nine with a demyelinating pattern also had a monoclonal gammopathy.

Comparison of multifactor-DSP to DM-DSP

The mean age, gender distribution, duration of diabetes and neuropathic symptoms, glycosylated haemoglobin levels, and the frequency of primary referrals, type I DM, and patients treated with insulin were similar between the groups (table 4). The frequency of sensory symptoms ($p = 0.001$) and sensory signs ($p = 0.003$) in the hands was substantially more common in the multifactor-DSP group. Weakness of the toe extensors was more common in the multifactor group but was not significant ($p = 0.04$). Similarly, there was a trend for a lower mean QSS score ($p = 0.05$) and reduced amplitude sensory potentials in the multifactor-DSP group (tables 4 and 5). The sural potential was absent more often in those with multifactor-DSP ($p = 0.01$; table 5). There was no relationship between a lower (worsening) QSS and increasing number of additional causes for DSP (Kruskal-Wallis test $p = 0.13$).

DISCUSSION

We found a surprisingly high frequency (55%) of additional causes of DSP in patients with DM. This is considerably higher than the 10% reported in patients from the Rochester Diabetic Neuropathy Study (RDNS),[3] and none of 60 diabetic patients from another study.[1] The higher frequency may be explained by differences in the evaluation; our patients had numerous laboratory studies that may not have been performed in other studies. In the RDNS, extensive laboratory studies were not standardised and were ordered at the discretion of the examiner.[3 18]

The most frequent contributing factors for DSP identified by history taking were related to neurotoxic medications and chronic alcohol use. Our experience suggests that some diabetic patients were taking medications that could be

Table 4 Patients with DSP and DM compared to those with DM and additional factors for neuropathy: clinical features

	DM as only cause for neuropathy (n = 48)		DM and another potential cause for neuropathy (n = 55)		
	Mean (SD)	Range	Mean (SD)	Range	p value
Demographic features					
Age (years)	66 (13)	33–92	63 (13)	26–81	0.38
Male gender	27/48		31/55		0.72
Duration of diabetes (years)	8.6 (8.7)	0.1–40	10.8 (8.9)	0.5–47	0.09
Duration of neuropathy symptoms (years)	3.3 (3.6)	0.15–20	3.7 (4.0)	0.17–20.0	0.86
Primary referral source	29/48		29/55		0.28
Type II DM	46/48		49/55		0.24
HbA1c level	7.2 (1.6)	4.6–12.9	7.7 (2.1)	5.1–14.2	0.32
Insulin therapy	10/48		15/55		0.50
Neuropathic symptoms					
Pain	28/48		41/55		0.10
Paraesthesias	32/48		33/55		0.54
Imbalance	25/48		28/55		0.68
Upper limb sensory symptoms	7/48		25/55		0.001*
Weakness	3/48		12/55		0.03
Progressive course	32/48		39/55		0.67
Examination findings					
Sensory score	63.2 (13.3)	22–78	57.0 (16.7)	14–78	0.05
Romberg present	13/48		20/55		0.40
Upper limb sensory loss	7/48		23/55		0.003*
Toe extensor weakness	4/48		14/55		0.04

*Significant p value.

discontinued or substituted for alternatives with less neurotoxicity. Similarly, counselling for alcoholism is warranted, as future abstinence might have a beneficial effect on neuropathic symptoms.[19] These observations highlight the importance of reviewing toxic exposures in diabetic patients evaluated for DSP.

Abnormal laboratory studies included greatly elevated triglyceride levels in 8% and low serum levels of vitamins B1 and B6 (in the absence of alcohol abuse) in approximately 10%. Hypertriglyceridaemia recently has been implicated as a cause of idiopathic axonal neuropathy, and, in rare cases, the neuropathy may improve after lowering triglyceride levels.[20 21] Indeed a recent study suggested that modification of lipid abnormalities may influence progression of diabetic neuropathy.[22] Vitamin B1 and B6 levels are not measured routinely in patients with neuropathy primarily because such deficiencies have been linked to readily identified conditions, notably alcoholism, malabsorption syndromes, or malnutrition.[19] However, others have documented low B1 and B6 levels in the absence of these conditions.[23–26] It is difficult to ascertain to what extent, if any, vitamin B1 or B6 deficiency contributed to DSP; however, the frequency of low vitamin levels suggests that vitamin B1 and B6 levels should be assessed in future studies of diabetic DSP.

Approximately 8% of our cohort had a monoclonal protein of undetermined significance detected by serum immunofixation. This frequency is higher than the 3% reported in the general population and similar to patients with idiopathic polyneuropathy.[27] Half had demyelinating features on EMG and anti-neuronal antibodies were found in five patients.

Table 5 Patients with DSP and DM compared to those with DM and additional risk factors for neuropathy: electrodiagnostic studies

Motor studies	n	DM as only cause for neuropathy (n = 48), mean (SD), range	n	DM and another potential cause for neuropathy (n = 55), mean (SD), range	p value
Median					
Amplitude (nl: >4 mV)	15	7.4 (2.5), 4.1–11.8	21	6.2 (4.0), 0.7–17.7	0.24
Conduction velocity (nl: >49 m/s)	15	49 (6), 38–61	21	47 (10), 33–68	0.47
Ulnar					
Amplitude (nl: >6 mV)	27	8.1 (2.1), 3.0–11.9	31	6.7 (3.0), 0.9–14.0	0.04
Conduction velocity (nl: >50 m/s)	27	52 (5), 37–62	31	49 (10), 32–68	0.17
Peroneal					
Amplitude (nl: >2 mV)	38	2.6 (2.1), 0–9.6	43	2.0 (2.6), 0–9.3	0.05
Conduction velocity (nl: >40 m/s)	34	38 (7), 21–49	30	39 (8), 22–64	0.98
Tibial					
Amplitude (nl: >4 mV)	44	4.5 (4.0), 0–15.3	50	4.1 (4.7), 0–19.2	0.23
Conduction velocity (nl: >40 m/s)	40	38 (6), 24–52	41	38 (6), 21–45	0.65
No. patients with conduction block		0/44		6/52	0.03
Distal leg denervation		13/42		26/50	0.06
Sensory nerve amplitude					
Median (nl: >15 μV)	16	8.0 (8.0), 0–24	23	7.9 (9.6), 0–32	0.76
Ulnar (nl: >10 μV)	25	10.0 (8.9), 0–33	32	6.0 (7.1), 0–24	0.03
Radial (nl: >20 μV)	21	15. 0 (9.9), 0–38	31	10.2 (8.0), 0–35	0.06
Sural (nl: >6 μV)	44	4.0 (5.4), 0–27	50	2.5 (4.8), 0–23	0.04
Absent sural sensory potential		19/44		34/50	0.01*

DM, diabetes mellitus; nl, normal value; SD, standard deviation.
*Significant p value.

Paraproteinaemic neuropathies have clinical features similar to DSP, especially early in the course. The detection of a monoclonal protein usually warrants further investigation for a plasma cell dyscrasia because these disorders may respond to immunotherapy.[27] Serum immunofixation should be obtained routinely in diabetic patients with DSP.

In contrast, routine laboratory evaluation for occult connective tissue disorders seldom yielded useful diagnostic information. Laboratory abnormalities were common but not specific and rarely led to an alternative diagnosis. Similarly, routine testing for HIV, hepatitis B and C infection, Lyme disease, and coeliac disease was unrewarding.

Several investigators have reported raised anti-neuronal antibodies, especially GM1, GD1b, GD1a, and GM3 in patients with diabetic neuropathy, but details of the clinical features and results of immunofixation were not reported.[28–30] Anti-neuronal antibodies *without* a monoclonal protein were detected in only two patients, and neither had demyelinating features on EMG. We concur with others and do not recommend routine anti-neuronal antibody testing in this population.[31]

We hypothesised that patients with multifactor-DSP would have a more severe sensory neuropathy compared to those with DM-DSP, and indeed there was a trend toward a lower QSS score, lower mean amplitudes of some of the sensory potentials, and more frequent toe extensor weakness in the multifactor-DSP that may have been more evident with a larger cohort. Only the sural sensory potential was absent significantly more often in the multifactor-DSP group. The lack of significant differences between the groups cannot be explained by any imbalance in the duration of DM, degree of sugar control, distribution of type I diabetics and those requiring insulin therapy, or the duration of neuropathic symptoms that would bias the analysis. We can only speculate that the deleterious effects of DM on the peripheral nerves supersedes any additional neuropathic risk factors. However, sensory symptoms and findings in the hands were more common in the multi-factor DSP group. The reasons for these findings are unknown but suggest that certain contributing factors may affect nerves in a non-length dependent manner (for example, B12 deficiency, paraproteinaemic demyelinating neuropathy). The presence of sensory symptoms or signs in the hands might alert clinicians to consider additional potential causes for DSP in diabetic patients.

Nerve conduction studies showed a distal, axonal loss pattern affecting predominantly sensory fibres in the majority of patients. However, nine of 98 patients (9%) had three or more demyelinating features, and 6% had conduction block. These findings are virtually identical to a previous study of diabetic polyneuropathy,[32] but lower compared to another study (17%).[33] This discrepancy may be related to patient selection. In the latter study patients were selected from electrodiagnostic records without considering the clinical phenotype.[33] Nonetheless, because some patients may have an immune demyelinating neuropathy detected only by electrodiagnostic evaluation,[33 34] electrodiagnostic studies remain an integral element of the evaluation of diabetic patients with DSP.

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REFERENCES

1 **Rosenberg NR**, Portegies P, de Visser M, *et al*. Diagnostic investigation of patients with chronic polyneuropathy: evaluation of a clinical guideline. *J Neurol Neurosurg Psychiatry* 2001;**71**:205–9.
2 **Johannsen L**, Smith T, Havsager AM, *et al*. Evaluation of patients with symptoms suggestive of chronic polyneuropathy. *J Clin Neuromusc Dis* 2000;**3**:47–52.
3 **Dyck PJ**, Kratz JL, Karnes JL, *et al*. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy and nephropathy in a population-based cohort. The Rochester Diabetic Neuropathy Study. *Neurology* 1993;**43**:817–24.
4 **England JD**, Gronseth GS, Franklin G, *et al*. Distal symmetric polyneuropathy: a definition for clinical research. *Neurology* 2005;**64**:199–207.
5 **Lozeron P**, Nahum L, Lacroix C, *et al*. Symptomatic diabetic and non-diabetic neuropathies in a series of 100 diabetic patients. *J Neurol* 2002;**249**:569–75.
6 **Straub RH**, Rokitzki L, Schumacher T, *et al*. Patients with type-II diabetes mellitus and neuropathy have no deficiency of vitamins A, E, beta-carotene, B1, B2, B6, B12 and folic acid. *Med Klin* 1993;**88**:453–7.
7 **Pourmand R**. Evaluating patients with suspected peripheral neuropathy: do the right thing, not everything. *Muscle Nerve* 2002;**26**:288–90.
8 Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;**20**:1183–97.
9 **Dyck PJ**. Detection, characterization, and staging of polyneuropathy: assessed in diabetics. *Muscle Nerve* 1988;**11**:21–32.
10 **Llewelyn JG**. The diabetic neuropathies: types, diagnosis and management. *J Neurol Neurosurg Psychiatry* 2003;**74**(suppl 2):ii15–19.
11 **Dyck PJ**, Dyck PJ, Grant IA, *et al*. Ten steps in characterizing and diagnosing patients with peripheral neuropathy. *Neurology* 1996;**47**:10–17.
12 **Simovic D**, Isner JM, Ropper AH, *et al*. Improvement in chronic ischemic neuropathy after intramuscular phVEGF165 gene transfer in patients with critical limb ischemia. *Arch Neurol* 2001;**58**:761–8.
13 **Notermans NC**, Wokke JHJ, Lokhorst HM, *et al*. Polyneuropathy associated with monoclonal gammopathy of undetermined significance. A prospective study of the prognostic value of clinical and laboratory values. *Brain* 1994;**117**:1385–93.
14 **Ponsford S**, Willison H, Veitch J, *et al*. Long-term clinical and neurophysiological follow-up of patients with peripheral neuropathy associated with benign monoclonal gammopathy. *Muscle Nerve* 2000;**23**:164–74.
15 **McLeod JG**. Investigation of peripheral neuropathy. *J Neurol Neurosurg Psychiatry* 1995;**58**:274–83.
16 **Albers JW**, Kelly JJ. Acquired inflammatory demyelinating polyneuropathies: clinical and electrodiagnostic features. *Muscle Nerve* 1989;**12**:435–51.
17 **Olney RK**. Consensus criteria for the diagnosis of partial conduction block. *Muscle Nerve* 1999;**22**(suppl 8):S225–9.
18 **Dyck PJ**, Kratz KM, Lehman KA, *et al*. The Rochester Diabetic Neuropathy Study: design, criteria for types of neuropathy, selection bias, and reproducibility of neuropathic tests. *Neurology* 1991;**41**:799–807.
19 **Windebank AJ**. Polyneuropathy due to nutritional deficiency and alcoholism. In: Dyck PJ, Thomas PK, Griffin JW, *et al*, eds. *Peripheral neuropathy*. Philadelphia: Saunders, 1993:1310–21.
20 **Hughes RA**, Umapathi T, Gray IA, *et al*. A controlled investigation of the cause of chronic idiopathic axonal polyneuropathy. *Brain* 2004;**127**:1723–30.
21 **McManis PG**, Windebank AJ, Kiziltan M. Neuropathy associated with hyperlipidemia. *Neurology* 1994;**44**:2185–6.
22 **Tesfaye S**, Chaturvedi N, Eaton SE, *et al*. Vascular risk factors and diabetic neuropathy. *N Engl J Med* 2005;**352**:341–50.
23 **Zenuk C**, Healey J, Donnelly J, *et al*. Thiamine deficiency in congestive heart failure patients receiving long term furosemide therapy. *Can J Clin Pharmacol* 2003;**10**:184–8.
24 **Koike H**, Iijima M, Sugiura M, *et al*. Alcoholic neuropathy is clinicopathologically distinct from thiamine-deficiency neuropathy. *Ann Neurol* 2003;**54**(1):19–29.
25 **Miller JW**, Green R, Mungas DM, *et al*. Homocysteine, vitamin B6, and vascular disease in AD patients. *Neurology* 2002;**58**:1471–5.
26 **Marcucci R**, Betti I, Cecchi E, *et al*. Hyperhomocysteinemia and vitamin B6 deficiency: new risk markers for nonvalvular atrial fibrillation? *Am Heart J* 2004;**148**:456–61.
27 **Ropper AH**, Gorson KC. Neuropathies associated with paraproteinemia. *N Eng J Med* 1998;**338**:1601–7.
28 **Shigeta H**, Yamaguchi M, Nakano K, *et al*. Serum autoantibodies against sulfatide and phospholipid in NIDDM patients with diabetic neuropathy. *Diabetes Care* 1997;**20**:1896–9.
29 **Mata S**, Betti E, Masotti G, *et al*. Motor nerve damage is associated with anti-ganglioside antibodies in diabetes. *J Peripher Nerv Syst* 2004;**9**:138–43.
30 **Alaedini A**, Brannagan TH, Sander HW, *et al*. Ganglioside GM3 antibodies in diabetic neuropathy. *Neurology* 2004;**62**(suppl 5):A192.
31 **Wolfe GI**, El-Feky WH, Katz JS, *et al*. Antibody panels in idiopathic polyneuropathy and motor neuron disease. *Muscle Nerve* 1997;**20**:1275–83.
32 **Abu-Shakra S**, Cornblath DR, Avila OL, *et al*. Conduction block in diabetic neuropathy. *Muscle Nerve* 1991;**14**:858–62.
33 **Sharma KR**, Cross J, Farronay O, *et al*. Demyelinating neuropathy in diabetes mellitus. *Arch Neurol* 2002;**59**:758–65.
34 **Rotta FT**, Sussman AT, Bradley WG, *et al*. The spectrum of chronic inflammatory demyelinating polyneuropathy. *J Neurol Sci* 2000;**173**:129–39.