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ORIGINAL ARTICLE

Causes of chronic neuropathies: a single-center experience

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Abstract

Objectives Chronic neuropathies are a common cause of neurological disability worldwide. However, few reports have evaluated, in real life, the prevalence of the several conditions which can cause it.

Patients and methods The authors reviewed informatic database for outpatient office to confirm identification of chronic neuropathy in a 3-year interval period.

Results Among the 100 selected patients with chronic neuropathies, almost one fifth (19%) remained idiopathic. The most common etiologies were diabetes (17%), dysimmune neuropathies (38%), and vitamin B12 deficiency (9%). In the "dysimmune neuropathies" group, we distinguished various etiologies, including dysimmune neuropathies associated or not with systemic autoimmune diseases (7 and 3%, respectively), chronic inflammatory polyneuropathy (CIDP) (8%), multifocal motor neuropathy (MMN) (3%), paraproteinemic (8%), celiac disease-related (6%), and paraneoplastic (3%) neuropathies.

Conclusions In this report from a single neurological center, treatable causes of chronic neuropathies, such as dysimmune neuropathies, including CIDP, and celiac disease-associated neuropathy, were common. These findings suggest the utility of routine screening with blood testing for dysimmune neuropathy and celiac disease for all patients presenting with idiopathic chronic polyneuropathy in whom primary diagnostic testings had failed to identify an etiology for the disease.

Significance Our results indicate that patients with peripheral neuropathy could receive a benefit from being evaluated routinely in a specialized neurological center, as many of the conditions that were discovered represented potentially treatable causes of neuropathy.

Keywords Chronic neuropathies · Diabetes · CIDP · Celiac disease

Introduction

Chronic neuropathies have a high prevalence among the general population: disorders of the peripheral nervous system account for 1.5 million visits to neurologists annually, with an estimated prevalence of 2 to 7% in the entire population, which increases at a rate of more than 10% in the elderly population [1–4].

The diagnostic workup for the identification of the causes of neuropathies requires the use of different tests of increasing complexity. Usually, a first-level evaluation (fasting glucose test, vitamin B12 dosage, serum protein electrophoresis, thyroid screening, and glucose tolerance tests) is performed in primary neurological centers whilst patients are referred to specialized centers for further evaluations (blood testing for autoimmune or paraneoplastic conditions, genetic tests, skin or nerve biopsy, ultrasound, or magnetic resonance of peripheral nerves) [5]. Although data exist about the main epidemiological stratification of patients after a first diagnostic evaluation by primary care physicians [1–5], few reports have evaluated the epidemiology and classification of chronic neuropathies on the basis of secondary diagnostic tests in specialized centers [6, 7].

The aim of this study was to report data obtained by a single tertiary neurological center in the classification of different possible etiologies of chronic neuropathies and to compare them with available literature data.

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Patients and methods

We performed a retrospective study adopting a previously validated [8] neuropathy case-capture method that involves screening all new patient visits for International Classification of Diseases, Ninth Revision (ICD-9) neuropathy symptoms and diagnostic codes (250.60, 356.0-356.2, 356.4, 356.8, 356.9, 357.1-357.7, 357.82, 357.89, 357.9, 729.5 [pain in the limb], and 782.0 [disturbance of skin sensation]) using our informatic database of the outpatient office (*MedArchiver vers. 8.7.9.9*), to confirm that the patients met our peripheral neuropathy definition. Our study was approved by the local Ethics Committee. No informed consent was required. The case-capture method was used from January 1, 2013, through March 31, 2015. All patients were visited in the outward ambulatory for neuromuscular diseases. Information abstracted included demographic characteristics, clinical characteristics (time since symptom onset, family history of neuropathy, pain, weakness on examination, and the signs of an atypical presentation, including relapsing appearance; asymmetry; non-length dependent; motor predominant; and prominent autonomic features), and all diagnostic tests ordered during the visit.

We also performed a neurophysiological examination, which is part of the routine diagnostic workup for neuropathy. Motor nerve conduction studies (NCSs) of the ulnar, peroneal, and tibial nerves were performed using standard techniques [9–11]. All studies were performed in a warm room and skin temperature was > 32 °C; if needed, an infrared lamp was used to warm the studied segment. Distal motor latency was measured at the onset of the compound muscle action potential, and the low- and high-frequency filters were set at 20 Hz and 10 kHz. Sensory NCSs of sural and radial nerves were performed using standard techniques [11–14]. For the sural nerve antidromic stimulation was used, whilst the orthodromic method was performed for sensory NCSs of the upper limbs. Sensory nerve action potential amplitude and nerve conduction velocity were measured as previously described [15–18]. Neuropathy was defined as (a) sensory axonal with a reduction of sensory nerve action potential amplitude at least in the sural nerve bilaterally or in more sensory nerves, (b) motor axonal with a reduction of the compound muscle action potential amplitude at least in the tibial nerve bilaterally or in more motor nerves, and (c) sensory-motor axonal in the presence of axonal involvement of both motor and sensory nerves. Finally, demyelinating neuropathy was diagnosed according to electrophysiological criteria for definite chronic inflammatory demyelinating neuropathy (motor distal latency prolongation, reduction of motor conduction velocity, prolongation or absence of F-wave latency, conduction blocks or excessive temporal dispersion) [14].

All patients were screened with laboratory testing for primary evaluation of chronic neuropathy including fasting glucose, vitamin B12, serum protein electrophoresis, glucose tolerance test, and thyroid hormone levels [15]. Patients with electrophoresis findings suggestive of paraproteinemia underwent secondary analysis with serum immunofixation.

Moreover, we proposed to all patients with negative results on primary screening test, according to neurophysiological sub-set, secondary laboratory evaluations for the detection of autoantibodies against peripheral nervous system antigens, including anti-myelin and anti-axon antibodies; anti-MAG and anti-SGPG antibodies (IgM); anti-ganglioside GM1, GQ1b, and GD1b antibodies (IgM and IgG), onconeural antibodies (anti-Hu, Yo, Ri, Amphipysine, Cv2, MA1, MA2/TA, GAD-65 antibodies); celiac disease screening antibodies (anti-tissue transglutaminase (tTG), anti-endomysial antibodies and antigliadin IgA and IgG antibodies assays); and autoantibodies for systemic connective tissue diseases and vasculitis (anti DS-DNA, anti Sm, anti U1 RNP, anti-Ro/SSA, anti-La/SSB, anti-citrullinated peptides, p-ANCA, c-ANCA antibodies, cryoglobulinemia testing), and laboratory evaluation for infective causes of neuropathy (HBV, HCV, Lyme disease serology). Selected patients with negative results underwent CSF examination by lumbar puncture, with analysis for protein level and white cells' count. Selected patients with high clinical suspicion for paraneoplastic neuropathy performed cancer screening with high-resolution contrast-enhanced CT scans of the chest, abdomen, and pelvis. Patient that were lost to follow-up were excluded by the study.

Results

We identified 100 patients with chronic peripheral neuropathy based on electrophysiological studies and clinical examination (including distal symmetric polyneuropathy and neuropathies with a clinical asymmetrical pattern or proximal involvement). The age range was 25–90 (mean 69 ± 12.7) years. The gender distribution was 66% men and 34% women. The demographic and clinical features are described in Table 1.

The majority of our patients (around 60%) had not been evaluated by neurologists before referring to our center.

A specific etiology for the neuropathy was identified in 81 patients (81%). The frequencies of the different etiologies are described in Table 2.

The most common cause was the diabetes mellitus (17%, mean level of Hb1Ac; 6.9%, mean level of fasting plasma glucose; 135 mg/dL). Eleven (11%) of these fulfilled the American Diabetes Association criteria for the diagnosis of diabetes, and six (6%) had altered glucose metabolism (impaired glucose tolerance (IGT)) based on the same criteria [19]. Ten patients (10%) were under treatment with antidiabetic medications (oral hypoglycemic agents or insulin). Typical clinical features of these patients included not only distal painful symmetrical sensory polyneuropathy (82.3%),

Table 1 Demographic characteristics and clinical features of patients with distal polyneuropathy

Variable	No. (%) of 100 patients
Age mean (SD), years	68.5 (12.7)
Male sex	66 (66)
Smokers	18 (18)
Symmetric involvement	76 (76)
Motor deficit	66 (66)
Abnormal sensory examination	65 (65)
Neuropathic symptoms	51 (51)
Decreased reflexes	61 (61)
Gait instability	45 (45)
Axonal neuropathies	75 (75)
Demyelinating neuropathies	13 (13)
Distal symmetric polyneuropathy	76 (76)
Multineuropathy	24 (24)
Sensory neuronopathy	23 (23)
Sensory-motor axonal neuropathy	29 (29)
Motor axonal neuropathy	14 (14)
Disease duration mean (SD), years	4.9 (5.8)

but also a significantly high rate of patients with gait instability and positive Romberg test (58.8%); electrodiagnostic tests revealed more commonly a sensory axonal neuropathy (84.8%).

In our study, we obtained a meaningful number of dysimmune neuropathies, with results similar to the report by Hanewinckel et al. [2]. We have further sub-categorized the group of "dysimmune neuropathies" allowing for a comprehensive inclusion of all the kind of neuropathies that share a common pathophysiological dysimmune trigger that has included CIDP (8%), dysimmune neuropathies other than CIDP, associated or not with systemic autoimmune diseases (7% and 3%, respectively), paraproteinemia-related neuropathy (8%), celiac disease-related neuropathy (6%), multifocal motor neuropathy (MMN) (3%), and paraneoplastic neuropathy (Table 2).

Eight patients (8%) were found to have chronic inflammatory demyelinating neuropathy (CIDP). The diagnosis was based on clinical features, typical nerve conduction study parameters, cerebrospinal fluid (CSF) protein assessment, and exclusion of other causes [14, 17]. In the CIDP group, two patients showed the typical presentation consisting of proximal and distal symmetrical motor weakness whilst the other five patients presented asymmetrical distal and proximal motor weakness: a variant of CIDP known as multifocal acquired demyelinating sensory-motor neuropathy (MADSAM) or Lewis-Sumner syndrome [18, 20]. In addition to motor weakness, neurological examination revealed sensory deficits and ataxia in three patients and decreased deep tendon reflexes in five patients. One patient presented high titers (> 1:100) anti-GQ1b antibodies; on neurological examination, this patient presented cranial nerve involvement (dysarthria) and large fiber sensory neuropathy with gait instability and ataxia (a clinical scenario compatible with a diagnosis of chronic ataxic neuropathy with anti-disialosyl antibodies, CANOMAD [21]).

Ten patients presented dysimmune neuropathies other than CIDP associated or not with systemic autoimmune disease (7% and 3%, respectively). Among patients with systemic

Table 2 Causes of peripheral neuropathy after initial diagnostic testing

Cause of peripheral neuropathy	Number of patients	Percent
Idiopathic	19	19%
Diabetes mellitus	17	17%
Vitamin B12 deficiency	9	9%
Dysimmune neuropathies		
Associated or not with autoimmune disease (other than CIDP)	7 + 3 associated with autoimmune disease (1 vasculitis, 2 connective tissue diseases)	7% + 3%
CIDP	8	8%
Paraproteinemia-related neuropathy	8	8%
Celiac disease	6	6%
Multifocal motor neuropathy (MMN)	3	3%
Paraneoplastic neuropathy	3	3%
Hypothyroidism	6	6%
Toxic causes	4	4%
Genetic polyneuropathy	3	3%
Infective causes	2	2%
Alcohol	1	1%
Chronic kidney disease	1	1%
Total	100	

autoimmune diseases, connective tissue disease was considered the cause of dysimmune neuropathy in two patients (2%); one patient had rheumatoid arthritis whilst the second presented Sjögren disease. Finally, vasculitis was the origin of dysimmune neuropathy in one patient (1%). This patient was affected by non-length dependent sensory-motor axonal neuropathy, positivity for antineutrophil cytoplasmatic autoantibodies, and systemic vasculitis.

In the other seven patients (7%), a probable dysimmune neuropathy (other than CIDP) was diagnosed. This characterization was based either on the presence of specific autoantibodies associated with connective tissue diseases or vasculitides on patient's serum analysis or mononeuritis multiplex pattern on nerve conduction studies, association with systemic autoimmune diseases, or elevated protein level on CSF examination with normal white cell count (albuminocytologic dissociation) and clinical improvement after immune therapy [14, 16]. The majority of these patients (70%) improved after immune therapy. The remaining three patients showed absent or poor response to immune-modulating agents (intravenous glucocorticoids, intravenous immunoglobulin (IVIG)). In one patient (10% of this group), we discovered the occurrence of anti-gangliosides antibodies on serum analysis. The patient presented, as collateral finding, high titer (> 1:100) anti-GD1a antibodies and symmetrical distal sensory-motor neuropathy with axonal features on NCS and distal motor weakness. One patient presented low-titer autoantibodies against unspecified peripheral nervous system antigens on serum analysis. The clinical and neurophysiological features were consistent with a motor axonal neuropathy presenting with distal symmetrical motor weakness.

Celiac disease was diagnosed after the onset of peripheral neuropathy in six patients (6%) by means of celiac disease antibodies positivity on serum analysis (anti-tissue transglutaminase (tTG), anti-endomysial antibodies, and antigliadin IgA and IgG antibodies), presented in five patients out of six, and/or typical small bowel biopsy (which was diagnostic in four patients out of six) [22]. The majority of these patients presented axonal sensory-motor distal symmetric polyneuropathy. Neuropathic symptoms were observed in just one patient, whilst sensory ataxia and gait instability were seen in four patients. All of them (six patients, 100%) greatly improved with the introduction of a gluten-free diet.

Paraproteinemic component was identified on serum electrophoresis and immunofixation in eight patients (8%) and was considered the cause of the neuropathy in these groups.

Six patients (6%) presented a monoclonal gammopathy of undetermined significance (MGUS). Among them, three patients presented IgM monoclonal component on serum analysis (two patients IgM-kappa, one patient IgM-lambda) and two patients presented IgG-kappa monoclonal component whilst the last patient had IgA-kappa monoclonal component. The majority of these patients presented a sensory-motor distal polyneuropathy with symmetrical involvement and mixed electrophysiological features (axonal and demyelinating) on NCS. Anti-MAG antibodies were identified in one patient with IgM monoclonal component.

All patients with MGUS performed fat aspirate in order to exclude AL amyloidosis, and they all showed negative results for amyloid deposition.

Two patients had Waldenstrom macroglobulinemia. High titers anti-MAG and anti-GD2 antibodies were identified in one patient. This patient was treated with rituximab without clinical recovery. The other patient had a history of kidney and colon cancer which underwent surgical excision.

Three patients (3%) presented multifocal motor neuropathy (MMN). All of them had high titers (> 1:100) anti-GM1 antibodies on serum analysis and asymmetrical multifocal motor involvement without a sensory deficit. However, no conduction blocks were observed in these patients. Two of these patients also presented other high titers' anti-ganglioside antibodies on serum analysis (anti-GD1b).

Paraneoplastic neuropathy was found as the cause of neuropathy in three patients (3%). Two patients presented sensory axonal neuropathy which improved after surgical treatment of lung adenocarcinoma. The last patient was affected by non-Hodgkin lymphoma which caused sensory-motor axonal polyneuropathy and did not improve after chemotherapy for the neoplastic disorder.

Vitamin B12 deficit was observed as the cause of neuropathy in nine patients (9%, vitamin B12 levels < 200 pg/ml in all patients); most of them (eight patients out of nine) improved after vitamin replacement. Typical electrophysiological findings were consistent with axonal large fiber sensory-motor symmetrical polyneuropathy.

In six patients (6%), hypothyroidism was found (TSH levels > 3.75 μUI/mL, fT4 levels < 9.8 pmol/L; fT3 levels < 4.29 pmol/L in all patients), and this was considered the cause of neuropathy. Most of them presented axonal sensory-motor polyneuropathy with symmetrical involvement and neuropathic pain symptoms with improvement after hormonal replacement therapy.

Toxic neuropathy was diagnosed in four patients (4%). One patient developed distal symmetrical sensory-motor neuropathy after treatment with vincristine for Hodgkin lymphoma. One patient presented asymmetrical demyelinating sensory-motor neuropathy after treatment with amiodarone. The last two patients had a history of professional-related toxic exposure. One patient developed symmetrical sensory distal axonal polyneuropathy after several years of exposure to an industrial solvent (flugene; 1,1,2-trichloro-1,2,2-trifluoroethane) [23]. The second patient worked as an anesthesiologist and developed sensory-motor axonal polyneuropathy years after professional exposure to volatile anesthesia (trichloroethylene, nitrous oxide, halogenated hydrocarbons) [24], no other possible explanation for peripheral neuropathy was discovered, and

a presumptive diagnosis of occupational-related neuropathy was made [25].

The cause of polyneuropathy was thought to be genetic in three patients (3%) because of family history and age of presentation although genetic testing was not performed. They both showed axonal sensory-motor neuropathy with prominent neuropathic pain symptoms.

Other causes of neuropathy were alcohol toxicity (1%), chronic kidney disease (1%), and infections (Lyme disease 1%, HBV infection 1%).

The etiology remained unknown in 19 patients (19%); this result was in agreement with other studies [2, 3, 7, 26, 27]. In the idiopathic group, the majority of patients (15 patients, 78.9%), presented an axonal neuropathy on electrodiagnostic studies, whilst four patients (21% of this group) presented mixed axonal and demyelinating features on NCS. The clinical features were consistent with distal symmetric polyneuropathy in all 19 patients (100%). An abnormal sensory examination was observed in nine patients (47.3%) whilst nine patients (47.3%) reported neuropathic symptoms (extremity pain and dysesthesia). Decreased reflexes were confirmed on neurological examination in nine patients (47.3%). Three patients (15.8%) presented gait instability and a positive Romberg test on physical examination.

Discussion

Chronic neuropathy is a common cause of neurological disability worldwide; however, few reports exist that testify the prevalence of the several conditions which can cause neuropathy in adult population after secondary diagnostic test in specialized neurological centers [6, 7]. Besides, most of those results were based on studies from the 1980s and 1990s [26, 27]. Since then, new clinical entities have been characterized and we have assisted to a remarkable boost in the arsenal of screening tests for patients with neuropathy.

Among our patients, we confirmed chronic idiopathic neuropathy in almost one fifth of patients presenting for evaluation of peripheral neuropathy (19%), with a similar rate to previous reports in the literature [2, 7, 26, 27].

Diabetic neuropathy is universally recognized as the most common cause of peripheral neuropathy and neuropathic pain worldwide, with a lifetime incidence of 45% in patients with type 2 diabetes mellitus and 55% for type 1 diabetes mellitus [29]. Our study showed a compatible result, and diabetic neuropathy was confirmed to be the most frequent cause of neuropathy in our group (17%).

We have observed a significative number of patient with dysimmune neuropathies, who were further sub-categorized according to different etiologies (Table 2).

Chronic inflammatory demyelinating neuropathy (CIDP) is the most common type of immune neuropathy [30]. No reliable biomarker exists by which to diagnose CIDP [30] whilst electrodiagnostic criteria, such as those proposed by the European Federation of Neurological Societies and the Peripheral Nerve Society, are valuable resources when diagnosing the disease [14]. Although the diagnostic tests used within these criteria are useful, they support rather than definitively confirm the diagnosis of CIDP [31]. Other dysimmune neuropathies include axonal polyneuropathy caused by vasculitis, paraproteinemias, other systemic diseases, and other dysimmune neuropathies associated with anti-ganglioside and anti-peripheral nerve antibodies; this group accounts for a significative portion of this case series.

The search for autoantibodies in CIDP and chronic dysimmune neuropathies has recently been boosted with the description of antibodies targeting the node of Ranvier in this subgroup of patients [32]. In our study, the investigation for anti-ganglioside and anti-peripheral nerve antigen detection helped to suggest the diagnosis in eight patients previously considered as affected by idiopathic chronic neuropathy.

Up to 23% of patients with established celiac disease have neurophysiologic evidence of a peripheral neuropathy [33]. Gluten neuropathy is defined as otherwise idiopathic neuropathy with typical small bowel biopsy findings or serologic evidence of gluten-related antibodies and clinical improvement after a gluten-free diet. The commonest types are symmetric sensorimotor axonal peripheral neuropathy and sensory ganglionopathy [34, 35]. Our study showed an interesting high rate of celiac disease-related neuropathies (6%), at a higher rate than in the report by Farhad et al. (1.4%) [7]. Other causes of neuropathy secondary to malabsorption (vitamin B12, B6, and B1 deficiency) were excluded in these patients. This high rate can be due to the systematic research for gluten-related antibodies in our group, especially in those presenting with suggestive clinical features (sensory ataxia or symmetric sensorimotor axonal peripheral neuropathy).

Paraproteinemia is a known cause of neuropathy [10, 36]. It was also a common cause of neuropathy in our patients. Serum protein electrophoresis was regularly performed in our group of patients as an essential component of the diagnostic workup, as MGUS is considered to be a pre-malignant lymphoplasmacytic proliferative disorder. Two patients either with IgM monoclonal gammopathy of undetermined significance and Wäldenstrom's macroglobulinemia had anti-MAG antibodies on serum analysis. The clinical syndrome associated with anti-MAG antibodies is the distal acquired demyelinating symmetrical (DADS) sensory-motor neuropathy, an entity distinct from classical CIDP [37]. We observed three patients who presented non-IgM MGUS associated polyneuropathy. In this subgroup of patients, we decided to ascribe a causative role to the monoclonal component on the basis of supportive clinical features (time to peak of the neuropathy > 2 years, chronic slowly progressive course without relapsing or remitting periods, demyelinating features on

NCSs) [36] and exclusion of other possible etiologic explanations, although the diagnosis remained presumptive since the clinical correlation of non-IgM MGUS and peripheral neuropathy is still controversial [38].

In our study, we identify three patients with paraneoplastic neuropathies. Paraneoplastic neurologic diseases are rare neuroimmunologic disorders that occur in patients with cancer [39]. Peripheral neuropathy represents one of the more common presentations [40]. Although these are rare diseases, clinical suspicion and appropriate diagnostic testing are extremely important because paraneoplastic syndrome can precede the identification of neoplasia. A definite diagnosis of a paraneoplastic neuropathy requires a distinct clinical presentation in the context of a well-characterized paraneoplastic autoantibody or contemporaneous diagnosis of cancer [41]. None of our patients showed paraneoplastic autoantibodies in serum analysis; however, all of them presented a simultaneous diagnosis of cancer, and the peripheral nerve symptomatology improved after cancer treatment. We showed a surprisingly high rate of paraneoplastic neuropathies in comparison to other reports [7]. This result is probably due to the regular evaluation for onconeural antibodies in patients with clinical suspicion for paraneoplastic disorder (constitutional symptoms or cancer risk factors) and suggestion for HR CT of the thorax, pelvis, and abdomen in this subgroup of patient, as paraneoplastic disorder usually appear prior to formal diagnosis of cancer and early recognition could have a dramatic effect on cancer prognosis.

Hypothyroidism and vitamin B12 deficit were also common causes of neuropathy in our study, with rates slightly inferior to other reports (6% for hypothyroidism and 9% for vitamin deficiency in our report versus 9% for hypothyroidism and 17% for vitamin deficiency in the Hanewinckel report [2]). This discrepancy could be due to the fact that these causes of neuropathy are more likely to be diagnosed by general practitioners and general neurologists, with lesser need for specialist neurological evaluation in a tertiary center for neuropathies.

We observed three patients with a suspected genetic cause of neuropathy. This rate is not as prevalent as in other reports described in the literature. The explanation could possibly be related to a diagnosis extrapolated by family history or skeletal leg abnormalities rather than confirmatory genetic testing in earlier studies [1–4]. The actual more diffuse use of screening genetic tests for hereditary neuropathy in pediatric tertiary referring centers may have allowed for a diagnosis to be made before the adult age. Moreover, since our center is more experienced in the diagnosis and management of acquired and dysimmune neuropathies, we could not exclude a selection bias towards the population of patients with genetic neuropathies.

We could not exclude the possibility of TTR amyloidosis-related neuropathy diagnosis among patients with chronic idiopathic axonal neuropathy since TTR-related neuropathy is an often under-recognized condition with a sneaky presentation, and it frequently shows unspecific clinical manifestations [28].

Other causes of neuropathy, although not common in our study, were toxic neuropathies and infective causes of neuropathy.

In this report from a single tertiary neurological center, potentially treatable causes of neuropathy, such as dysimmune neuropathy, including CIDP and celiac disease-associated neuropathy, and vitamin deficiencies were common. These findings could raise the possibility to suggest routine screening with blood testing for dysimmune neuropathy (anti-gangliosides antibodies) and celiac disease for all patients presenting with idiopathic chronic polyneuropathy in whom primary diagnostic testings had failed to identify an etiology for the disease, offering a chance of effective and safe therapeutical options for these patients.

Compliance with ethical standards

Ethical Publication statement We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest The authors declare that they have no conflict of interests.

Abbreviations **CD**, celiac disease; **CIDP**, chronic inflammatory demyelinating polyneuropathy; **CMAP**, compound muscle action potential; **CSF**, cerebrospinal fluid; **DML**, distal motor latency; **GBS**, Guillain-Barrè syndrome; **HR CT**, high-resolution computed tomography; **MCV**, motor conduction velocity; **MGUS**, monoclonal gammopathy of undetermined significance; **SCV**, sensory conduction velocity; **SNAP**, Sensory nerve action potential

References

1. McLeod JG, Tuck RR, Pollard JD, Cameron J, Walsh JC (1984) Chronic polyneuropathy of undetermined cause. J Neurol Neurosurg Psychiatry 47:530–535
2. Hanewinckel R, Drenthen J, van Oijen M, Hofman A, van Doorn PA, Ikram MA (2016) Prevalence of polyneuropathy in the general middle-aged and elderly population. Neurology 87:1892–1898
3. Pasnoor M, Nascimento OJM, Trivedi J, Wolfe GI, Nations S, Herbelin L, de Freitas MG, Quintanilha G, Khan S, Dimachkie M, Barohn R (2013) North America and South America (NA-SA) neuropathy project. Int J Neurosci 123:563–567
4. Hughes RA (1995) Epidemiology of peripheral neuropathy [editorial]. Curr Opin Neurol 8:335–338
5. Pasnoor M, Dimachkie MM, Barohn RJ (2013) Cryptogenic sensory polyneuropathy. Neurol Clin 31:463–476
6. Callaghan BC et al (2014) Role of neurologists and diagnostic tests on the management of distal symmetric polyneuropathy. JAMA Neurol 48104:1–7
7. Farhad K, Traub R, Ruzhansky KM, Brannagan TH (2016) Causes of neuropathy in patients referred as 'idiopathic neuropathy'. Muscle Nerve 53:856–861. https://doi.org/10.1002/mus.24969

8. Callaghan B, Kerber K, Longoria R, Feldman E, Lisabeth L (2012) Capturing cases of distal symmetric polyneuropathy in a community. Muscle Nerve 46:943–947
9. Kimura J (1989) Electrodiagnosis in disease of the nerve and muscle: principles and practice
10. Luigetti M, Padua L, Mazza S, Rossini PM, Sabatelli M, Lo Monaco M (2013) Clinical-neurophysiological correlations in a series of patients with IgM-related neuropathy. Clin Neurophysiol 124:1899–1903
11. Luigetti M, Sauchelli D, Primiano G, Cuccagna C, Bernardo D, Lo Monaco M, Servidei S (2016) Peripheral neuropathy is a common manifestation of mitochondrial diseases: a single-centre experience. Eur J Neurol 23:1020–1027
12. Merolli A, Luigetti M, Modoni A, Masciullo M, Lucia Mereu M, Lo Monaco M (2013) Persistence of abnormal electrophysiological findings after carpal tunnel release. J Reconstr Microsurg 29:511–516
13. Luigetti M, Quaranta D, Modoni A, Mereu ML, Lo Monaco M (2012) Nerve conduction studies of the sural nerve: normative data from a single-center experience. Clin Neurophysiol 123:1891–1892
14. Joint Task Force of the EFNS and the PNS (2010) European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripher. J Peripher Nerv Syst 15:1–9
15. England JD, Gronseth GS, Franklin G, Carter GT, Kinsella LJ, Cohen JA, Asbury AK, Szigeti K, Lupski JR, Latov N, Lewis RA, Low PA, Fisher MA, Herrmann DN, Howard JF Jr, Lauria G, Miller RG, Polydefkis M, Sumner AJ, American Academy of Neurology (2009) Practice parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review): report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and Am. Neurology 72:185–192
16. Karam C, Tramontozzi LA (2016) Rapid screening for inflammatory neuropathies by standardized clinical criteria. Neurol Clin Pract 6:384–388
17. Rajabally YA, Nicolas G, Piéret F, Bouche P, Van Den Bergh PYK (2009) Validity of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy: a multicentre European study. J Neurol Neurosurg Psychiatry 80:1364–1368
18. Lewis RA, Sumner AJ, Brown MJ, A A (1982) Multifocal demyelinating neuropathy with persistent conduction block. Neurology 32:958–964
19. American Diabetes Association (2012) Standards of medical care in diabetes—2012. Diabetes Care 35(suppl 1):S12
20. Saperstein DS, Katz JS, Amato AA, Barohn RJ (2001) Clinical spectrum of chronic acquired demyelinating polyneuropathies. Muscle Nerve 24:311–324
21. Willison HJ et al (2001) The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies. Brain 124:1968–1977
22. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA (2013) ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol 108:656–676
23. Raffi GB, Violante FS (1981) Is freon 113 neurotoxic? A case report. Int Arch Occup Environ Health 49:125–127
24. Sharp CW & Rosenberg NL (1992) Volatile Substances Subst Abus A Compr Textb 303–327
25. Kestenberg SH, Young ER (1988) Potential problems associated with occupational exposure to nitrous oxide. Dent Assoc 54:277–286
26. Barohn RJ (1998) Approach to peripheral neuropathy and neuronopathy. Semin Neurol 18:7–18
27. Dyck PJ, Oviatt KF, Lambert EH (1981) Intensive evaluation of feferred unclassdied neuropahes yields improved diagnosis. Ann Neurol 10:222–226
28. Luigetti M, Conte A, Del A, Giulia G (2013) TTR-related amyloid neuropathy: clinical, electrophysiological and pathological findings in 15 unrelated patients. Neurol Sci 34:1057–1063. https://doi.org/10.1007/s10072-012-1105-y
29. Zilliox L, Russell JW (2011) Treatment of diabetic sensory polyneuropathy. Curr Treat Options Neurol 13:143–159
30. Latov N (2014) Diagnosis and treatment of chronic acquired demyelinating polyneuropathies. Nat Rev Neurol 10:435–446
31. Brannagan TH (2011) Current diagnosis of CIDP: the need for biomarkers. J Peripher Nerv Syst 16:3–13
32. Querol L, Illa I (2015) Paranodal and other autoantibodies in chronic inflammatory neuropathies. Curr Opin Neurol 28:474–479
33. Luostarinen L, Himanen SL, Luostarinen M, Collin P, Pirttilä T (2003) Neuromuscular and sensory disturbances in patients with well treated coeliac disease. J Neurol Neurosurg Psychiatry 74:490–494
34. Hadjivassiliou M, Sanders DS, Grünewald RA, Woodroofe N, Boscolo S, Aeschlimann D (2010) Gluten sensitivity: from gut to brain. Lancet Neurol 9:318–330
35. Hadjivassiliou M, Sanders DS, Gru RA (2010) Sensory ganglionopathy due to gluten sensitivity. Neurology 75(11):1003–1008
36. Ramchandren S, Lewis RA (2009) Monoclonal gammopathy and neuropathy. Curr Opin Neurol 22:480–485
37. Katz JS, Saperstein DS, Gronseth G, Amato AA, Barohn RJ (2000) Distal acquired demyelinating symmetric (DADS) neuropathy. Neurology 54:615–620
38. Notermans NC, Franssen H, Eurelings M, Van Der Graaf Y, Wokke JHJ (2000) Diagnostic criteria for demyelinating polyneuropathy associated with monoclonal gammopathy. Muscle Nerve 23:73–79
39. Darnell RB, Posner JB (2003) Mechanisms of disease: paraneoplastic syndromes involving the nervous system. Nejm 349:1543–1554
40. Gundogdu B, Rosenfeld M. R. & Rudnicki SA (2013) Paraneoplastic neuromuscular disorders. Neuromuscul Disord Clin Pract 1501–1514. doi:https://doi.org/10.1007/978-1-4614-6567-6_75
41. Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, Honnorat J, Smitt PS, Vedeler Ch, Verschuuren JJ, Vincent A, Voltz R (2004) Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 75:1135–1140