Chronic idiopathic axonal polyneuropathy: a systematic review

Article *in* Journal of Neurology · March 2016

DOI: 10.1007/s00415-016-8082-7

5 authors, including:

Ptolemaios Georgios Sarrigiannis
Sheffield Teaching Hospitals NHS Foundatio…
37 PUBLICATIONS **188** CITATIONS
SEE PROFILE

Channa Hewamadduma
Sheffield Teaching Hospitals NHS Foundatio…
13 PUBLICATIONS **171** CITATIONS
SEE PROFILE

Marios Hadjivassiliou
The University of Sheffield
207 PUBLICATIONS **5,058** CITATIONS
SEE PROFILE

J Neurol
DOI 10.1007/s00415-016-8082-7

REVIEW

Chronic idiopathic axonal polyneuropathy: a systematic review

Panagiotis Zis[1,2] · Ptolemaios Georgios Sarrigiannis[1] · Dasappaiah Ganesh Rao[1] · Channa Hewamadduma[1] · Marios Hadjivassiliou[1,2]

Received: 2 February 2016 / Accepted: 25 February 2016

Abstract Chronic idiopathic axonal polyneuropathy (CIAP) is a term describing neuropathies with both sensory and motor involvement in a length dependant distribution where neurophysiology reveals axonal damage, neuropathy onset is insidious and shows slow or no progression of the disease over at least 6 months with no aetiology being identified despite appropriate investigations. This entity merits further consideration given how common it is, the absence of clarity regarding aetiopathogenesis, natural history and therapies. A systematic computer-based literature search was conducted on PubMed database. We used two Medical Subject Headings terms in title. Term A was "axonal", "cryptogenic", "idiopathic" or "unknown" and Term B was "neuropathy" or "polyneuropathy". This search strategy resulted in the identification of 658 articles. After eligibility assessment, 48 papers were used for this review. CIAP is usually diagnosed in the sixth decade of life and it is more prevalent in males (ratio 3:2). It is usually slowly progressive. Some data support a potential role of autoimmunity in CIAP and further larger prospective studies are required to address such potential link and any treatment implications. CIAP is a common type of polyneuropathy but the least studied. Increasing awareness and research into this entity may result in better understanding and in the development of treatment strategies.

Keywords Polyneuropathy · Idiopathic · CIAP · Axonal

✉ Panagiotis Zis
takiszis@gmail.com

[1] Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

[2] University of Sheffield, Sheffield, UK

Introduction

The term peripheral neuropathy refers to any disorder of the peripheral nervous system including single and multiple (asymmetric) mononeuropathy, and symmetrical involvement of many nerves (polyneuropathy) [1]. Further classification depends on a mixture of phenomenological, neurophysiological, pathological and aetiological parameters [1].

The temporal evolution of symptoms divides polyneuropathy into acute or chronic. Acute peripheral neuropathy, e.g., Guillain-Barré syndrome is rare but an important entity to recognise because whilst at times severe, it is treatable. Most peripheral neuropathies are chronic and usually develop over several months [2].

Based on neurophysiological assessments and pathological findings (e.g., nerve and skin biopsy), neuropathies can be broadly classified into small or large fiber neuropathies. Unmyelinated C and thinly myelinated Aδ fibers are considered small fibers whereas myelinated Aα and Aβ fibers are considered large fibers [3]. In small fiber neuropathy, somatic or autonomic fibers, or both, may be involved [4].

Large fiber neuropathy can be axonal, where axons are affected, most commonly in proportion to their length (length dependent polyneuropathy). Large fibre demyelinating neuropathy affects the myelin sheath around axons impairing the ability of the axons to speedily conduct electrical impulses resulting in slow or no conduction (conduction block); Neuronopathy also known as ganglionopathy is another large fibre neuropathy affecting the cell bodies of the sensory neurones located in the dorsal root ganglia. Finally in pure motor neuropathy there is involvement of only the lower motor neurones. Based on the distribution, peripheral neuropathies can be both

Published online: 09 March 2016

symmetrical and asymmetrical whereas sensory ganglionopathy is almost always asymmetrical at the onset [5].

Many aetiological factors have been implicated in the development of peripheral neuropathy. The type of neuropathy may offer some aetiological clues. The term chronic idiopathic axonal polyneuropathy (CIAP) refers to those symmetrical, length dependant peripheral neuropathies where neurophysiology reveals axonal damage involving large fibers, their their onset is insidious and show slow or no progression of the disease over at least 6 months [6] and no aetiology can be identified despite extensive and appropriate investigations. Figure 1 provides a proposed algorithm of the diagnostic approach needed when investigating a patient with axonal neuropathy.

The authors acknowledge the fact that the label of "idiopathic" depends on the expertise and extend of investigations performed in an attempt to achieve a diagnosis of the cause of neuropathy. Most workers in the field, however, accept that even in the hands of experts in a substantial proportion of patients with peripheral neuropathy no diagnosis can be made, hence the proposed terminology of CIAP. The aim of this work was to systematically review all the available studies on CIAP in an attempt to clarify current thinking of aetiopathological mechanisms and natural history that may prove useful for any clinician when faced with a patient with CIAP.

Methods

Literature search strategy

A systematic computer-based literature search was conducted on January 27, 2016 on PubMed database. For each individual search we used two Medical Subject Headings (MeSH) terms in title. Term A was "axonal",

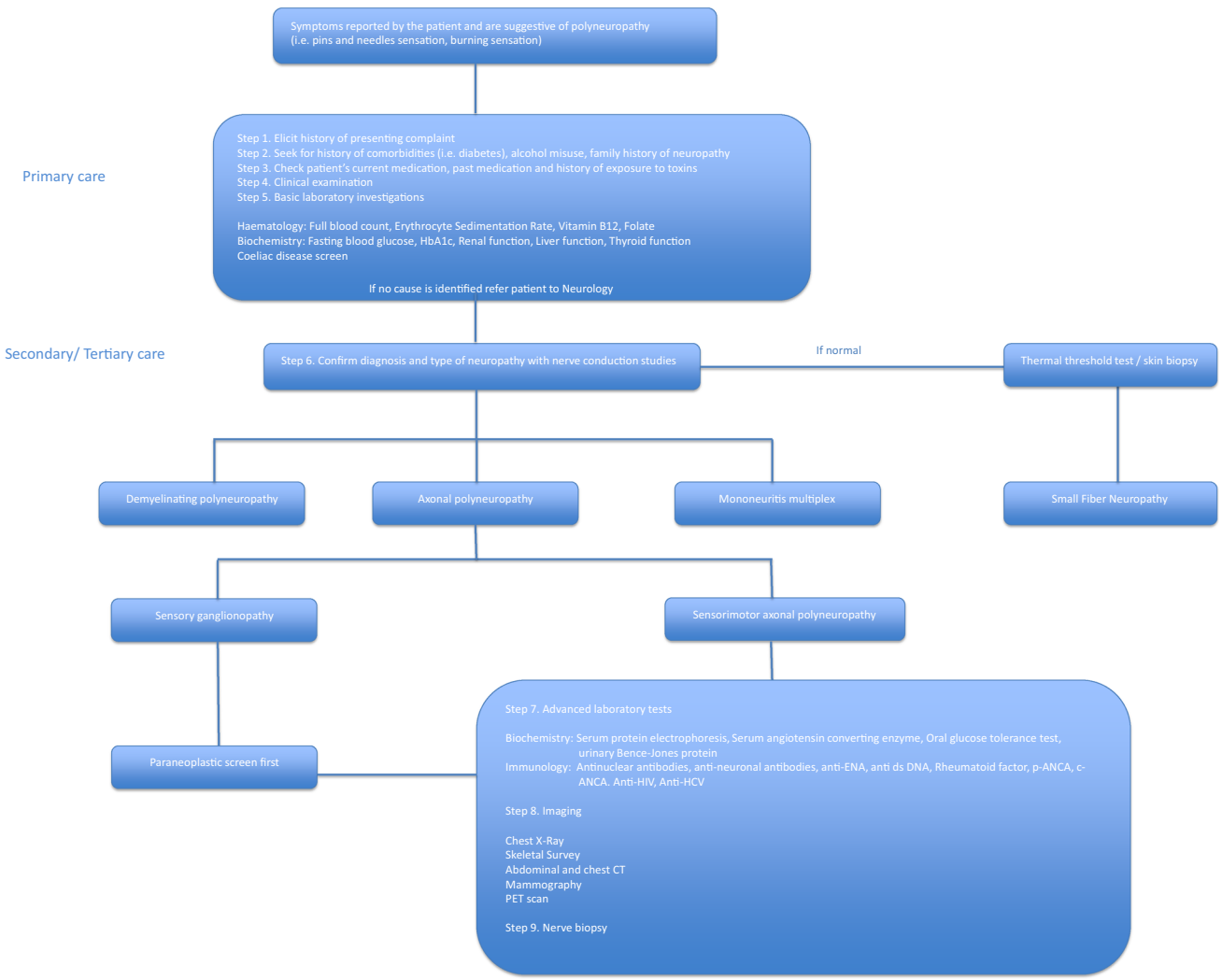

Fig. 1 A proposed algorithm of the diagnostic approach needed when investigating a patient with axonal neuropathy

"cryptogenic", "idiopathic" or "unknown" and Term B was "neuropathy" or "polyneuropathy". Limitations included species to be humans and language to be English. We also perused the reference lists of the papers since the drafting of this paper so as to try and include further CIAP papers not found through the above strategy.

Inclusion and exclusion criteria

To be included in the review, the articles had to meet the following criteria:

1. To study case series of patients with CIAP
2. To study human adult subjects
3. To provide clinical information

Exclusion criteria included:

1. Case reports
2. Book chapters, reviews, letters to the editor and editorials that did not provide new data
3. Papers relating to familial, genetic or congenital neuropathies

Results

Search results

This search strategy resulted in the identification of 658 articles. After the eligibility assessment, 615 articles were excluded. In total, 43 papers met the inclusion criteria. Scanning the reference lists five more papers were identified. In total, 48 papers were used for this review (Online supplement). Table 1 summarizes the characteristics of these papers. Figure 2 illustrates the study selection process.

Table 1 Characteristics of papers included in the review

Number of CIAP patients studied	
Total number of CIAP patients	3904
Range	3–381
Mean number of patients per study (SD)	81.3 (82.4)
Median	56
Demographics	
Male:female	3:2
Mean age	60.4 years
Year of publication	
Range	1985–2015
Number of publications per decade	
Until 1990	4
1991–2000	13
2001–2010	24
2011–2015	7

Clinical presentation

The onset of CIAP is usually in the sixth decade of life and it is more prevalent in males (male:female ratio 3:2) [7, 8].

Symptoms can be divided into sensory and motor. Sensory symptoms included tingling, pins and needles, numbness, tightness, burning, pain and sensory ataxia. Motor symptoms included muscle cramps, stiffness, weakness and wasting [6]. Sensory symptoms are more prominent in CIAP and occur earlier in the course of the disease [9]. Numbness is the most commonly reported presenting symptom [9, 10]. Early onset (before the age of 65 years) CIAP patients report more frequently numbness, tingling, pain, muscle cramps and stiffness compared to late onset CIAP patients [9].

Pain is the presenting sole symptom in up to 10 % of the patients [10]. The prevalence of pain varies across studies and ranges from 31 % [10] to 70 % [11]. In a study of pain in CIAP, Erdmann et al. reported that among CIAP patients with pain, 43 % had neuropathic, 40 % non-neuropathic and 17 % mixed pain [11].

CIAP is sensorimotor. In the early stages the cutaneous sensations are predominantly affected, and by the time the proprioceptive modalities are involved, motor weakness is almost always present [12]. It has been estimated that about 3 out of 5 patients with CIAP at diagnosis will have both sensory and motor symptoms, with 2 having only sensory symptoms [9, 13–15]. However patients with initially sensory idiopathic neuropathy will eventually develop motor involvement [14].

Epidemiology of CIAP

Robust epidemiological data on polyneuropathies of any cause are lacking. Very few studies have accurately assessed the prevalence of polyneuropathy in the general population. The current estimates are between 2.4 % [16] and 8.0 % [17]. In none of these studies was neurophysiology used to make the diagnosis.

No epidemiological study on the prevalence of CIAP exists as yet. Estimates of prevalence of CIAP amongst polyneuropathies range between 11 % [18] and 31 % [19]. The percentage of idiopathic polyneuropathies has declined with time [20] and the explanation for this is threefold. Firstly, with time and adequate follow up more causes of polyneuropathy—hereditary or acquired—have been recognised; secondly more diagnostic tests have become available; thirdly, investigations about possible causes of polyneuropathy may have been incomplete.

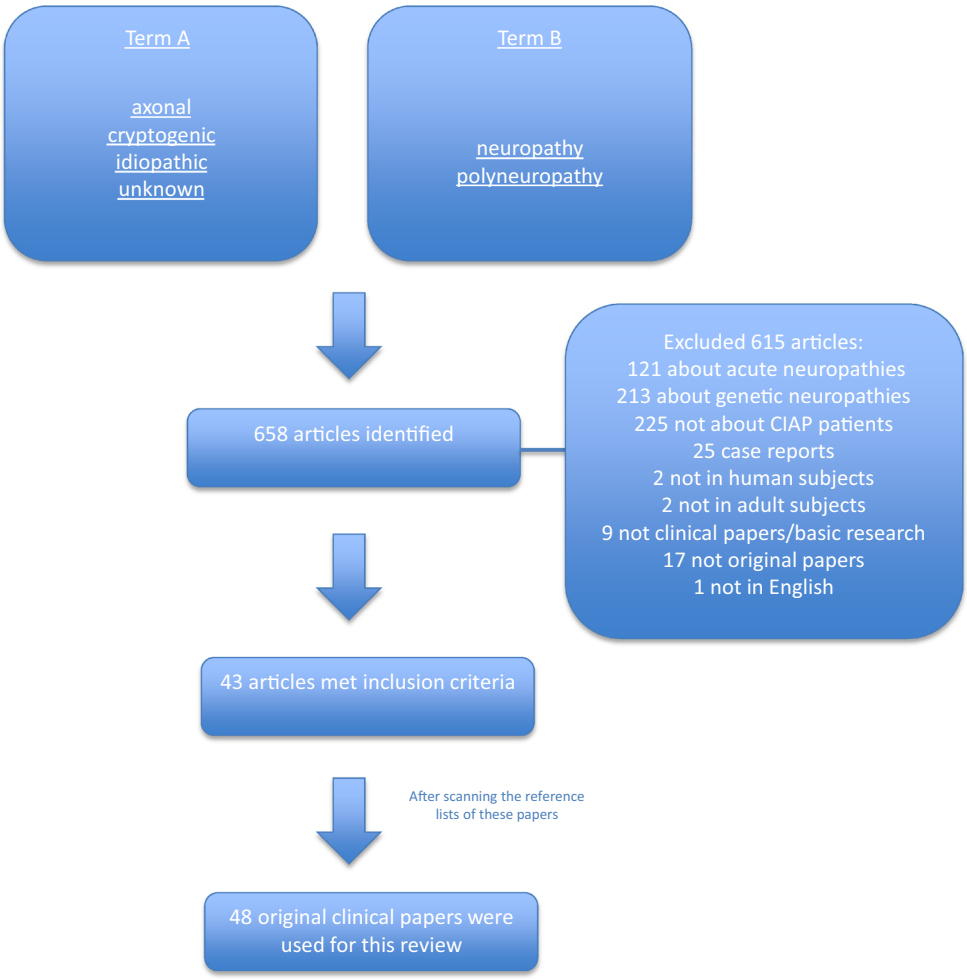

Fig. 2 PRISMA chart illustrating the study selection process

Long-term follow-up of CIAP patients [14, 21] or even just a careful review of the notes [22] have demonstrated that a cause may be identified in more than 50 % of the cases.

Natural history of CIAP

The natural history of CIAP remains obscure. Only few studies have attempted to describe the clinical and neurophysiological progression of CIAP. In a 5-year follow up study of 75 CIAP patients, Notermans et al. demonstrated that CIAP is slowly progressive and that the clinical course had two distinct patterns: in sensorimotor type the course was slowly progressive whereas in sensory neuropathy (however this is likely to be referring to cases of sensory ganglionopathy which for the purpose of this review is not included under CIAP) the clinical course often had a tendency to stabilize [14].

In their study, Sachedina and Toth followed up 606 patients with neuropathy, including a group 228 patients with CIAP [23] for 3 years. Clinically, the neuropathy was progressive in all groups. CIAP progression rate did not differ significantly compared to B12 or thiamine deficiency neuropathies. CIAP patients however, showed slower progression over time when compared to patients with diabetic neuropathy.

On neurophysiology, progression in cases of CIAP appeared to be slower than in cases of diabetic polyneuropathy.

CIAP vs. neuropathy of known aetiology

Axonal polyneuropathies may be caused by genetic defects, diabetes and other endocrinopathies, thiamine, vitamin B12 and other deficiencies, gluten sensitivity, liver failure, renal failure, cancer, toxin exposure and many prescribed drugs [2]. Following the diagnostic algorithm (see Fig. 1) is crucial in identifying potentially treatable causes. Detail and complete study of such patients will probably identify aetiological factors including exposure to several toxins [24, 25].

Although there is an obvious contradiction between the term idiopathic and the identification of aetiological risk factors, many reports concentrated on trying to identify such aetiological factors in the context of presumed CIAP.

One such example relates to impaired glucose tolerance ("pre-diabetes"). This is a stage in which not all of the parameters required to diagnose diabetes are found, but blood glucose is abnormally high. The relationship between pre-diabetes and neuropathy is a source of debate [26]. It is estimated that 23–62 % of the patients with idiopathic polyneuropathy may have abnormal glucose metabolism, as 13–44 % had impaired glucose tolerance and 3–24 % undiagnosed diabetes [27–32]. Patients with neuropathic pain in particular had a higher frequency of abnormal glucose metabolism [27, 33]. These studies highlighted that the 2-h oral glucose tolerance test had the highest diagnostic yield [19], it was more sensitive than other measures of glucose metabolism [19] and that it should be part of the routine diagnostic work-up of patients with CIAP. However, since 2010, the American Diabetes Association (ADA) standards of care for diabetes, based largely on the opinion of an international expert committee, added hemoglobin A1c (HbA1c) as a diagnostic criterion for diabetes (≥6.5 %) and prediabetes (5.7–6.4 %) [34].

Hypertriglyceridaemia has been proposed as an independent risk factor for CIAP [35]. In a cohort of 50 patients with CIAP Hughes et al. showed that after adjustment for body mass index as well as age and sex, patients with CIAP had higher triglyceride concentrations compared to controls and that this differences were even more significant when studying the group of patients with painful CIAP [35]. This finding was also confirmed in a study by Smith et al. involving 219 patients with CIAP [32].

Hypercholesterolaemia has also been proposed as risk factor for CIAP by some researchers [32] although others have not confirmed this [35]. This uncertainty is further complicated by the fact that some studies suggested that statins might increase the risk of polyneuropathy [36] whilst others did not [37].

Metabolic syndrome is characterized by obesity, dyslipidemia, hyperglycemia, and arterial hypertension [38]. In their study, Smith et al. estimated that 54 % of idiopathic neuropathy patients with normal glucose tolerance test and 86 % of idiopathic neuropathy patients with IGT had metabolic syndrome. They defined metabolic syndrome as having at least three of the following criteria; IGT or diabetes, systolic blood pressure >130 or diastolic >85 mmHg, obesity (BMI >30 kg/m^2), HDL <40 mg/dl for women and <50 mg/dl for men, and triglycerides >150 mg/dl [32]. Visser et al. studied a cohort of 249 CIAP patients and found that 55 % fulfilled the metabolic syndrome criteria compared with 34 % of controls. After adjusting for age and gender, multivariate analysis showed that arterial hypertension and abdominal obesity were significantly more prevalent in CIAP patients than in controls [39].

Some hypothesize that in the majority of patients with CIAP, impaired glucose tolerance and metabolic syndrome are the consequence rather than the cause of the neuropathy. Their argument was that in many CIAP patients symptoms such as pain precede the finding of IGT, and also that increased age, chronic pain, weakness, stress and depression which are common predispose to the development of the metabolic syndrome and IGT [40].

However, IGT and metabolic syndrome are strongly related to diabetes, a major cause of axonal polyneuropathy and thus, more than likely, IGT and metabolic syndrome may have a direct effect to axonal damage and predispose to the development of neuropathy. This fact could also explain the observation by Teunissen et al. showing that cardiovascular disease and CIAP often coexist, and although they concluded that cardiovascular disease may be a cofactor in the development of chronic axonal polyneuropathy it is more likely that they both share common risk factors [41].

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic plasma cell disorder occurring in more than 4 % of adults over 50 years of age. It can progress to symptomatic disease either through proliferation of the plasma cell clone, giving rise to multiple myeloma and other lymphoplasmacellular neoplasms, or through organ damage caused by monoclonal protein deposition [42]. Although, neuropathy associated with MGUS in the presence of IgM monoclone and Myelin Associated Glycoprotein (anti-MAG) is typically a predominantly distal demyelinating process, MGUS can also be present in CIAP patients [43]. MGUS is considered to be coincidental in most patients with axonal polyneuropathy [13]. However, some limited data derived from nerve biopsies have shown pathological differences between such patients and those with CIAP and no MGUS [44].

Role of autoimmunity

An underlying immunological process has been proposed after circulating T cell clones were found in some patients with CIAP [45].

In a prospective study of 57 patients with CIAP that were tested for reactivity against sulfated glucuronyl paragloboside (SGPG), myelin-associated glycoprotein (MAG), GM1, asialo-GM1, GD1b, Hu and sulfatide only 3 (5.3 %) were positive, one for SGPG, one for asialo-GM1 and one for Hu (without malignancy) [46].

The role of autoimmunity may be further supported by the fact that some pathological studies suggest that CIAP may be due to autoimmune vasculopathy [44, 47]. Moreover, other studies showed that some CIAP patients have responded to immunosuppressive treatment and plasma exchange.

The concept of a primary autoimmune neuropathy, i.e., peripheral nerves being the primary target of an autoimmune response has not been investigated but merits further consideration. It is plausible that a number of patients with CIAP may have an immune mediated neuropathy.

Pathological findings

No cellular infiltration or vasculitis was observed in nerve biopsies from a case series of CIAP published in 1993 by Sobue et al. [48].

Teunissen et al. investigated the endoneurial vessels in sural nerve biopsies of 18 patients with CIAP [49]. Basal lamina area thickness, endoneurial cell area and number of endothelial cell nuclei in CIAP were increased in comparison to hereditary neuropathy patients, with the basal lamina area thickness being in the same range as diabetic neuropathy. The structure of the basal lamina area in CIAP differed compared to diabetic neuropathy, with larger number of lamellae in the latter group, but with increased collagen in CIAP. In CIAP patients with peripheral vascular disease, basal lamina area thickness was increased and it was therefore suggested that ischemia may play a part in the development of the neuropathy [49].

In 2002, Kelkar et al., reviewed the findings from sural nerve biopsies from 11 patients with sensory-predominant, painful CIAP [47]. Four patients (36.4 %) had large perivascular mononuclear inflammatory infiltrates (>50 cells) when another four (36.4 %) had smaller infiltrates (10–20 cells). Similarly, Eurelings et al. compared the presence of T cells in sural nerves of 23 patients with CIAP and MGUS (12 IgM, 11 IgG), with 15 patients with CIAP without MGUS [44]. T cells were found in all the nerve biopsies. The sural nerves from seven patients (30 %) with CIAP and MGUS showed increased T cells with one biopsy showing evidence of previous necrosis of the vessel wall with intimal proliferation and perivascular infiltration. This along with the fact that some patients responded to steroid treatment suggested that vasculitis might play a role in the pathogenesis of some CIAP cases.

In contrast Vrancken et al., compared 12 CIAP patients with 10 patients with vasculitic neuropathy and with 10 patients with idiopathic neuropathy of acute onset [50]. Vasculitis-associated findings of ischemic injury or inflammation were found in 4/10 patients with progressive idiopathic axonal neuropathy of acute onset, in all patients with vasculitic neuropathy, but were absent in all patients with CIAP [50]. Indeed most patients with a vasculitic peripheral neuropathy are likely to have an asymmetrical onset (mononeuropathy multiplex) and usually follow a rapidly progressive course that would be atypical for CIAP.

Disability and quality of life

Although CIAP progress slowly it causes significant limitations in daily activities. Besides known impairments of muscle strength and sensation, CIAP patients also suffer from fatigue [11, 51]. This combination markedly interferes with their daily functioning [51].

Teunissen et al. study looking into quality of life in 57 CIAP patients used the RAND 36-item Health Survey questionnaire (RAND-36) [52]. RAND-36 assesses eight domains: physical and social functioning, role limitations due to physical and emotional problems, pain, mental health, vitality and general health perception. The authors compared the CIAP patients to 33 patients with hereditary neuropathy, with similar degree of impairment. They found that the two groups differed only in the area of "vitality," as the hereditary neuropathy patients were rated worse despite their younger age. In total, patients had worse scores than the reference population on all areas of the RAND-36, except for role limitations due to emotional problems. As expected, more affected patients rated lower in physical and emotional areas [52].

Several studies using other validated instruments, such as the SF-36 and the EQ-5D, have been used to compare the quality of life of CIAP patients with the general population and all agree that overall, patients with CIAP have a lower QOL compared to the general population [53, 54]. Although the differences were noted in all SF-36 areas in the study of 42 CIAP patients conducted by Rudolph et al. in 2009 [54], in a more recent study of 62 CIAP, Lindh et al. did not find any difference in the mental health scores between patients and controls [53].

Treatment

Intravenous immunoglobulin (IVIg), plasma exchange and immunosuppression with steroids or cyclophosphamide have been tried in very small series of patients with CIAP with reported response in some [44, 55–58] and no response in others [12]. Such reports are biased by the fact that only patients with rapid progression and severe neuropathy are likely to have been treated with such immunotherapies and such patients are unlikely to have CIAP. No randomised controlled trials have been performed in CIAP patients [59].

The management largely, therefore, remains symptomatic. Neuropathic pain in CIAP is usually better managed [11] using published guidelines [60]. An open-label study of lidocaine patch 5 % in 20 patients with painful CIAP showed that the patch was well tolerated and potentially effective [61].

Finally, the symptoms of the disease along with its impact on the activities of daily living may lead to the development of depression and therefore antidepressant treatment and/or psychotherapy may prove to be helpful. In a study, Schröder et al. showed that control perception (person's perception of ease or difficulty of performing behavior) contributes to activity limitations and, therefore, by increasing the patients' perception of control, via behavioral therapy, might enhance the patients'

performance of daily activities, even without changes in impairment [62].

Conclusion

To our knowledge, this is the first systematic review of CIAP. This review indicates the following key points:

1. Research in CIAP is limited but on the rise. This is exemplified in our data (Table 1), which shows that the number of papers on CIAP since 2001 has already almost doubled the number of papers on CIAP up until 2000, a period spanning over 15 years.
2. While initial studies on CIAP patients were uncontrolled and of cross sectional design, many are now controlled and longitudinal.
3. Large-scale prospective studies using patients with well-defined CIAP patients in whom all other causes of neuropathy have been eliminated over an adequate period of follow-up are needed, in order to better understand the natural history both on clinical and neurophysiological parameters.

Compliance with ethical standards

Conflicts of interest Nothing to disclose.

References

1. Martyn CN, Hughes RA (1997) Epidemiology of peripheral neuropathy. J Neurol Neurosurg Psychiatry 62(4):310–318
2. Hughes RA (2002) Peripheral neuropathy. BMJ (Clini Res ed) 324(7335):466–469
3. Sveen KA, Karime B, Jorum E, Mellgren SI, Fagerland MW, Monnier VM et al (2013) Small- and large-fiber neuropathy after 40 years of type 1 diabetes: associations with glycemic control and advanced protein glycation: the Oslo Study. Diabetes Care 36(11):3712–3717
4. Lacomis D (2002) Small-fiber neuropathy. Muscle Nerve 26(2):173–188
5. Marquez-Infante C, Murphy SM, Mathew L, Alsanousi A, Lunn MP, Brandner S et al (2013) Asymmetric sensory ganglionopathy: a case series. Muscle Nerve 48(1):145–150
6. Visser NA, Notermans NC, Degen LA, de Kruijk JR, van den Berg LH, Vrancken AF (2014) Chronic idiopathic axonal polyneuropathy and vitamin B6: a controlled population-based study. J Periph Nerv Syst JPNS 19(2):136–144
7. Lindh J, Tondel M, Osterberg A, Vrethem M (2005) Cryptogenic polyneuropathy: clinical and neurophysiological findings. J Periph Nerv Syst JPNS 10(1):31–37
8. Vrancken AF, Franssen H, Wokke JH, Teunissen LL, Notermans NC (2002) Chronic idiopathic axonal polyneuropathy and successful aging of the peripheral nervous system in elderly people. Arch Neurol 59(4):533–540
9. Teunissen LL, Notermans NC, Franssen H, van der Graaf Y, Oey PL, Linssen WH et al (1997) Differences between hereditary motor and sensory neuropathy type 2 and chronic idiopathic axonal neuropathy. A clinical and electrophysiological study. Brain J Neurol 120(Pt 6):955–962
10. Wolfe GI, Baker NS, Amato AA, Jackson CE, Nations SP, Saperstein DS et al (1999) Chronic cryptogenic sensory polyneuropathy: clinical and laboratory characteristics. Arch Neurol 56(5):540–547
11. Erdmann PG, van Genderen FR, Teunissen LL, Notermans NC, Lindeman E, van Wijck AJ et al (2010) Pain in patients with chronic idiopathic axonal polyneuropathy. Eur Neurol 64(1):58–64
12. Dalakas MC (1986) Chronic idiopathic ataxic neuropathy. Ann Neurol 19(6):545–554
13. Notermans NC, Wokke JH, van den Berg LH, van der Graaf Y, Franssen H, Teunissen LL et al (1996) Chronic idiopathic axonal polyneuropathy. Comparison of patients with and without monoclonal gammopathy. Brain J Neurol 119(Pt 2):421–427
14. Notermans NC, Wokke JH, van der Graaf Y, Franssen H, van Dijk GW, Jennekens FG (1994) Chronic idiopathic axonal polyneuropathy: a five year follow up. J Neurol Neurosurg Psychiatry 57(12):1525–1527
15. Notermans NC, Wokke JH, Franssen H, van der Graaf Y, Vermeulen M, van den Berg LH et al (1993) Chronic idiopathic polyneuropathy presenting in middle or old age: a clinical and electrophysiological study of 75 patients. J Neurol Neurosurg Psychiatry 56(10):1066–1071
16. Bharucha NE, Bharucha AE, Bharucha EP (1991) Prevalence of peripheral neuropathy in the Parsi community of Bombay. Neurology 41(8):1315–1317
17. Italian General Practitioner Study Group (IGPSG) (1995) Chronic symmetric symptomatic polyneuropathy in the elderly: a field screening investigation in two Italian regions. I. Prevalence and general characteristics of the sample. Neurology 45(10):1832–1836
18. Rosenberg NR, Vermeulen M (2004) Chronic idiopathic axonal polyneuropathy revisited. J Neurol 251(9):1128–1132
19. Smith AG, Singleton JR (2004) The diagnostic yield of a standardized approach to idiopathic sensory-predominant neuropathy. Arch Intern Med 164(9):1021–1025
20. Singer MA, Vernino SA, Wolfe GI (2012) Idiopathic neuropathy: new paradigms, new promise. J Periph Nerv Syst JPNS 17(Suppl 2):43–49
21. Vilming ST, Stave R (1987) Idiopathic polyneuropathy. A prospective study including gastrointestinal investigation. J Oslo City Hosp 37(11–12):129–134
22. Rajabally YA, Shah RS (2011) Dyslipidaemia in chronic acquired distal axonal polyneuropathy. J Neurol 258(8):1431–1436
23. Sachedina S, Toth C (2013) Progression in idiopathic, diabetic, paraproteinemic, alcoholic, and B12 deficiency neuropathy. J Periph Nerv Syst JPNS 18(3):247–255
24. Latov N, Kumar G, Vo ML, Chin RL, Carey BT, Langsdorf JA et al (2015) Elevated blood mercury levels in idiopathic axonal neuropathy. JAMA Neurol 72(4):474–475
25. Tondel M, Lindh J, Jonsson P, Vrethem M, Persson B (2006) Occupational determinants of cryptogenic polyneuropathy. Neuroepidemiology 26(4):187–194
26. Smith AG (2012) Impaired glucose tolerance and metabolic syndrome in idiopathic neuropathy. J Periph Nerv Syst JPNS 17(Suppl 2):15–21
27. Novella SP, Inzucchi SE, Goldstein JM (2001) The frequency of undiagnosed diabetes and impaired glucose tolerance in patients with idiopathic sensory neuropathy. Muscle Nerve 24(9):1229–1231
28. Singleton JR, Smith AG, Bromberg MB (2001) Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. Diabetes Care 24(8):1448–1453

29. Sumner CJ, Sheth S, Griffin JW, Cornblath DR, Polydefkis M (2003) The spectrum of neuropathy in diabetes and impaired glucose tolerance. Neurology 60(1):108–111
30. Hoffman-Snyder C, Smith BE, Ross MA, Hernandez J, Bosch EP (2006) Value of the oral glucose tolerance test in the evaluation of chronic idiopathic axonal polyneuropathy. Arch Neurol 63(8):1075–1079
31. Nebuchennykh M, Loseth S, Jorde R, Mellgren SI (2008) Idiopathic polyneuropathy and impaired glucose metabolism in a Norwegian patient series. Euro J Neurol Off J Euro Feder Neurol Soc 15(8):810–816
32. Smith AG, Rose K, Singleton JR (2008) Idiopathic neuropathy patients are at high risk for metabolic syndrome. J Neurol Sci 273(1–2):25–28
33. Singleton JR, Smith AG, Bromberg MB (2001) Painful sensory polyneuropathy associated with impaired glucose tolerance. Muscle Nerve 24(9):1225–1228
34. American Diabetes Association (2010) Standards of medical care in diabetes–2010. Diabetes Care 33(Suppl 1):S11–S61
35. Hughes RA, Umapathi T, Gray IA, Gregson NA, Noori M, Pannala AS et al (2004) A controlled investigation of the cause of chronic idiopathic axonal polyneuropathy. Brain J Neurol 127(Pt 8):1723–1730
36. Gaist D, Jeppesen U, Andersen M, Garcia Rodriguez LA, Hallas J, Sindrup SH (2002) Statins and risk of polyneuropathy: a case-control study. Neurology 58(9):1333–1337
37. Anderson JL, Muhlestein JB, Bair TL, Morris S, Weaver AN, Lappe DL et al (2005) Do statins increase the risk of idiopathic polyneuropathy? Am J Cardiol 95(9):1097–1099
38. Fitchett D (2015) The metabolic syndrome is an important concept in therapeutic decision-making. Canadian J Cardiol 31(5):596–600
39. Visser NA, Vrancken AF, van der Schouw YT, van den Berg LH, Notermans NC (2013) Chronic idiopathic axonal polyneuropathy is associated with the metabolic syndrome. Diabetes Care 36(4):817–822
40. Rezania K, Soliven B, Rezai KA, Roos RP (2011) Impaired glucose tolerance and metabolic syndrome in idiopathic polyneuropathy: the role of pain and depression. Med Hypotheses 76(4):538–542
41. Teunissen LL, Franssen H, Wokke JH, van der Graaf Y, Linssen WH, Banga JD et al (2002) Is cardiovascular disease a risk factor in the development of axonal polyneuropathy? J Neurol Neurosurg Psychiatry 72(5):590–595
42. Merlini G, Palladini G (2012) Differential diagnosis of monoclonal gammopathy of undetermined significance. Hematol Edu Prog Am Soc Hematol Am Soc Hematol Edu Prog 2012:595–603
43. Gorson KC, Ropper AH (1997) Axonal neuropathy associated with monoclonal gammopathy of undetermined significance. J Neurol Neurosurg Psychiatry 63(2):163–168
44. Eurelings M, van den Berg LH, Wokke JH, Franssen H, Vrancken AF, Notermans NC (2003) Increase of sural nerve T cells in progressive axonal polyneuropathy and monoclonal gammopathy. Neurology 61(5):707–709
45. Gherardi RK, Farcet JP, Creange A, Claudepierre P, Malapert D, Authier FJ et al (1998) Dominant T-cell clones of unknown significance in patients with idiopathic sensory neuropathies. Neurology 51(2):384–389
46. Wolfe GI, El-Feky WH, Katz JS, Bryan WW, Wians FH Jr, Barohn RJ (1997) Antibody panels in idiopathic polyneuropathy and motor neuron disease. Muscle Nerve 20(10):1275–1283
47. Kelkar P, McDermott WR, Parry GJ (2002) Sensory-predominant, painful, idiopathic neuropathy: inflammatory changes in sural nerves. Muscle Nerve 26(3):413–416
48. Sobue G, Yasuda T, Kachi T, Sakakibara T, Mitsuma T (1993) Chronic progressive sensory ataxic neuropathy: clinicopathological features of idiopathic and Sjogren's syndrome-associated cases. J Neurol 240(1):1–7
49. Teunissen LL, Notermans NC, Jansen GH, Banga JD, Veldman H, Wokke JH (2000) Thickness of endoneurial vessel basal lamina area in chronic idiopathic axonal polyneuropathy. Acta Neuropathol 100(4):445–450
50. Vrancken AF, Notermans NC, Jansen GH, Wokke JH, Said G (2004) Progressive idiopathic axonal neuropathy–a comparative clinical and histopathological study with vasculitic neuropathy. J Neurol 251(3):269–278
51. Erdmann PG, Teunissen LL, van Genderen FR, Notermans NC, Lindeman E, Helders PJ et al (2007) Functioning of patients with chronic idiopathic axonal polyneuropathy (CIAP). J Neurol 254(9):1204–1211
52. Teunissen LL, Eurelings M, Notermans NC, Hop JW, van Gijn J (2000) Quality of life in patients with axonal polyneuropathy. J Neurol 247(3):195–199
53. Lindh J, Tondel M, Persson B, Vrethem M (2011) Health-related quality of life in patients with cryptogenic polyneuropathy compared with the general population. Disabil Rehabil 33(7):617–623
54. Rudolph T, Larsen JP, Farbu E (2009) Is there a need for long-term follow-up in chronic idiopathic polyneuropathy? Acta Neurol Scand 120(5):347–352
55. Takeuchi H, Misu K, Hattori N, Nagamatsu M, Sobue G (2000) Immunoglobulin therapy for idiopathic chronic sensory ataxic neuropathy. Neurology 54(4):1008–1010
56. Deleplanque P, Pourrat O, Alcalay D, Robert R, Neau JP, Gil R (1990) Treatment of idiopathic chronic polyneuropathy with plasma exchange alone. Prog Clin Biol Res 337:293–296
57. Coyle PK, Schutzer SE, Sterman AB, Peress N, Miller F (1985) Humoral abnormalities in three patients with idiopathic chronic polyneuropathy. New York State J Med 85(6):248–250
58. Uncini A, Sabatelli M, Mignogna T, Lugaresi A, Liguori R, Montagna P (1996) Chronic progressive steroid responsive axonal polyneuropathy: a CIDP vaariant or a primary axonal disorder? Muscle Nerve 19(3):365–371
59. Vrancken AF, van Schaik IN, Hughes RA, Notermans NC (2004) Drug therapy for chronic idiopathic axonal polyneuropathy. Cochrane Database Syst Rev 2004(2):Cd003456
60. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS et al (2010) EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Euro J Neurol Off J Euro Feder Neurol Soc 17(9):1113-e88
61. Herrmann DN, Barbano RL, Hart-Gouleau S, Pennella-Vaughan J, Dworkin RH (2005) An open-label study of the lidocaine patch 5% in painful idiopathic sensory polyneuropathy. Pain Med (Malden, Mass) 6(5):379–384
62. Schroder C, Johnston M, Teunissen L, Notermans N, Helders P, van Meeteren N (2007) Perceived control is a concurrent predictor of activity limitations in patients with chronic idiopathic axonal polyneuropathy. Arch Phys Med Rehabil 88(1):63–69