A controlled investigation of the cause of chronic idiopathic axonal polyneuropathy

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Summary
To investigate the aetiology of chronic idiopathic axonal polyneuropathy (CIAP), 50 consecutive patients were compared with 50 control subjects from the same region. There were 22 patients with painful neuropathy and 28 without pain, 26 with sensory neuropathy and 24 with sensory and motor neuropathy. The typical picture was a gradually progressive sensory or sensory and motor neuropathy. It caused mild or sometimes moderate disability, and reduced the quality of life. There was no evidence that alcohol, venous insufficiency, arterial disease or antibodies to peripheral nerve antigens played a significant part. There was a possible history of peripheral neuropathy in the first or second-degree relatives of six patients and no controls (P = 0.01), and claw toes were present in 12 patients and four controls (P = 0.03). Thirty-two per cent of the patients and 14% of the controls had impaired glucose tolerance or fasting hyperglycaemia but, after adjusting for age and sex, the difference was not significant (P = 0.45), even in the painful neuropathy subgroup. The mean (SD) fasting insulin concentrations were significantly (P = 0.01) higher in the patients [75.9 (44.4) mmol/l] than the controls [47.3 (37.9) mmol/l], and the mean was higher still in the painful neuropathy subgroup [92.2 (37.1) mmol/l] (P < 0.0001). However, insulin resistance as assessed using the homeostasis model assessment formula was not significantly greater in the patients, even in those with pain, than the controls. After adjustment for body mass index as well as age and sex, there was no significant difference in the serum cholesterol concentrations, but there were significantly higher triglyceride concentrations in the patients [mean 1.90 (1.41) mmol/l] than the controls [mean 1.25 (0.79) mmol/l] (P = 0.02). In the patients with painful peripheral neuropathy, the mean triglyceride concentration was 2.37 (1.72), which was even more significantly greater compared with the controls (P = 0.003). In conclusion, CIAP is a heterogeneous condition. A logistic regression analysis identified environmental toxin exposure and hypertriglyceridaemia, but not glucose intolerance or alcohol overuse as significant risk factors that deserve further investigation as possible causes of CIAP.

Keywords: chronic idiopathic axonal polyneuropathy; diabetes mellitus; hypertriglyceridaemia; toxin

Abbreviations: BMI = body mass index; CIAP = chronic idiopathic axonal polyneuropathy; HOMA = homeostasis model assessment; IFG = impaired fasting glycaemia; Ig = immunoglobulin; IGT = impaired glucose tolerance; SF-36 = short form 36.


Introduction
Despite intensive investigation 10–40% of patients with peripheral neuropathy referred to specialist centres lack a causative diagnosis (Dyck et al., 1981; McLeod et al., 1984; Verghese et al., 2001). Most such patients have a slowly progressive axonal sensory and motor or purely sensory neuropathy (Verghese et al., 2001; Notermans et al., 1993, 1994; Jann et al., 2001; Vrancken et al., 2002). Fisher described four patients under the title ‘late-life chronic peripheral neuropathy of obscure nature’ (Fisher, 1982). McLeod and colleagues referred to ‘chronic polynoypathy of undetermined cause’ (McLeod et al., 1984). Notermans and colleagues (Notermans et al., 1994; Notermans and Wokke, 1996) coined the term chronic idiopathic axonal polyneuropathy (CIAP), which we have adopted. Although progression is slow and the initial
symptoms are mild, 30 out of 35 patients had progressed from mild to moderate disability after 5 years (Notermans et al., 1994). In another series, 40 patients showed little or no progression after 4 years (Jann et al., 2001). In a third series, 93 patients with a cryptogenic sensory neuropathy had a slowly progressive course (Wolfe et al., 1999). There are no precise estimates of the prevalence of CIAP. The prevalence of cryptogenic polyneuropathy in a Norwegian county in 1999 was 33 per 100,000, but this was restricted to hospital referred patients and may have included other entities than CIAP (Mygland and Monstad, 2001).

Theoretically, CIAP might be due to many different mechanisms of which impaired glucose metabolism has been much discussed. Attention has been drawn to a high prevalence of impaired glucose tolerance in patients with CIAP, especially those with pain (Russell and Feldman, 2001; Novella et al., 2001; Singleton et al., 2001; Sumner et al., 2003). However, glucose intolerance is common in the elderly population and there was a need for a controlled study to establish that impaired glucose tolerance (IGT) is a risk factor for CIAP (Russell and Feldman, 2001). Alternative hypotheses include abnormal oxidative stress (Halliwell, 1992), exposure to environmental toxins, autoimmune responses to axonal antigens, and genetic susceptibility to the development of late onset peripheral nerve axonal degeneration.

We hypothesized that CIAP is a heterogeneous group of conditions in which there are number of discrete entities in each of which different factors might play a part in pathogenesis. We classified patients with CIAP into clinical subgroups according to the presence or absence of pain, the type of sensory impairment and the presence of motor deficit. Taking into account these subgroups, we compared parameters of interest in the patients with a control group from the same geographical area. To test the hypotheses in question, we sought evidence of impaired glucose metabolism, insulin resistance, hyperlipidaemia, vitamin C or vitamin E deficiency, environmental toxin exposure, and family history of neuropathy.

Subjects and methods

Subjects
We invited for review all those patients who had been diagnosed in our peripheral neuropathy clinic—receiving patients largely from the south-east Thames region—between September 1997 and November 2002 as having a late onset symmetrical peripheral neuropathy of undetermined cause. Their previous investigation had included at least a clinical history and examination, urine analysis, blood count, sedimentation rate, renal, liver and thyroid profiles, random glucose, glycosylated haemoglobin, vitamin B12 and folate concentrations, serum protein electrophoresis, antinuclear factor and chest radiograph. In the absence of a practical solution to obtaining randomly selected controls from the same population as the patients, we invited the patients to bring with them a friend or non-blood relative (e.g. a spouse), who did not have a known peripheral neuropathy, diabetes mellitus or cancer. Since insufficient such subjects were available, we also sought volunteer control subjects from the staff and public attending our institution. The ethics committee of Guy’s Hospital approved the project and each participant was fully informed and gave signed consent.

Clinical data collection
One of two investigators (R.A.C.H. and T.U.) interviewed the patients and controls with a semi-structured questionnaire seeking information about symptoms of peripheral neuropathy, past medical history, family history including first and second degree relatives, personal habits and exposure to alcohol, cigarettes and environmental toxins. Alcohol consumption was quantified using the questionnaire devised for the 1996 Health Survey of England (Hedges and di Salvo, 1996). To measure impairment, we undertook a detailed neurological and general medical examination, scored strength in 14 muscle groups on each side with the Medical Research Council scale and assessed sensation including position sensation, light touch, vibration, pin prick and two point discrimination on both sides with standard clinical techniques scored according to our modification of the sensory sum score (Merkies et al., 2002). We measured warm, cold and vibration sensation on the non-dominant hand and foot with a thermal and vibratory sensory analyser, TSA-2001-VSA-3000 (Medoc Ltd., Ramat-Yishai, Israel) by the method of limits (Jamal et al., 1985). For temperature, a thermode was placed on the palm overlying the metacarpophalangeal joints of the index and middle fingers. For vibration, the palmar surface of the index finger and the plantar surface of the hallux were positioned on the vibrator. The subject was instructed and attempted a practice before each test. The mean of four tests for each sensation was recorded. To measure disability, we recorded the upper limb, lower limb and overall disability status score (Merkies et al., 2000). To assess quality of life, we used the short form 36 (SF-36) (Ware and Sherbourne, 1992; McHorney et al., 1993).

Neurophysiological testing
All patients had undergone neurophysiological testing before entry into the study and been shown to have neurophysiological abnormalities of sensory or sensory and motor axonal neuropathy without features of demyelination (Nicolas et al., 2002).

Blood tests
Venous blood samples were collected from the forearm with the patient seated and resting after an overnight fast. The patient drank Lucozade containing 75 g glucose and a second blood sample was taken 2 h later. The serum was separated and stored in aliquots at −70°C.

Vitamins C and E were measured by methods based on previously published techniques (Deutsch and Weeks, 1965; Pannala et al., 1998). Antibodies to gangliosides were measured by enzyme-linked immunosorbent assay (ELISA) and immuno-overlay (Gregson et al., 1997). Antibodies to nerve proteins were examined by western blotting with a homogenate obtained of fresh frozen sections of human cauda equina separated on a 10% acrylamide gel by sodium dodecyl sulphate–polyacrylamide gel electrophoresis (SDS–PAGE). Bound immunoglobulin (Ig) was detected with alkaline phosphatase conjugated mouse monoclonal anti-human IgG or IgM. Neurofilament antibodies to neurofilament 68 kDa light chain (CBL 62008; Cymbus Biotech, Flanders, NJ, USA) and 200 kDa heavy chain (CBL 62010; Cymbus Biotech), actin (Biogenesis, Poole, Dorset, UK) and tubulin (Sigma, Gillingham, Dorset, UK) were sought by ELISA (Eikelenboom et al., 2003).
Statistical analysis

An analysis to describe the patients with respect to their clinical characteristics was performed using means, proportions and frequency distributions. Patients and subgroups were then compared with the controls with respect to variables representing their current status and, potentially, the aetiology of the condition. For categorical variables, this was performed by comparing distributions using χ² tests and for measured variables by comparing means using t tests with appropriate test of the normal assumptions required. Where these were not satisfied due to skewed data distributions, logarithmic transformations were used. Finally, to assess and allow for confounding among the clinical characteristics in the group comparisons and to assess the relative importance of potential aetiological variables, logistic regression was used.

Results

Demographic features

Of the 400 patients who had attended the peripheral neuropathy clinic between September 1997 and November 2002, 50 patients entered the study. These patients and the same number of control subjects were recruited between February 2001 and November 2002. The mean age (SD) of the patient group, 66.9 (9.6) years, was significantly older (P = 0.0026) than the control group, 61.5 (7.9) years (see Table 1). Thirty-four out of 50 in the patient group were men, significantly more than in the control group in which only 19 out of 50 were men (P = 0.005). Consequently, all subsequent statistical comparisons of the two groups took age and sex into account.

Clinical features

There were 22 patients with painful neuropathy and 28 without pain, 26 with sensory neuropathy and 4 with sensory and motor neuropathy. The mean (SD) age of onset was 58.6 (10.7) years in all patients, 58.2 (10.8) years in patients without pain and 59.1 (10.8) years in patients with painful neuropathy. The onset had been gradual in 36 patients, sudden in 13 and one was not sure. In 12 patients, it had stabilized after a mean of 3.8 (2.6) years, but was still progressing in 38. In one patient, the disease had pursued a relapsing–remitting course responsive to steroids and azathioprine (Chroni et al., 1995). Pain was not significantly more common in those with clinically pure sensory neuropathy as opposed to sensory and motor neuropathy (14 out of 26 or 54% compared with 9 out of 24 or 38%; P = 0.4).

The pattern of neuropathy was consistently that of a distally predominant sensory or sensory and motor neuropathy, so that the impairment of cool, warm and vibration detection and disability were greater in the feet than the hands (Table 2). It caused significant impairment such that walking was significantly slower in the patients than the controls, and disability such that 17 of the patients had overall disability status scores >3. The arm disability (P < 0.05) and overall disability (P < 0.05) were both greater in the patients with painful neuropathy than in those without, but the difference in leg disability was not different between these groups. There was reduction in the perceived quality of life of the patients compared with population norms (Table 3).

After adjusting for age and sex, there was no significant difference between the patients and the controls in weight, height or body mass index (BMI) (Table 1). After similar adjustments, however, the patients with painful neuropathy were on average significantly heavier than the controls (P = 0.01) and had significantly greater body mass indices (P = 0.007), although they were not significantly different in height.

Of the 50 in each group, 12 patients and four control subjects had claw toes (P = 0.06) and nine patients and one control had high arched feet (P = 0.02). Eleven patients and nine control subjects had abnormal foot pulses. Thirteen patients and 17 control subjects had varicose veins, and four patients and three control subjects had venous pigmentation of their ankles.

Environmental toxin exposure

Alcohol use was not greater in the patients than the controls (P = 0.29). Seven patients and 14 controls had alcohol consumption falling into bands 4 or 5, defined respectively as cumulative weekly alcohol consumption of more than 21 and 35 units for males and 14 and 21 units for females, respectively, but this difference was not significant (P = 0.14). Each unit of alcohol is 8 g of ethanol, and is the amount contained in half a pint of ordinary beer or lager, or in a small glass of wine, or in a measure of spirits.

Thirty-four patients and only 25 control subjects had smoked, but after adjusting for age and sex, this difference was not significant (P = 0.64). Seventeen patients and only seven control subjects reported exposure to recognized potentially neurotoxic substances (patients were questioned specifically about insecticides, organic solvents and lead). Statistical

Table 1 Demographic features of patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patients with pain</th>
<th>Patients without pain</th>
<th>Controls</th>
<th>P (all patients versus controls)</th>
<th>P (patients with pain versus controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>50</td>
<td>22</td>
<td>28</td>
<td>50</td>
<td>0.003</td>
<td>0.012</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.9 (9.6)</td>
<td>67.3 (10.6)</td>
<td>66.6 (8.9)</td>
<td>61.5 (7.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>34/16</td>
<td>15/7</td>
<td>19/9</td>
<td>19/31</td>
<td>0.005</td>
<td>0.035</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.3 (13.1)</td>
<td>84.4 (11.4)</td>
<td>77.1 (13.7)</td>
<td>72.1 (11.6)</td>
<td>0.129</td>
<td>0.006</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.1 (9.4)</td>
<td>171.4 (7.6)</td>
<td>172.6 (10.7)</td>
<td>167.2 (8.7)</td>
<td>0.380</td>
<td>0.73</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1 (3.4)</td>
<td>28.7 (2.9)</td>
<td>25.8 (3.3)</td>
<td>25.7 (3.4)</td>
<td>0.313</td>
<td>0.007</td>
</tr>
</tbody>
</table>

M = male; F = female.
comparison of these proportions taking into account age and sex was not significant \( (P = 0.34) \), but exposure to environmental toxins did emerge as significant in a logistic regression analysis (see below).

**Family history**

Six patients and none of the controls reported a history of abnormalities in the feet in first-degree relatives that might have been due to peripheral neuropathy \( (P = 0.01) \). It was not possible to confirm or refute this history in any of these cases because the relative had died or was inaccessible. Of the nine patients with pes cavus, three had a possible family history compared with three of the remainder without pes cavus, but this apparent association was not quite significant \( (P = 0.07) \). Among the 12 patients with claw toes, three had a possible family history compared with three of the 38 patients without claw toes; this does not reach significance \( (P = 0.14) \).

**Glucose tolerance and insulin resistance**

Glycosylated haemoglobin, fasting glucose and 2-h glucose concentrations were not significantly different between the whole patient group and the control group (Table 4). The proportions with IGT or impaired fasting glycaemia (IFG) were also similar. However, the painful neuropathy subgroup had an elevated mean 2-h glucose concentration compared with the controls \( (P = 0.016) \). The average fasting insulin was significantly greater in the patients than the controls \( (P = 0.0001) \) especially in the painful cases \( (P = 0.0005) \) and those without pain no different \( (P = 0.74) \).

**Hypertriglyceridaemia**

After adjusting for BMI as well as age and sex, there were significantly higher triglyceride concentrations in the patients.
Table 4 Glucose tolerance in patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patients with pain</th>
<th>Patients without pain</th>
<th>Controls</th>
<th>P (all patients versus controls)</th>
<th>P (patients with pain versus controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (mmol/l)</td>
<td>5.28 (0.37)</td>
<td>5.26 (0.42)</td>
<td>5.30 (0.34)</td>
<td>5.31 (0.71)</td>
<td>0.91</td>
<td>0.83</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.23 (0.76)</td>
<td>5.24 (0.97)</td>
<td>5.22 (0.54)</td>
<td>5.18 (0.80)</td>
<td>0.85</td>
<td>0.98</td>
</tr>
<tr>
<td>2-h glucose (mmol/l)</td>
<td>6.59 (2.14)</td>
<td>7.28 (2.15)</td>
<td>5.97 (1.98)</td>
<td>5.85 (2.62)</td>
<td>0.14</td>
<td>0.016</td>
</tr>
<tr>
<td>Normal glucose tolerance (n)</td>
<td>33</td>
<td>11</td>
<td>22</td>
<td>42</td>
<td>0.88*</td>
<td>0.74*</td>
</tr>
<tr>
<td>IFG (n)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGT (n)</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGT, IFG or diabetes mellitus</td>
<td>16/49</td>
<td>11/22</td>
<td>5/27</td>
<td>7/49</td>
<td>0.45</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Figures are numbers or means (standard deviations) and P values have been adjusted for age and sex.

*This test compares the distribution of the subcategories of glucose tolerance between the patients and the controls.

(mean 1.90 (1.41) mmol/l) than the controls (mean 1.25 (0.79) mmol/l) (P = 0.02). After the same adjustment in the patients with painful peripheral neuropathy, the mean triglyceride concentration was 2.37 (1.72) mmol/l, which was even more significantly different compared with the controls (P = 0.003).

Vitamin C and E

The mean plasma concentration of vitamin C was 48.3 (22.2) μmol/l in the patients and 44.9 (23.3) μmol/l in the control subjects. The mean plasma concentration of vitamin E was 14.2 (3.9) μmol/l in the patients and 14.7 (5.9) μmol/l in the control subjects. The concentrations of these two vitamins were not significantly different between the patients and the controls.

Autoantibodies

In the ELISA for IgM antibodies to ganglioside GM1 at a serum dilution of 1/200, there was no significant difference in the mean optical density of the patients, which was 215 (97) compared with that of the controls which was 240 (96). No patients or controls had IgG antibodies against GM1. In the immunoblot test for IgM antibodies, four patient sera reacted with GM1 compared with three control sera but none had IgG antibodies. Antibodies against other gangliosides were not detected. In the western blot test for IgG antibodies, eight patient and 13 control sera reacted at a dilution of 1/250 with bands in human cauda equina. In the similar test for IgM antibodies, three patient and one control sera reacted with bands. There were no characteristic IgG or IgM bands in the patients compared with the control sera. There were no significant differences in the proportions of patients compared with controls having antibodies to neurofilament light chain (five out of 49 compared with three out of 49), heavy chain (two out of 49 compared with two out of 49), actin (five out of 49 compared with five out of 50) or tubulin (three out of 49 compared with two out of 50).

Further statistical analysis

To assess whether the associations identified in the single ‘explanatory’ variable analyses above were independent of each other, a logistic regression analysis was performed to assess simultaneously the associations between cigarette and alcohol consumption, exposure to environmental toxins, BMI, insulin resistance, glucose intolerance, triglyceride, cholesterol and HbA1c levels and CIAP, allowing for age and sex differences.

This analysis also showed no association with cigarette consumption, but there was a significant positive association with exposure to environmental toxins (P = 0.01). There was also a
strong, but complicated association with alcohol consumption ($P = 0.007$). Compared with the controls, the CIAP patients were less likely to be non- or heavy drinkers.

No significant evidence was found for associations with insulin resistance, glucose intolerance, BMI, HBA1c or cholesterol. Increasing triglyceride levels were found to be highly significantly associated with the likelihood of being a CIAP case ($P = 0.0024$). Regressions using only the non-painful cases and then only the painful cases gave different results for BMI, alcohol consumption and exposure to chemical agents, but showed the same pattern of association with triglyceride and lack of association with cholesterol for both types of case. These results are consistent—apart from the associations with glucose concentrations—with those obtained from the single variable analyses.

**Discussion**

As in previous reports, our patients were elderly, included more men than women and were mildly or moderately disabled (Notermans *et al.*, 1993). The features were those of a gradually progressive symmetrical length dependent axonal neuropathy affecting sensory or sensory and motor nerve fibres. Autonomic symptoms were not prominent but pain was. The disease was associated with significantly reduced quality of life.

Previous uncontrolled reports have suggested an association between CIAP (especially when painful) and IGT. After adjustment for age and sex, our results did not confirm this association, although there was a trend towards more impairment of glucose tolerance in CIAP than the controls (especially in those with pain). The patients with pain were significantly more obese and had significantly higher BMIs than the controls. The fasting insulin concentrations were highly significantly greater in the patients than the controls and, in the painful neuropathy subgroup, the mean insulin resistance was just significantly different from the controls. Our study could be criticized because the glucose tolerance test was not performed after loading the diet with carbohydrate for 4 days, which is known to increase the proportion of patients with blood concentrations in the impaired glucose tolerance range (Alberti and Zimmet, 1998). Since the test was performed in the same way for the patients and the controls, this would have been unlikely to affect the relative proportions of patients and controls with IGT.

An interesting and novel finding was that patients with CIAP as a whole and patients with painful neuropathy had significantly higher serum triglyceride concentrations than the control subjects. Exactly similar observations have rarely been reported. Teunissen and colleagues reported that, in contradiction to our study, the odds ratio of having hypercholesterolaemia was greater [3.395% confidence interval (CI) 1.5–7.3] in 97 patients with CIAP compared with age–sex matched controls, but did not report triglyceride concentrations (Teunissen *et al.*, 2002). Sorenson and Windebank reported (in an abstract) serum triglycerides that were above the 90th percentile in 79% of 27 patients with painful small fibre neuropathy (Sorenson and Windebank, 2000). Windebank and colleagues reported six patients with predominantly small fibre sensory neuropathy with marked hyperlipidaemia, especially hypertriglyceridaemia (Windebank *et al.*, 2002). These observations and our own raise the hypothesis that an abnormality of triglyceride metabolism not necessarily linked to diabetes mellitus is responsible for a significant proportion of cases of CIAP, especially those with small fibre involvement and pain. If this were true, further investigation of lipid metabolism would be appropriate and measures to lower triglyceride concentrations worth exploring.

Previous observational but not controlled studies stressed the importance of hyperglycaemia and IGT as a cause of CIAP. Our controlled observations showed no significant association with diabetic category and only a weak association with the 2-h glucose concentration in patients with pain. On the other hand, there was a significant association between CIAP and hypertriglyceridaemia. This association could be explained in two ways. First, it might be because hypertriglyceridaemia is a marker for the metabolic syndrome of increased BMI, IGT, impaired insulin resistance, and hyperlipidaemia. This metabolic syndrome is becoming increasingly common in the developed world (Modan *et al.*, 1985; Wannamethee *et al.*, 1998). The lack of association with hyperglycaemia raises the important hypothesis that CIAP is not due to hyperglycaemia per se but to a common abnormality underlying the metabolic syndrome, whose cause is also not clear. The second explanation would be an undescribed but more specific abnormality of triglyceride handling, not linked to the metabolic syndrome.

We included in our series six patients with a history in first-degree relatives that might have been compatible with a late onset familial peripheral neuropathy. It is a moot point whether such patients should be excluded from a series of patients with CIAP. We argued that, in these elderly families, it might not be possible to confirm or refute whether these other family members did or did not have a neuropathy and that to exclude such patients would prevent us from detecting a subgroup of patients with a genetic cause for CIAP. Others might regard such patients as having late onset Charcot–Marie–Tooth disease type 2, which may sometimes present in the elderly (Harding and Thomas, 1980). However, our patients usually had more sensory than motor deficit and the presence of pes cavus did not correlate with a family history of possible neuropathy. The presence of claw toes did correlate with a family history, but also occurred in the control subjects.

We did not identify a positive association between CIAP and alcohol consumption in this patient group, possibly because patients overusing alcohol had been diagnosed and excluded from the study and as a result there were more heavy drinkers in the controls. Although none of the patients had been considered to have had so much exposure to environmental toxins that their neuropathy could be considered to be neurotoxic in origin, exposure to environmental toxins did emerge as a significant factor in the logistic regression analysis. Solvents and organophosphate insecticides are recognized causes of acute
neuropathy, but there is no convincing evidence that chronic low level exposure causes peripheral neuropathy (Committee on Toxicity of Chemicals in Food, 1999). However there may have been recall bias of toxin exposure in this patient population compared with the control subjects.

We found no evidence of reduced vitamin E or vitamin C concentrations to support the hypothesis that CIAP is due to a deficiency of provision or absorption of these anti-oxidants. However, we have not excluded the possibility that CIAP is due at least in part or in some cases to a failure of the dorsal root ganglion and anterior horn cells to cope with oxidative stress and so to be subject to premature axonal degeneration.

Low levels of IgM antibody to ganglioside GM1 but not other gangliosides and of IgG and IgM antibodies to some unidentified neural proteins were found in some patients, but not more commonly than in controls. These results did nothing to support the hypothesis that autoimmunity to axonal antigens contributes to the pathogenesis of CIAP, as has been suggested in some forms of acute and chronic inflammatory neuropathy (Willison and Yuki, 2002).

We took the opportunity to test previous hypotheses that CIAP is related to impaired venous or arterial insufficiency. Patients with venous insufficiency have been reported to have abnormal cool, warm and vibration thresholds in the feet and prolonged distal motor latencies in the peroneal nerve (Reinhardt et al., 2000). There was no clinical evidence that venous insufficiency played a significant part in the pathogenesis in our patient sample. While this study was being completed, another case control study showed an increased frequency of cardiovascular disease compared with age sex matched controls (Teunissen et al., 2002). In our study, 10 patients and 4 controls had personal histories of heart disease, cerebrovascular disease or treatment for hyperlipidaemia (P = 0.15).

In conclusion, CIAP can usefully be classified clinically into painful and painless categories with different associations with metabolic abnormalities. The impairments that CIAP produces cause mild or moderate disability, and adversely affect all aspects of the quality of life. These effects are greater in those with pain than those without. A trend towards IGT and significantly increased high fasting serum insulin was observed in CIAP, especially in patients with pain. However, the only factors that emerged as significant in a logistic regression analysis, apart from alcohol consumption which is probably due to selection or behaviour modification in the patients, were environmental toxin exposure and hypertriglyceridaemia, which deserve further investigation as possible causes of CIAP in both clinical practice and research.

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References


