Coexistent hereditary and inflammatory neuropathy

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Summary
Classically, the course of Charcot–Marie–Tooth (CMT) disease is gradually progressive. We describe eight atypical patients who developed acute or subacute deterioration. Seven of these had genetically proven CMT disease type 1A (CMT1A) due to chromosome 17p11.2–12 duplication, and one had X-linked disease (CMTX) due to a mutation in the GJB1 gene. In this group there was sufficient clinical, electrophysiological and neuropathological information to indicate a diagnosis of a superimposed inflammatory neuropathy. The age range of the patients was 18–69 years, with a mean of 39 years. A family history of a similar neuropathic condition was present in only four patients. All eight had an acute or subacute deterioration following a long asymptomatic or stable period. Seven had neuropathic pain or prominent positive sensory symptoms. Nerve biopsy demonstrated excess lymphocytic infiltration in all eight patients. Five patients were treated with steroids and/or intravenous immunoglobulin, with variable positive response; three patients received no immunomodulatory treatment. Inflammatory neuropathy has previously been recognized in patients with hereditary neuropathy, with uncharacterized genetic defects and with CMT1B. We present detailed assessments of patients with CMT1A and CMTX, including nerve biopsy, and conclude that coexistent inflammatory neuropathy is not genotype-specific in hereditary motor and sensory neuropathy. Although this was not a formal epidemiological study, estimates of the prevalence of CMT disease and chronic inflammatory demyelinating polyneuropathy indicate that the association is more frequent than would be expected by chance. This has implications for understanding the pathogenesis of inflammatory neuropathies and raises important considerations in the management of patients with hereditary neuropathies. If a patient with CMT disease experiences an acute or subacute deterioration in clinical condition, treatment of a coexistent inflammatory neuropathy with steroids or immunoglobulin should be considered.

Keywords: Charcot–Marie–Tooth disease; chronic inflammatory demyelinating polyneuropathy; peripheral nerve; nerve biopsy; neuropathy

Abbreviations: CIDP = chronic inflammatory demyelinating polyneuropathy; CMT = Charcot–Marie–Tooth; CMT1A = Charcot–Marie–Tooth disease type 1A; CMT1B = Charcot–Marie–Tooth disease type 1B; CMTX = X-linked Charcot–Marie–Tooth disease; MCV = motor nerve conduction velocity; MPZ = myelin protein zero gene; PMP22 = peripheral myelin protein 22; SAP = sensory nerve action potential

Introduction
Until the last quarter of the twentieth century there was significant uncertainty in the classification of the chronic demyelinating neuropathies. Thus, many patients given a generic diagnosis of hypertrophic interstitial neuropathy (Thomas et al., 1975) undoubtedly had a hereditary neuropathy when a family history was lacking. Others would now be diagnosed as having chronic inflammatory demyelinating polyneuropathy (CIDP). With the advent of validated clinical and electrophysiological criteria for the hereditary motor and sensory neuropathies (Harding and Thomas, 1980) followed by the advances in molecular analysis of the last decade, most patients with a genetic basis for their neuropathy can now be given a firm and specific diagnosis (Boerkoel et al., 2002). Similarly, strict criteria now exist for the diagnosis of CIDP,

Even before the developments in the molecular genetics of peripheral neuropathy, however, there was evidence that this separation of hereditary causes from CIDP was sometimes too rigid: there were patients who apparently had both conditions. Thus, individuals were identified who had the phenotype of Charcot–Marie–Tooth (CMT) disease and a positive family history, yet were steroid-responsive (Dyck et al., 1982; Bird and Sladky, 1991). With the arrival of molecular techniques, it has proved possible to classify such patients according to genotype, notably for mutations in the myelin protein zero (MPZ) gene (Donaghy et al., 2000).

Indeed, it has recently been suggested that coexistent inflammation in CMT disease may be genotype-specific to the type 1B disease (CMT1B) due to MPZ mutations (Watanabe et al., 2002). In an immunological study of patients with CMT1A, however, a subgroup was thought to have superimposed inflammation (Gabriel et al., 2002). This conclusion was based on their stepwise (as opposed to gradual) disease progression and, in some instances, a response to immunomodulatory therapy. CMT1A, an autosomal dominant condition, is the commonest form of CMT disease and is usually the result of a 1.5 Mb duplication at chromosome 17p11.2–12 (Lupski et al., 1991; Raeymaekers et al., 1991) involving the gene for peripheral myelin protein 22 (PMP22) (Matsumani et al., 1992; Patel et al., 1992; Timmerman et al., 1992; Valentijn et al., 1992).

Here we describe in detail a patient with proven CMT1A due to the chromosome 17p11.2–12 duplication, who had coexistent inflammatory neuropathy, as evidenced by clinical, neurophysiological and neuropathological features and a marked positive response to treatment with intravenous immunoglobulin. This patient’s presentation prompted a review of our departmental diagnostic database for neuropathies, based on nerve biopsies, which yielded six other patients (seven CMT1A and one CMTX), the majority were examined by at least one of the authors (L.G.); otherwise, clinical and paraclinical information was obtained from the case notes.

DNA analysis
In all cases, the molecular genetic diagnosis was obtained using DNA extracted from blood by standard methods. The chromosome 17p11.2–12 duplication was detected using fluorescent quantitative polymerase chain reaction (PCR) of five microsatellite markers from within the 1.5 Mb duplicated region. Samples were analysed on an Applied Biosystems 3100 Genetic Analyser (Applied Biosystems, Foster City, CA, USA) using Genescan software (Genescan Europe AG, Freiburg, Germany). The presence of the duplication was confirmed by the detection of three alleles at one or more marker loci or by gene dosage. The GJB1 mutation was detected by sequencing the entire coding region of the gene (Bergoffen et al., 1993; Fairweather et al., 1994).

Neurophysiology
All patients had undergone sensory and motor nerve conduction studies in the upper and lower extremities using standard techniques (Medelec Sapphire, Oxford Instruments, Woking, Surrey, UK).

Nerve biopsy
Sural or radial nerve fascicular biopsies had been obtained under local anaesthesia from standard sites. The bulk of each patient’s specimen was fixed in buffered 2.5% glutaraldehyde, postosmicated, dehydrated and embedded in epoxy resin (Durcupan, Fluka, Buchs, Switzerland). Semithin sections (0.5 m) were stained with thionine and acridine orange (Sievers, 1971). The remainder of the specimen was snap-frozen in liquid nitrogen. Frozen sections were stained immunocytochemically for B lymphocytes (CD22), T lymphocytes (CD4 and CD8), early macrophage marker (CD68) and late macrophage product (Mac387). Image analysis was performed using a Zeiss Axioplan microscope (Zeiss UK Ltd, Welwyn Garden City, Herts, UK) fitted with an automated stage (Gerbr MaÈrzhaÈuser, Wetzlar, Germany and using KS400 imaging system (Zeiss UK Ltd, Welwyn Garden City, Herts, UK). All myelinated fibres in all available fascicles were counted and measured.

Methods
Patient ascertainment
The nerve biopsy database in the Department of Clinical Neurosciences at the Royal Free Hospital, London, was searched for all patients listed as having a final diagnosis of CMT disease. As it is not routine practice to biopsy patients with a classical CMT syndrome, we deduced that these patients were in some way atypical. They may have been biopsied because CMT disease had not been suspected beforehand, presumably in the absence of a family history. Alternatively, patients with known CMT disease may have been biopsied because of an unusual disease course. Either way, the selected patients were judged likely to be a fertile source for the present study. Seventeen patients were identified initially. Of these, five were eliminated because of incomplete molecular genetic information. The remainder all had CMT1A due to the chromosome 17p11.2–12 duplication, apart from the one patient with a GJB1 mutation. Another four patients were excluded through lack of clinical and/or pathological data (only patients whose nerve biopsies had been subject to immunocytochemical analysis in addition to standard histological techniques were included). Of the remaining patients (seven CMT1A and one CMTX), the majority were examined by at least one of the authors (L.G.); otherwise, clinical
Results

**Index case history (case 1)**

This 39-year-old woman had never been keen to participate in sports at school. Deformities of both feet were noted in childhood. She first came to the attention of neurologists at the age of 25 years, with subacute progression of her lower limb weakness associated with paraesthesiae in the feet. Her gait continued to deteriorate, albeit more slowly, and she required surgery to both feet at the age of 32 years, since which time she started to wear ankle-foot orthoses. At the age of 39 years, she presented with a 1-month history of worsening weakness, numbness and paraesthesiae of the hands. She developed difficulty holding a cup or pen. There was no history of neck pain but she had been aware of weakness of her neck. Sphincter control was normal.

Her previous medical history was otherwise remarkable for a diagnosis of ulcerative colitis, made in her mid-thirties. In her family history, several members, including her father, had a similar, but milder, neurological disorder.

Examination showed normal cognitive function. In the cranial nerves, there was bilateral ptosis, more marked on the left, and weakness of neck flexion. There was distal symmetrical wasting and weakness of the upper and lower limbs. A postural tremor was present in both upper limbs. Tendon reflexes were absent and plantar responses were unobtainable. Sensory testing revealed impaired joint position and vibration sense in the fingers and toes. Cutaneous sensation to pin, temperature and light touch was diminished to the mid-forearm and knee bilaterally. She had bilateral pes cavus and scars of previous foot surgery. Peripheral nerves were not thickened.

Routine haematological and biochemical investigations were normal. DNA analysis confirmed the duplication at chromosome 17p11.2–12. Tests directed to excluding the remote possibility of coexistent myasthenia gravis (because of the ptosis and neck weakness) were negative, including anti-acetylcholine receptor antibodies. Examination of the CSF showed an acellular specimen with elevated protein concentration at 0.78 g/l; the glucose concentration was normal. Oligoclonal bands were present in CSF and serum.

Nerve conduction studies showed marked slowing of motor nerve conduction velocities (MCV) to 18 m/s in the median nerve and 19 m/s in the ulnar nerve. Distal motor latencies were prolonged (8.6 ms in the median nerve, 8.2 ms in the ulnar nerve) and sensory nerve action potentials (SAP) were absent. These findings are typical of a severe demyelinating motor and sensory neuropathy, as seen in CMT1A. More unusually, however, partial motor conduction block was detected, initially only proximally in the Erb’s to elbow segment of the median nerve, but on subsequent occasions in distal segments of the median and ulnar nerves.

Sural nerve fascicular biopsy confirmed the typical hypertrophic changes of CMT1A (Fig. 1A) but also showed epineurial and endoneurial T-cell infiltrates on immunostaining (Fig. 2A).

On the basis of the clinical, CSF, neurophysiological and biopsy findings, the patient was treated with intravenous immunoglobulin (2 g/kg over 5 days). She improved clinically (corresponding to one point on the Rankin scale), regaining hand function (confirmed by quantitative myometry), and electrophysiologically. Most strikingly, partial motor conduction block was no longer apparent after the therapy (Fig. 3).

She has since been stable on maintenance infusions of immunoglobulin, 2 g/kg every 5–6 weeks. With longer intervals, her strength and sensory symptoms deteriorate.

**Patients with CMT1A: composite analysis (cases 1–7)**

**Clinical features**

These patients had a mean age at the time of nerve biopsy of 39 years (range 18–69). There were four females and three males. A family history consistent with autosomal dominant inheritance was present in only three cases. No patient had a previous history of any general medical condition commonly associated with peripheral neuropathy; in particular, none was diabetic. There was evidence of the neurological disease in the first decade of life in three patients and in the second in two. The remainder presented in adult life. By the time of their nerve biopsy, all patients had at least minimal evidence of neuropathy, i.e. loss of reflexes, but none had a pure classical CMT syndrome of gradually progressive distal weakness, areflexia, foot deformity and minor sensory involvement. All seven patients had come to nerve biopsy because of an acute or subacute deterioration following a long asymptomatic or stable period. Six patients had neuropathic pain or prominent positive sensory symptoms. Cranial nerve signs were noted in five patients (ptosis and weakness of neck flexion in case 1, ptosis and weakness of eye closure in case 2, sensorineural deafness and weakness of neck flexion in case 3, patchy facial sensory impairment in case 5 and sensorineural deafness and weakness of neck flexion in case 6). One patient (case 1) had a significant upper limb postural tremor, suggesting the Roussy–Lévy variant of CMT disease. Two patients had no detectable weakness on clinical examination. In one (case 7), this was probably simply a reflection of his relative youth (age 18 years) at the time of assessment and high baseline level of strength, potentially masking any minor weakness. The other patient (case 5) was unusual, presenting in adult life with episodes of pain and stiffness in the limbs, muscle cramps, fasciculations and calf muscle hypertrophy. This patient has previously been reported and more extensively discussed (as case 56) in a series illustrating the range of phenotypic manifestations of the duplication at chromosome 17p11.2–12 (Thomas et al., 1997). Likewise, cases 2 and 3 of the present study correspond to cases 15 and 30 respectively in that series. Regarding skeletal and other
features of the genetic defect, only three patients had foot deformities, in the form of pes cavus (cases 1, 3 and 7). One patient (case 6) had echocardiographic evidence of hypertrophic cardiomyopathy. Peripheral nerve thickening was not a feature of the patients in this study.

**Blood and CSF findings**

Routine haematological and biochemical investigations were normal in all patients. In particular, none had evidence of a serum paraprotein. The results of CSF examination were available in six patients. All specimens were acellular with a normal glucose concentration. The mean protein concentration was 0.87 g/l (range 0.43–1.85). Four patients had significantly elevated CSF protein concentrations (>0.7 g/l). Oligoclonal bands were present in CSF and serum in one

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**Fig. 1** Semithin resin sections from nerve biopsies of patients with CMT disease (thionine and acridine orange). (A) Case 1, showing widespread hypertrophic changes typical of CMT1A. The fibres at the centres of some onion bulbs have no demonstrable myelin (arrow) (bar = 50 μm). (B) Case 7, showing extensive subperineurial oedema (asterisk) in addition to the hypertrophic changes in another CMT1A patient (bar = 100 μm). (C) Case 8, showing loss of large myelinated fibres and effete onion bulbs (arrows) in a CMTX patient (bar = 100 μm).
Neurophysiology

Upper limb MCV (usually for the median nerve, recording from abductor pollicis brevis) ranged from 6 to 34 m/s (distal motor latency 6.8–8.6 ms). Values for the lower limbs were rarely obtained due to severe denervation of the small foot muscles. The SAPs were generally absent, except in case 5, where the radial and sural SAPs were obtainable (6 and 7 μV respectively), median and ulnar SAPs being absent. Partial motor conduction block was detected in three patients.

Nerve biopsy

Fascicular nerve biopsy in all seven patients showed depletion of the myelinated fibre population with marked loss of the largest fibres (Fig. 4).

Prominent onion-bulb hypertrophic changes were seen in all cases. Thinly myelinated fibres were evident in six
biopsies, suggesting remyelination or regeneration. Recent (as indicated by the presence of demyelinated axons) or active demyelination was seen in four biopsies. Active axonal degeneration was not found in any specimen but there was evidence of axonal regeneration (clusters of axonal sprouts) in six. Extensive subperineurial oedema was noted in one biopsy (case 7; Fig. 1B). Immunostaining showed prominent T-lymphocyte infiltration in the same specimen (Fig. 2B).

Lymphocytic infiltration in excess of that seen in control sections from patients with amyloid neuropathy (where none was evident) was found in all cases.

Response to treatment
Two patients received corticosteroids in the form of prednisolone (cases 3 and 4). Both responded clinically but in case 4 the response was transient and subsequent treatment with intravenous immunoglobulin was unsuccessful. Two other patients were treated with intravenous immunoglobulin (cases 1 and 2). Both responded clinically and in one (case 1, see above) this was supported by myometric and electrophysiological measurements. The other three patients (cases 5–7) did not receive immunomodulatory treatment.

Summary of atypical features in CMT1A patients
Taken as a group, these patients showed several clinical and paraclinical features which were atypical for CMT disease. The presence or absence of each of these features for the seven patients is summarized in Table 1.

Patient with CMTX (case 8)
This 43-year-old man had undergone corrective surgery to both ankles at the age of 13 years. Further surgery to the left foot was required 20 years later. At the age of 40 years, he developed pain and numbness in the left arm. At the age of 40 years, he developed pain and numbness in the left arm. The sensory disturbance spread to involve the right leg, then the left leg and finally, 1 year later, the right arm. He experienced burning sensations in the arms and stabbing pain in both lower limbs, affecting his gait. There had been two episodes of left facial numbness, each lasting 1 h. Sphincter control remained normal and there was no history of neck or back pain. In his family history, a maternal uncle was said to have had hammer toe deformities.

On examination, cognitive function was normal, as were the cranial nerves, apart from a residual visual field defect on the left, secondary to a retinal detachment at the age of 31 years. There was mild distal symmetrical wasting and weakness in the upper and lower limbs. Tendon reflexes were absent and plantar responses were downgoing. Sensory testing showed impaired joint position sense to the ankles. Vibratory sensation was absent to the anterior superior iliac spines and to the elbows. Temperature perception was reduced distally bilaterally to the knees and the mid forearms. Pin and light touch sensation were diminished to mid-thigh level. In the upper limbs, there was impairment of these modalities of cutaneous sensation to the elbow on the right and to the upper arm on the left. Romberg’s test was positive.

Fig. 3 Upper limb nerve conduction studies in case 1, showing partial motor conduction block in the forearm segments of the right median and ulnar nerves and its reversal following treatment with intravenous immunoglobulin. (A) Median nerve before treatment. (B) Median nerve after treatment. (C) Ulnar nerve before treatment. (D) Ulnar nerve after treatment. In each panel, the upper trace shows the compound muscle action potential (recorded from abductor digiti minimi in the median nerve study, abductor digiti minimi in the ulnar nerve) evoked by supramaximal stimulation at the wrist. The response to supramaximal stimulation at the elbow is shown in the lower trace. An amplitude reduction of 76% before treatment in the median nerve study became 22% after immunoglobulin treatment. For the ulnar nerve study, the equivalent figures were 56 and 3% respectively (corresponding to reductions in the area under the action potential curve of 63 and 8%).
He had bilateral pes cavus and scars of previous corrective surgery. There was also a scar from excision of an occipital lipoma. Peripheral nerves were not thickened.

Routine haematological and biochemical tests were normal. The CSF was acellular, protein concentration 0.5 g/l and glucose concentration normal. MRI of brain and whole spine was normal. DNA analysis excluded a duplication at chromosome 17p11.2–12. Further molecular genetic studies revealed a Cys173Arg (TGC/CGC) mutation in the coding region of the \( GJB1 \) gene, which has been described previously (Inherited Peripheral Neuropathies Mutation Database online, 2003) and is likely to be pathogenic.

Nerve conduction studies showed slowing of MCV to 31, 32 and 25 m/s in the median, ulnar and peroneal nerves respectively. F waves were uniformly absent, as were SAPs. Partial motor conduction block was not detected.

Sural nerve fascicular biopsy showed chronic neuropathic features with prominent clumps of Schwann cells but few classical onion-bulb formations (Fig. 1C). Immunostaining revealed numerous T cells around epineurial blood vessels and in the perineurium (Fig. 2C).

The patient was treated with intravenous immunoglobulin (2 g/kg), with dramatic improvement in his pain and other sensory symptoms for a 6-week period. Unfortunately, subsequent infusions were progressively less effective and a trial of prednisolone was also unsuccessful. He has since been treated with drugs used in the management of neuropathic pain, with varying benefit.

**Discussion**

As would be expected for a condition arising on a hereditary degenerative basis, the usual course of CMT disease is gradually progressive. The archetypal pattern which results is one of symmetrical distal muscle wasting and weakness, areflexia, foot deformity and minor sensory abnormalities. Considerable phenotypic heterogeneity has been reported, however, both between and within families, for CMT1A, the commonest form of the disease (Thomas et al., 1997). The patients with CMT1A in the present study deviate from a classical CMT syndrome in several respects (Table 1). These atypical features correspond closely to those suggested by others as pointing to a coexistent inflammatory neuropathy (Bird and Sladky, 1991).

Taken individually, the characteristics listed in Table 1 vary in their specificity as indicators of an inflammatory process. Thus, in all seven patients there was a history of stepwise deterioration with acute or subacute relapses after periods of clinical stability; this would be most unusual for a classical inherited neuropathy. Similarly, all patients but one had positive sensory symptoms or neuropathic pain; this again favours an acquired inflammatory disorder. Elevated CSF protein values are less specific but the result in case 7 (1.85 g/l) is difficult to explain in any way other than an inflammatory neuropathy, particularly when taken in combination with the neuropathological features in his case (Figs 1B and 2B). Of the four patients who received immunomodulatory therapy, persistent benefit was observed in three cases, with only transient benefit in the fourth. Objective

**Table 1. Summary of CMT1A patients**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Positive sensory symptoms</th>
<th>Step-wise deterioration</th>
<th>Conduction block</th>
<th>Increased CSF protein*</th>
<th>Inflammatory infiltrate in biopsy</th>
<th>Response to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ (0.78)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>F</td>
<td>+</td>
<td>+</td>
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<td>0</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>F</td>
<td>0</td>
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<td>F</td>
<td>+</td>
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<td>+ (0.99)</td>
<td>+</td>
<td>n/g</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+ (1.85)</td>
<td>+++</td>
<td>n/g</td>
</tr>
</tbody>
</table>

*Values of CSF protein concentration, for patients in whom it was increased, are given in parentheses in g/l. n/a = not available; n/g = immunomodulatory treatment not given; 0 = absent; + = present; +/- = partial; +++ = marked inflammatory cell infiltrate (>100 CD4 lymphocytes per section).
evidence of benefit is an issue but in at least one patient (case 1) the clinical impression of a positive response to intravenous immunoglobulin was supported by electrophysiological data (Fig. 3).

Electrodiagnostic evidence of an acquired inflammatory demyelinating process is difficult to adduce in the context of patients who already have marked slowing of nerve conduction velocity as a consequence of the inherited disorder. Indeed, the degree of slowing typically seen in CMT1 effectively precludes many of the electrophysiological criteria used in the diagnosis of CIDP (Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force, 1991). The major remaining potential method of distinguishing an acquired demyelinating neuropathy from an inherited disorder electrically is by measures which indicate patchy, multifocal nerve involvement in the former as opposed to the more homogeneous features seen in hereditary disease (Lewis and Sumner, 1982). Thus, partial motor conduction block was observed in three CMT1A patients in the present study, in keeping with superimposed inflammation, and in case 1 the block was reversed by immunomodulatory therapy.

Nerve biopsies suffer from drawbacks in interpretation similar to those for electrodiagnostic data, many of the features of acquired demyelination potentially being masked by the chronic changes of the hereditary disease. Some of the neuropathological findings in our CMT1A patients suggest a superimposed inflammatory process, i.e. the presence of inflammatory cell infiltrates and endoneurial or subperineurial oedema, but caution is required to avoid overinterpretation even of these aspects (Gabreels-Festen et al., 1993). It is perhaps noteworthy that there was evidence of active and/or recent demyelination in four out of seven biopsies in the present series, compared with only one out of 10 in the study of the phenotypic manifestations of chromosome 17p11.2 duplication cited previously (Thomas et al., 1997). The degree of T-lymphocyte infiltration was marked in several of our patients (e.g. Fig. 2). Although such infiltrates have been reported in biopsy series of CMT disease (Gabreels-Festen et al., 1993), they are generally regarded as helpful in the diagnosis of inflammatory neuropathy, especially when immunocytochemical markers are used to highlight lymphocyte subsets (Schmidt et al., 1996). The difficulty lies in determining quantitatively whether the cellular infiltration exceeds that found in control biopsy specimens. Contrary to the findings in all seven patients in the present series, no significant additional inflammatory infiltration was seen in four biopsies examined in the immunological study of CMT1A mentioned previously (Gabriel et al., 2002). This difference may be methodological, reflecting possible reduced sensitivity of immunostaining in paraffin compared with frozen sections and the differing panels of antibodies used for immunocytochemical staining in the two studies, or may simply be a consequence of sampling error. It is potentially relevant that biopsies from patients with chronic idiopathic axonal polyneuropathy (presumed to be non-inflammatory) were used as controls in the previous immunological study (Gabriel et al., 2002); some of these patients may have had CIDP (Vallat et al., 2003).

Despite the caveats attached to the individual attributes listed in Table 1, the composite picture that emerges is one of a subgroup of CMT1A patients with coexistent inflammatory neuropathy. This is particularly evident in the index case (case 1), in which all the markers of superimposed inflammation are positive. This patient also had a diagnosis of ulcerative colitis, which is associated with peripheral neuropathy, notably a perineuritis (Chad et al., 1986). The first subacute deterioration in the neuropathy, however, occurred years before the onset of inflammatory bowel disease and subsequent neuropathic activity was not associated temporally with relapses of colitis.

The patient with CMTX also had evidence of a superimposed inflammatory process. The classical phenotype of CMTX resembles CMT1 with the exception that slowing of nerve conduction velocity is usually milder (Nicholson and Nash, 1993). Our patient (case 8) deviates from the archetype in several of the characteristics listed in Table 1. Thus, he had a subacute deterioration after a long period of stability, positive sensory symptoms and neuropathic pain, inflammatory infiltrates on nerve biopsy and a response, albeit transient, to immunomodulatory therapy. This is the first detailed description of coexistent inflammatory neuropathy in CMTX, though there have been hints from electrophysiological data that the phenomenon may occur (Tabaraud et al., 1999; Gutierrez et al., 2000).

Does the evidence for an inflammatory neuropathy in these cases signify anything more than the chance occurrence of CIDP in a proportion of CMT patients? Epidemiological studies of CIDP are few but a point prevalence of 1 in 100 000 has been quoted for a comparable general population (Lunn et al., 1999). The prevalence of CMT disease as a whole has been estimated at 1 in 2500 (Skre, 1974). Applying these figures to the present study is complicated by the fact that some of the patients came from the region served by the Department of Clinical Neurosciences at the Royal Free Hospital, whereas others were referred from further afield. The catchment population for the department is approximately 2.5 million, of whom ~1000 should, therefore, have CMT disease at any given time. Of the eight patients in the study, four were referred from within the region, giving an estimated prevalence of 1 in 250 for coexistent inflammation in CMT disease. This calculation does not allow for the difference between point and period prevalence (the four cases were ascertained between 1995 and 2001). Despite this drawback, an estimate of 1 in 250 compared with that for the prevalence of CIDP in the general population (1 in 100 000) still implies that the inflammatory process cannot be explained by mere coincidence of CIDP and CMT disease. If anything, a value of 1 in 250 is probably an underestimate of the frequency of superimposed inflammation in CMT disease because of the method of case ascertainment. Only patients for whom there was complete neuropathological information, i.e. semithin sections and immunocytochemical
stains, were included. Thus, at least two cases from the series of Thomas et al. (1997) (cases 44 and 46) were excluded through lack of histopathological data, though both had histories suggesting an inflammatory component. Another two CMT patients with a history of stepwise deterioration and positive sensory symptoms have been seen in the Royal Free Hospital peripheral nerve clinic since the end of the period of ascertainment (2001), but were not biopsied.

The pathogenetic mechanism by which inflammation occurs in the context of CMT disease is unknown. An initial question is whether the hereditary disorder always involves an inflammatory component, which remains subclinical in the majority of patients. As noted by others (Gabriel et al., 2002), there are precedents for inherited neurological diseases commonly being associated with inflammation. This applies in the central nervous system, as in adenoleucodystrophy (Schaumburg et al., 1975), and peripherally, notably in hereditary myopathies, such as facioscapulohumeral muscular dystrophy (Fitzsimons, 1994). In experimental studies of peripheral neuropathy, mice heterozygous deficient in the murine equivalent of the MPZ gene show less severe neurological disease if the animals are also immunodeficient (Schmid et al., 2000). In the case of human CMT disease, however, most patients are unresponsive to immunosuppressant therapy (Prensky and Dodson, 1984) and histopathological changes suggesting inflammation are present only in a minority of biopsies (Gabreels-Festen et al., 1993). Our own preliminary calculations, given above, indicate a relatively small proportion of CMT patients with coexistent inflammation, albeit a much greater proportion than would be predicted simply by coincidence of CIDP and CMT disease.

An alternative view, therefore, would be that only a subgroup of CMT patients is predisposed to superimposed inflammation, presumably as a result of an additional genetic susceptibility to immunological neuropathy. This subgroup is envisaged as exhibiting an exaggerated immune response against myelin autoantigens expressed by the inherited neuropathy. For patients with the chromosome 17p11.2–12 duplication, it has been suggested that there may be genes within the duplicated segment which are capable of modifying the immune response (Gabriel et al., 2002). Such a mechanism could not apply, however, to patients who have coexistent inflammation in the context of point mutations in the MPZ gene (Donaghy et al., 2000; Watanabe et al., 2002) or in the GJB1 gene, as described above.

A pathogenetic role has been proposed for antibodies against PMP22 in CMT1A and in other neuropathies (Gabriel et al., 2000; Ritz et al., 2000). Experimental autoimmune neuritis can be induced by exposure to PMP22 (Gabriel et al., 1998) and anti-PMP22 antibodies are found in a significant proportion of patients with CIDP or Guillain–Barré syndrome (Gabriel et al., 2000). Only a minority of patients with CMT1A have these antibodies, however, and there is no clinical difference between those with the antibody and the remainder (Gabriel et al., 2002). Once again, a mechanism involving the gene product in CMT1A is unlikely to be relevant to inflammation in CMT1B or CMTX.

The development of an inflammatory process in CMT disease may relate to a disturbance of the normal function of the protein encoded by the affected gene. Both PMP22 and MPZ are central to the formation of compact myelin (D’Urso et al., 1990, 1999; Filbin et al., 1990). It has been suggested that unstable myelin compaction in CMT1B could allow ‘circulating immune elements access to normally sequestered endoneurial components’ (Bird and Sladky, 1991; Watanabe et al., 2002). A different mechanism would need to be advanced for CMTX, in which the normal function of the GJB1 gene product, connexin-32, is as a gap junction protein, believed to be involved in the control of molecular transport in the paranodal regions of Schwann cells (Bruzzone et al., 1996; Balice-Gordon et al., 1998). A potential unifying hypothesis linking inflammation with Schwann cell and/or myelin dysfunction in the hereditary peripheral neuropathies would be the putative capacity of Schwann cells to act as antigen-presenting cells (Lilje, 2002).

In conclusion, despite these uncertainties about the underlying immunological mechanism(s), there is accumulating evidence for a superimposed inflammatory process in a subgroup of patients with CMT disease. The phenomenon is not genotype-specific. It may contribute to the explanation of the considerable phenotypic heterogeneity seen even within families with the various genotypes (Thomas et al., 1997; Donaghy et al., 2000; Gutierrez et al., 2000). Finally, the recognition of an inflammatory component creates therapeutic opportunities for some CMT patients, beyond the time-honoured measures of physiotherapy, orthotics, orthopaedic surgery and genetic counselling.

Acknowledgements
We wish to thank Drs Heather Angus-Leppan, Jeremy Gibbs and Linda Parsons for permission to publish details of patients under their care. We are also grateful to Jane Workman for technical assistance. All DNA analyses were carried out in the Neurogenetics Laboratory at the Institute of Neurology, Queen Square, London.

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