Nerve granulomas and vasculitis in sarcoid peripheral neuropathy
A clinicopathological study of 11 patients

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Summary
Peripheral neuropathy is a rare, yet treatable manifestation of sarcoidosis, a multisystem disorder characterized by the presence of non-caseating granulomas that are seldom found in nerve biopsy specimens. In order to learn more about the subject, we reviewed our clinical and pathological findings in a series of 11 patients (six men and five women aged 26–83 years) with symptomatic neuropathy associated with characteristic granulomas in nerve biopsy specimens. Only two patients were known to have sarcoidosis before the occurrence of the neuropathy. The neuropathy was focal or multifocal in six patients, including one with a multifocal neuropathy associated with conduction blocks, and one with a multifocal axonal motor deficit. Four patients had a distal symmetrical deficit and one patient had a Guillain–Barré-like syndrome with facial diplegia and respiratory failure. Serum angiotensin-converting enzyme concentration was elevated in only two patients. Epineurial granulomas and perineuritis were present in all nerve specimens. The inflammatory infiltrates invaded the endoneurium, following connective tissue septae and blood vessels, in five patients. Multinucleated giant cells were found in eight patients and necrotizing vasculitis in seven. Inflammatory lesions were associated with variable, asymmetrical involvement of nerve fascicles and axon loss. A muscle specimen was sampled during the same procedure in 10 patients. It showed inflammatory infiltrates and granulomas in nine patients and necrotizing vasculitis in two. Immunolabelling showed a mixed inflammatory infiltrate of T cells (predominantly CD4+ cells) and macrophages, in keeping with a delayed hypersensitivity reaction. In addition to nerve involvement, all patients had at least one other tissue or organ affected, including muscle in nine patients, lungs and/or intrathoracic lymph nodes in eight, skin in three, arthritis in two, and peripheral lymph nodes, stomach and eye in one patient each. Most patients improved on corticosteroids. Two patients remain free of symptoms after 7 years. Severe side-effects of long-term treatment with corticosteroids occurred in two patients, leading to death in one. This study illustrates the wide range of clinical manifestations of sarcoid neuropathy and the frequent association of granulomatous inflammatory infiltrates with necrotizing vasculitis and with silent or symptomatic involvement of other organs.

Keywords: sarcoidosis; sarcoid neuropathy; necrotizing vasculitis; granulomatous vasculitis; nerve conduction blocks

Abbreviations: CMAP = compound muscle action potential; ESR = erythrocyte sedimentation rate; GBS = Guillain–Barré syndrome; SAP = sensory action potential

Introduction
Sarcoidosis is an inflammatory plurisystemic disease of unknown origin. Pulmonary localization is by far the most common, but other organs can be involved, including the skin, eyes, liver and lymph nodes. By contrast, neurological symptoms are rare, affecting an estimated 5% of patients with sarcoidosis (Matthews, 1984; Stern et al., 1985; Chapelon et al., 1990; Sharma, 1997). Cranial nerves are predominantly

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affected, and peripheral facial nerve palsy, often bilateral, is the most common neurological manifestation of sarcoidosis. Definite diagnosis of sarcoid neuropathy rests ideally on the histological demonstration of sarcoid granulomas in nerve specimens, especially in patients who present with isolated neuropathy. In fact, sarcoid granulomas have seldom been found in nerve biopsy specimens and only occasional, isolated cases have been reported so far (Oh, 1980; Nemni et al., 1981; Vital et al., 1982; Galassi et al., 1984).

In order to illustrate the various aspects of sarcoid neuropathy and to better understand its pathophysiology, we performed a retrospective study of the clinical and pathological findings of 11 patients with different patterns of peripheral neuropathy and characteristic granulomatous nerve lesions in biopsy specimens diagnosed in our service. In this paper, we show the pathogenic role played both by the invasion of peripheral nerves by granulomatous infiltrates and by associated necrotizing vasculitis.

Patients and methods

Patients

The inclusion criterion was the presence of non-caseating sarcoid granulomas in nerve biopsy specimens of patients referred for symptomatic polyneuropathy. Eleven patients referred between 1989 and 2000, with different patterns of acquired peripheral neuropathy and characteristic sarcoid lesions in peripheral nerve biopsy samples, were thus included. They were six men and five women, aged 23–83 years. Their clinical and biological data were analysed retrospectively.

Methods

Clinical examination

Neurological examination was carried out in all patients. Muscle performance was scored on a five-point scale (Medical Research Council global motor score). Tendon reflexes, light touch, pinprick, temperature sensation at 4 and 40°C, vibratory sensation and position sense were tested to explore the functions of different subpopulations of axons.

Laboratory investigations

Routine blood tests, CSF examination and appropriate investigations were performed as needed to exclude other causes of neuropathy. In addition, all patients had chest imaging, evaluation of respiratory, liver and renal function, serum assay of angiotensin-converting enzyme, skin tests for tuberculosis and ophthalmological examination.

Neurophysiological investigations

Electrophysiological tests included the evaluation of motor and sensory conduction velocities in all four limbs. Nerve and muscle compound action potentials and nerve conduction velocity, distal motor and F-wave latencies were measured by standard methods. The skin temperature was controlled. Nerve conduction studies were performed according to standard techniques and included sural, superficial peroneal, median, radial and ulnar sensory studies. Motor studies included peroneal, posterior tibial, radial, median and ulnar nerves on both sides. The sensory action potentials (SAPs) were recorded antidromically. When SAPs were not detectable by surface electrodes, the near-nerve needle method was used. Electromyographic examination of muscles in clinically affected territories was performed using a monopolar needle.

Morphological studies

After informed consent had been obtained from the patients, a nerve biopsy was performed in a territory recently affected clinically. The superficial peroneal nerve and the peroneus brevis muscle were sampled during the same procedure in all patients except Patient 2, who underwent sural nerve biopsy without muscle sampling.

The nerve samples were fixed at 4°C in 3.6% glutaraldehyde buffered at pH 7.4. One nerve fragment was embedded in paraffin and cut at 5 μm thickness. We examined serial sections stained with H&E (haematoxylin and eosin) and Masson’s trichrome. Another fragment was postfixed in 1% osmium tetroxide in buffer for 3 h at 4°C and embedded in epon. Transverse sections (1 μm thick) stained with thionin were used for morphometry and sections (0.1 μm thick) stained with uranyl acetate and lead citrate were used for electron microscopy. The density of myelinated fibres was calculated on 1-μm thick sections and compared with the control values of the laboratory.

Nerve fragments were snap-frozen in liquid nitrogen for immunopathological studies. Nerve fragments showing prominent inflammatory infiltrates on H&E staining were labelled for the identification of subsets of cells. Immunolabelling of cellular infiltrates was performed on frozen and/or paraffin-embedded specimens from patients whose nerve biopsy specimens showed inflammatory infiltrates. Monoclonal antibodies to the common leucocyte antigens CD68, CD3, CD4, CD8 and CD20 were used (Dako, Glostrup, Denmark).

A teased fibre study was carried out by postfixing a nerve fragment in osmium tetroxide, macerating it in 66% glycerin for 48 h then dissecting it in pure glycerin. One hundred consecutive nerve fibres were isolated over >10 internodes, and classified according to their morphology.

Paraffin-embedded muscle specimens taken by biopsy of the peroneus brevis muscle during the nerve biopsy procedure were examined after staining serial sections with H&E and Masson’s trichrome. Permission to use this material was obtained from the local ethics committee (Hopital de Bicêtre).
Results

Clinical data

Only two patients (Patients 2 and 5) were known to have sarcoidosis before the onset of neuropathy. Patients 1, 4 and 5 were black West Indians and the others were Caucasian. General manifestations, including fever, fatigue and weight loss, were present in three patients (Patients 1, 5 and 8). Clinical manifestations that could be attributed to sarcoidosis included erythema nodosum and arthritis in Patient 1, skin lesions and enlarged peripheral lymph nodes in Patient 2, arthritis and liver dysfunction in Patient 4, cough and dyspnoea in Patient 5, purpura of the legs in Patient 7 and bilateral uveitis in Patient 8. The tuberculin test was negative in all patients except Patient 1. The erythrocyte sedimentation rate (ESR) was normal in Patients 2, 6, 7, 9 and 10, mildly elevated in Patients 1, 3, 4 and 11, and was increased to 100 mm/h in Patient 8. The concentration of angiotensin-converting enzyme was increased to 162 and 62 U in Patients 4 and 6, respectively. It was normal in the others (normal range <28 U). The patients were negative for antineutrophil cytoplasmic antibodies. Pulmonary involvement was found in six patients (Patients 2, 4, 5, 7, 8 and 11) (Table 1).

The neuropathy was focal, motor and sensory in Patient 1, multifocal motor and sensory neuropathy in Patients 4, 7 and 10, and multifocal sensory in Patient 2. Distal symmetrical sensory polyneuropathy was present in Patients 6, 8 and 9. Loss of vibratory sensations in the distal lower limbs was the only neurological sign in Patient 5, who complained of pains in the legs, and Patient 11 manifested a multifocal deficit of the lower limbs without actual sensory loss. In all patients, the course of the neuropathy was subacute and progressive. None of the patients had CNS manifestations. An asymptomatic hypersignal on T2-weighted imaging of the spinal cord was found in Patient 9.

More details of three patients with uncommon manifestations are given below.

Guillain–Barré syndrome (GBS)-like onset of sarcoid neuropathy

One week after a flu-like episode, Patient 3, a 64-year-old man, complained of hand numbness and clumsiness followed by walking difficulties within 2 days. Five days later, he was admitted to an intensive care unit because of rapid respiratory failure, which required assistance. On examination, he had facial diplegia, diffuse asymmetrical weakness that was more marked in the lower limbs and generalized areflexia. Minor sensory changes were noted in the feet. One week later, he manifested bradycardia and severe postural hypotension. CSF examination showed 36 lymphocytes/ml and a protein concentration of 1.28 g/l. The patient received intravenous immunoglobulins at 2 g/kg body weight over 5 days. Routine laboratory investigations, including the ESR and C-reactive protein concentration, were normal. Serum tests were negative for borreliosis, Epstein–Barr virus infection, hepatitis viruses and HIV. His neurological condition improved slowly, allowing ventilatory support to be withdrawn after 2.5 months. Four months later, he was able to walk 150 m with two crutches, but still complained of paraesthesiae, mainly in the left leg. He was then referred to our service because of slight worsening of his neurological condition. We performed a nerve and muscle biopsy because of the uncommon presentation of this neuropathy, which showed features of an axonal pattern on electromyographical testing. For example, the right median nerve SAP was 0.5 µV and sensory conduction velocity 39 m/s; the left median nerve motor conduction velocity was 45.8 m/s, the compound muscle action potential (CMAP) was 2.2 mV and the distal latency 5.2 ms. The right peroneal nerve motor conduction velocity was 38.5 m/s, CMAP 1.15 mV and distal latency 7 ms. On the left side, the peroneal nerve motor conduction velocity was 38 m/s, CMAP 0.18 mV and distal latency 7.1 ms. The nerve and muscle biopsy specimens both showed characteristic sarcoid granulomas. Characteristic giant-cell granulomas were also seen in biopsy specimens of the gastric mucosa obtained by gastroscopy before starting long-term treatment with corticosteroids. The lungs were normal except for decreased carbon monoxide diffusion. The patient’s motor deficit improved gradually under treatment with corticosteroids. Sensory abnormalities remained unchanged after 6 months.

Multifocal neuropathy in a diabetic patient

Patient 4, a 63-year-old insulin-dependent diabetic man, was referred in 1989 for paraesthesiae in the feet and progressive weakness of the left foot of a few weeks’ duration, associated with fever, fatigue, weight loss and arthritis. His medical history included insulin-dependent diabetes, mild chronic renal failure and several episodes of arthritis of unknown origin. His general condition was poor. Muscle strength was decreased to 1/5 in the left peroneal nerve territory. Deep tendon reflexes were abolished in the lower limbs. Pain and temperature sensations were impaired bilaterally to the knee level. EMG showed severe motor and sensory axonal involvement in the distal lower limbs. The ESR was elevated. Giant-cell granulomas were found in nerve, skin and liver biopsy specimens. The angiotensin-converting enzyme concentration was markedly elevated. A dramatic improvement of his arthritis was followed by slow improvement of motor deficit on treatment with prednisone at 1 mg/kg/day. The biological markers of inflammation returned to normal levels. During the following years, he experienced three relapses with similar manifestations, which all responded to increased dosage of corticosteroids. He subsequently developed anguiullulosis, tuberculosis and skin Kaposi’s disease associated with prolonged treatment with high doses of prednisone, and he died in 1997 of cardiac failure.
Table 1  Clinical data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender/age (year)</th>
<th>Chest stage/CT scan</th>
<th>Interval between first manifestations of sarcoidosis and neuropathy</th>
<th>Neurophy pattern</th>
<th>First neurological manifestations</th>
<th>Clinical examination</th>
<th>Cranial nerve involvement</th>
<th>CSF cells/ml</th>
<th>Protein (g/l)</th>
<th>Follow-up</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/51</td>
<td>0/N</td>
<td>5 years</td>
<td>Focal sensory neuropathy</td>
<td>Numbness in left foot for 3 months</td>
<td>Isolated sensory loss in the left superficial peroneal nerve territory</td>
<td>No</td>
<td>n.d.</td>
<td>0.7</td>
<td>Stable</td>
<td>Stable 6 months</td>
</tr>
<tr>
<td>2</td>
<td>M/23</td>
<td>0/N</td>
<td>12 years</td>
<td>Chronic multifocal sensory neuropathy</td>
<td>Tingling in both feet and forearms for 4 months</td>
<td>Bilateral sensory loss in both sural nerve territories</td>
<td>No</td>
<td>n.d.</td>
<td>1.28</td>
<td>Stable</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M/64</td>
<td>0/N</td>
<td>0 years</td>
<td>GBS-like syndrome</td>
<td>Pains and paraesthesiae in the LL</td>
<td>Isolated loss of vibratory sensations in distal LL</td>
<td>No</td>
<td>3 lymph. 1.28</td>
<td>Complete improvement of neurological and pulmonary signs after 1 month. Stable without treatment after 7 years</td>
<td>0.67</td>
<td>Stable</td>
</tr>
<tr>
<td>4</td>
<td>M/63</td>
<td>IV/interstitial infiltration</td>
<td>5 years</td>
<td>Subacute MFN</td>
<td>Painful legs</td>
<td>Isolated loss of ankle reflexes</td>
<td>No</td>
<td>3 lymph. 0.7</td>
<td>Complete improvement of neurological and pulmonary signs after 1 month. Stable without treatment after 7 years</td>
<td>0.58</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>5</td>
<td>M/26</td>
<td>I/left hilar and mediastinal lymph nodes and interstitial infiltration</td>
<td>2 months</td>
<td>Chronic symmetrical sensory polyneuropathy</td>
<td>Paraesthesiae in both feet for 1 year; walking difficulty, hand weakness, more on the right for 1 month</td>
<td>5 lymph. 0.52</td>
<td>Complete improvement of neurological and pulmonary signs after 1 month. Stable without treatment after 7 years</td>
<td>0.52</td>
<td>Stable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F/70</td>
<td>0/n.d.</td>
<td>2 years</td>
<td>Subacute MFN</td>
<td>Paraesthesiae and tingling in the feet and thighs for 4 months</td>
<td>&lt;1</td>
<td>Complete improvement of neurological and pulmonary signs after 1 month. Stable without treatment after 7 years</td>
<td>&lt;1</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F/83</td>
<td>III/n.d.</td>
<td>2 years</td>
<td>Chronic symmetrical sensory polyneuropathy</td>
<td>Paraesthesiae and tingling in the feet and thighs for 6 months</td>
<td>&lt;1</td>
<td>Complete improvement of neurological and pulmonary signs after 1 month. Stable without treatment after 7 years</td>
<td>&lt;1</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M/83</td>
<td>I/left hilar and mediastinal lymph nodes</td>
<td>0 years</td>
<td>Length-dependent sensory polyneuropathy</td>
<td>Walking instability for 10 years and pains for the last 3 years, more at night</td>
<td>&lt;1</td>
<td>Complete improvement of neurological and pulmonary signs after 1 month. Stable without treatment after 7 years</td>
<td>&lt;1</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>F/65</td>
<td>N/N</td>
<td>0 years</td>
<td>MFN with conduction blocks Subacute</td>
<td>Progressive walking difficulty for 10 months. Transient numbness of the right foot</td>
<td>&lt;1</td>
<td>Complete improvement of neurological and pulmonary signs after 1 month. Stable without treatment after 7 years</td>
<td>&lt;1</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M/69</td>
<td>N/N</td>
<td>0 years</td>
<td>MFN with conduction blocks Subacute</td>
<td>Progressive walking difficulty for 10 months. Transient numbness of the right foot</td>
<td>&lt;1</td>
<td>Complete improvement of neurological and pulmonary signs after 1 month. Stable without treatment after 7 years</td>
<td>&lt;1</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>F/70</td>
<td>II/bilateral hilar lymph nodes</td>
<td>0 years</td>
<td>MFN with conduction blocks Subacute</td>
<td>Progressive walking difficulty for 10 months. Transient numbness of the right foot</td>
<td>&lt;1</td>
<td>Complete improvement of neurological and pulmonary signs after 1 month. Stable without treatment after 7 years</td>
<td>&lt;1</td>
<td>0.5</td>
<td></td>
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</table>

DTR = deep tendon reflexes; LL = lower limbs; ACE = angiotensin-converting enzyme; n.d. = not done; N = normal. Staging of chest abnormalities: 0 = normal, I = mediastinal or hilar nodes, II = pulmonary diffuse infiltration plus enlarged lymph nodes, III = pulmonary diffuse infiltration without nodes and fibrosis, IV = fibrosis. MFN = multifocal neuropathy; MF = myelinated fibres; NA = necrotizing arteritis. SD = segmental demyelination; WD = Wallerian degeneration.
**Multifocal neuropathy with conduction blocks**

Patient 10 was a 69-year-old man who was in good health when he noticed gradual weakness of right foot dorsiflexion in August 1999. A month later he experienced numbness of the second and third fingers of the right hand and in the left median nerve territory. Numbness extended gradually over the other fingers and to both feet, up to mid-leg level. At referral in December 1999, muscle strength was 3/5 in the left peroneal nerve territory, 4/5 in the right hand and normal in the other territories. He had glove-and-stockin hypoesthesia. His position sense was normal but ankle jerks were decreased. Routine biological tests and radiograms and CT (computed tomography) scans were normal. CSF protein was 0.68 g/l with 2 lymphocytes/ml.

Electrophysiological studies showed 80% conduction block in the left median nerve, with conduction velocity 27 m/s. The CMAP was 4.4 mV after nerve stimulation at the wrist level versus 0.9 mV after stimulation at the elbow level. A 60% conduction block was noted in the left ulnar nerve in the forearm, with CMAP 2.7 mV after stimulation at the wrist level versus 1.2 mV after stimulation of the ulnar nerve below the elbow. A 40% conduction block was found for the median nerve at the forearm level. There was 50% conduction block in the left peroneal nerve at the knee level and decreased SAP in the left sural nerve (1.1 μV, conduction velocity 30.9 m/s).

Multifocal neuropathy with conduction blocks was suspected, but the presence of motor deficit in the lower limbs with electrophysiological signs of axonal lesions of the sural nerve prompted us to perform nerve and muscle biopsy in the affected territory. Numerous perineurial sarcoid granulomas and conspicuous lesions of granulomatous angiitis were present in biopsy specimens. After 6 months on corticosteroids, the patient’s motor deficit had improved in the lower limbs but upper limb involvement remained unchanged. The conduction blocks were no longer detectable and the electrophysiological pattern was that of multifocal axonal lesions. After stimulation of the left median nerve at the elbow and wrist levels, the CMAPs were 3.4 and 3.9 mV, respectively, distal latency was 4.5 ms and conduction velocity 39.4 m/s. Motor conduction of the left ulnar nerve was 40.5 m/s and distal latency 5.6 ms. The CMAP after nerve stimulation below the elbow level was 1.3 mV versus 2.1 mV after stimulation at the wrist level. A year after the onset, the patient’s neurological condition had continued to improve and corticosteroids were withdrawn. The patient retained contact dysaesthesiae of the tip of some fingers on both sides.

**Electrophysiological data (Table 2)**

All patients had features of axonal nerve lesions with the exception of Patient 10, who had multifocal conduction blocks on motor nerves on first examination and an axonal pattern without detectable conduction blocks 6 months later.

**Nerve biopsy findings (Table 2)**

Histopathological studies showed epineurial granulomas in all patients, and perineurial inflammatory infiltrates associated with variable, asymmetrical involvement of nerve fascicles and axon loss (Fig. 1). Endoneurial inflammatory infiltrates and granulomas were found in Patients 1, 2, 4 and 10. They were especially prominent in nerve specimens from Patients 2 and 7. Granulomas predominated around nerve blood vessels (Figs 1–3). They were associated with lymphocytic necrotizing vasculitis in six patients (Patients 1, 2, 4, 7, 8 and 10) (Fig. 2).

Fibre loss varied markedly between nerve fascicles. Patient 5 had nearly normal nerve fibre density in all nerve fascicles and no abnormality on teased fibre preparations. By contrast, Patient 2 had lost most nerve fibres in all but two nerve fascicles (Fig. 1). In most patients, nerve fibre density varied greatly between nerve fascicles, with a high proportion of fibres at different stages of Wallerian degeneration and numerous Büngner’s bands (Table 2). In the nerve specimens with mild endoneurial infiltrates, the infiltrates predominated in the subperineurial space and around endoneurial capillaries. Mononuclear cells also adhered to the endothelium of some capillaries and sometimes occluded the lumen, as confirmed on electron microscopic examination (Figs 1, 3 and 4).

On electron microscopic examination, the unmyelinated fibres were also affected and their density decreased roughly in parallel with that of myelinated fibres. Immunohistochemical labelling revealed that the infiltrates consisted predominantly of macrophages and T cells. CD68+ macrophages constituted the vast majority of cells in the granulomas. Multinucleated giant cells, which result from the fusion of activated macrophages, were also heavily decorated by the monoclonal anti-CD68 antibody (Fig. 2). The proportion of CD4+ T cells was higher than that of CD8+ cells, in keeping with a delayed-type hypersensitivity reaction.

**Muscle biopsy findings**

Besides the non-specific neurogenic atrophy, characteristic non-caseating sarcoid granulomas were found in nine out of the 10 patients who underwent a muscle biopsy. Muscle granulomas were associated with necrotizing vasculitis in two patients (Fig. 2). Due to the difference in thickness of tissue sections, multinucleated giant cells are better seen on paraffin than on plastic embedded specimens (Fig. 2).

In summary, the diagnosis of sarcoid neuropathy was based on the demonstration of multorgan involvement with non-caseating granulomatous infiltrates. Granulomatous infiltrates, with giant cells in most cases, were present in all nerve biopsy specimens. This was the selection criterion. In addition to nerve involvement, all patients had at least one other tissue or organ affected histologically, including muscle in nine patients, lungs and/or intrathoracic lymph nodes in eight, skin in three, arthritis in two and peripheral lymph
Fig. 1 Sarcoid nerve lesions on semithin sections. **Top left**: Patient 4. Cross-section, 1 μm thick, of nerve specimen showing inflammatory granuloma (G) in the epineurial space. The density of nerve fibres is normal in the neighbouring fascicles. Thionin blue staining. Scale bar = 20 μm. **Top right**: Patient 2. Cross-section, 1 μm thick, of nerve specimen showing inflammatory granuloma in the epineurial space spreading to the perineurium (P) and endoneurium, following blood vessels. Only a few nerve fibres are left in this fascicle. Thionin blue staining. Scale bar = 20 μm. **Bottom left**: Patient 2. Cross-section, 1 μm thick, of nerve specimen showing inflammatory granuloma in the endoneurial space. The infiltrate predominates around endoneurial capillaries (V). The density of nerve fibres is also markedly decreased in this fascicle. Thionin blue staining. Scale bar = 20 μm. **Bottom right**: Patient 2. Cross-section, 1 μm thick, at the same level as that of the same nerve specimen shown in the top right and bottom left panels. A normal nerve fascicle is shown, illustrating the asymmetrical involvement of nerve fascicles in sarcoid neuropathy. Thionin blue staining. Scale bar = 20 μm.
nodes, stomach and eye in one patient each (see tables). Thus, all patients had a nerve and at least one other tissue involved, and no other cause of neuropathy.

Discussion
The 11 patients included in this series had been referred for symptomatic peripheral neuropathy that required a nerve biopsy during a period extending from 1989 to 2000. These 11 patients account for 0.31% of the 3475 patients who underwent a nerve biopsy for symptomatic neuropathy in our centre during the same period. In spite of its rarity, this diagnosis should not be missed since it represents a treatable cause of neuropathy.

The spectrum of sarcoid neuropathy
The neuropathic manifestations of sarcoidosis observed in our patients included multifocal subacute and chronic sensorimotor neuropathy and chronic symmetrical sensory polyneuropathy, in keeping with the few cases of sarcoid neuropathy reported so far. One patient presented with a multifocal motor neuropathy that was mistaken for motor neurone disease until the results of muscle and nerve biopsies were available.

Presentation as a GBS-like syndrome with pleocytosis is much less common in sarcoidosis. Although multiple, symmetrical neuropathy roughly mimicked a subacute inflammatory polyneuritis with a progressive onset extending over 3 months in the patient reported by Strickland and Moser (1967), a rapid onset, as in GBS, is very uncommon. Of the two patients reported by Schott et al. (1968), the first manifested a subacute, painful, motor deficit restricted to the lower limbs, with normal nerve conduction velocity and pleocytosis in the CSF, which fits well with the diagnosis of sarcoid neuropathy but not with that of GBS. The patient recovered when treated with corticosteroids. The second patient had a typical but coincidental GBS, from which he recovered spontaneously in a matter of days. In another report, one patient manifested GBS, but nerve granulomas have not been demonstrated in this setting so far (Zuniga et al., 1991). In our patient with the GBS-like neuropathy, the nerve and muscle biopsies were performed because uncommon features of GBS were present, including a relapsing course, electrophysiological signs of axonal involvement and mild pleocytosis in the CSF.

A subacute, multifocal, sensorimotor neuropathy with conduction blocks, as observed in Patient 10, has not been reported in sarcoidosis. Conduction blocks, which typically point to focal demyelination of bundles of nerve fibres, occur in different patterns of acquired inflammatory demyelinating polyneuropathies. This observation shows that typical conduction blocks also occur in peripheral nerves invaded by inflammatory granulomas, as it does in nerves invaded by malignant cells (Said et al., 2000). It is worth noting that, in subsequent electrophysiological recordings performed a few months after starting corticotherapy, only features of axonal neuropathic features were seen.

Facial palsy, which is by far the most common PNS manifestation in sarcoidosis (Matthews, 1984; Stern et al., 1985), was encountered in the only patient of this series who manifested a GBS-like syndrome. In fact, patients with the combination of uveitis, parotid gland enlargement, facial palsy and fever (also called uveoparotid fever or Heerfordt’s syndrome) were not included in our series since they did not require a nerve biopsy for diagnosis. During the same period, we observed three additional patients with prominent facial palsy who we did not include in the study. In two of them the diagnosis of Heerfordt’s syndrome was made. In the last one, facial palsy was associated with a subacute polyradiculoneuropathy and CSF pleocytosis that was attributed to sarcoidosis by biopsying a skin lesion, which made nerve and muscle biopsy unnecessary. This patient responded well to treatment with corticosteroids. She was not included in our series because histological evidence of sarcoidosis was already available from the skin biopsy. Heerfordt’s syndrome was associated with numbness and tingling in the hands and unsteadiness in a patient reported by Feiling and Veiner (1922). These observations show that some overlap is possible between classical Heerfordt’s syndrome and more diffuse meningoarteritis inflammatory involvement in sarcoidosis.

Systemic manifestations of sarcoidosis and neuropathy
Sarcoidosis had been diagnosed before the onset of neuropathic manifestations in only two patients of this series. In six additional patients, several extraneurological manifestations that had occurred 2 months to 12 years prior to the neurological symptoms could be linked to sarcoidosis retrospectively. These manifestations included uveitis (Patient 8), skin lesions (Patients 1, 2 and 7) and arthritis (Patients 1 and 4). Mediastinal lymph nodes or pulmonary involvement were found in eight patients. In three of them, chest involvement was looked for after discovery of granulomas in nerve and muscle biopsy specimens. This proportion of chest involvement in sarcoid peripheral neuropathy in our series is in agreement with that found in a large series in which 78% of the patients with neurosarcoidosis had abnormal findings on chest radiographs, including 54% with only bilateral hilar lymphadenopathy (Sharma, 1997). Thus, even when peripheral neuropathic manifestations are clinically isolated, multi-system involvement is the rule, with mediastinal lymph nodes and muscle lesions as the most common silent lesions. Serum calcium levels were normal in all patients; the concentration of angiotensin-converting enzyme, which was normal in all cases except two (Patients 4 and 6), was a good indicator of disease activity only in Patient 4. This observation confirms that the serum concentration of angiotensin-converting enzyme is of limited value in this sarcoidosis (American
### Table 2  Electrophysiological and pathological findings

<table>
<thead>
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<th>Variable</th>
<th>Patient</th>
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</tr>
<tr>
<td>Electrophysiological data</td>
<td>ASMMN</td>
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<td>MF density (normal range 7500–8000/mm²)</td>
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</tr>
<tr>
<td>Teased fibre preparations</td>
<td>65% WD, 2% SD, 33% normal</td>
</tr>
<tr>
<td>Necrotizing vasculitis</td>
<td>Yes</td>
</tr>
<tr>
<td>Other tissues or organs affected</td>
<td>Muscle</td>
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</table>

Two nerve fibre densities are given for the nerve specimens showing the largest variation in fibre density between fascicles. ASMMN = axonal sensory-motor multifocal neuropathy; NA = necrotizing arteritis.
The antineutrophil cytoplasmic antibodies were within the normal range. It is interesting to note that the skin tuberculin test was negative in all patients but one. Four patients (Patients 3, 6, 9 and 10) had no systemic manifestations of sarcoidosis other than mild elevation of angiotensin-converting enzyme in Patient 6 and alteration of carbon monoxide diffusion in Patient 3, but silent involvement of other organs cannot be excluded. Gallium scans were not performed to look for silent involvement of organs with sarcoidosis, because the results would not have modified the management of the patients. In addition, the specificity of 67Ga scans seems questionable (Rehm, 1999; Abe et al., 2000; Schattner et al., 2001). It is of interest to note that CNS manifestations are not usually associated with peripheral neuropathy, suggesting that the antigen(s) that triggers the hypersensitivity reaction have some tissue specificity.

All patients, except Patient 11, whose neurological deficit was stable before referral, received corticosteroids, with marked and sustained improvement in two patients (Patients 5 and 6). Partial improvement or stabilization was achieved in the other patients. Severe complications of corticotherapy occurred in two patients, leading to death in one (Patient 7). Sarcoid neuropathy often responds well to corticosteroids, but relapses are common and the long-term prognosis remains uncertain.

**Pathophysiological aspects of sarcoid neuropathy**

Sarcoid granulomas were present in nerve and muscle biopsy specimens of our patients and were associated with granulomatous angiitis in six of them. Only a few case of sarcoid granulomas in nerve biopsy specimens have been reported (Oh, 1980; Nemni et al., 1981; Vital et al., 1982; Galassi et al., 1984). Association of sarcoidosis with angiitis has been recognized at autopsy in the CNS and the meninges (Meyer et al., 1953; Alajouanine et al., 1958). In the study of Meyer et al., as in the two autopsy cases of patients with CNS, meningeal and ophthalmological signs reported by Caplan et al. (1983), the granulomas were in the perivascular spaces and adventitia throughout the subarachnoid space and CNS. The granuloma often extended into the media and small arteries often showed acute necrosis of all layers and recent thrombosis. Vasculitis was also found in two patients with sarcoid neuropathy (Oh, 1980; Vital et al., 1982). In six patients in this series, epineurial and perineurial granulomatous angiitis was found, which, considering the small size of the specimens biopsied, shows that necrotizing vasculitis is relatively common in this setting. Epineurial necrotizing vasculitis leads to nerve ischaemia with subsequent axonal degeneration and thus contributes to the onset of symptomatic neuropathy. The six patients with demonstrated necrotizing vasculitis had no specific clinical presentation, but axonal lesions were more pronounced than in the other patients. The occurrence of necrotizing vasculitis in association with granuloma stresses the need to exclude other causes of granulomatous angiitis, especially Wegener’s granulomato-

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**Fig. 2** Muscle lesions in patients with sarcoid neuropathy: granulomas and necrotizing vasculitis. *Top:* Patient 5. Intramuscular sarcoid granuloma showing a multinucleated giant cell in the middle of the inflammatory infiltrate. H&E staining. Scale bar = 50 μm. *Middle:* Patient 5. Anti-CD68-labelled, paraffin-embedded nerve section showing a large granuloma containing many CD68+ macrophages and a multinucleated CD68+ giant cell (arrow). Scale bar = 100 μm. *Bottom:* Patient 7. H&E-stained longitudinal section of a paraffin-embedded muscle specimen showing typical necrotizing arteritis (arrow) with fibrinoid necrosis and leucocytoclasis. Scale bar = 50 μm.

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sis. However, clinical features and biological markers sharply differentiate the two diseases (Urich, 1977; DeReeme, 1994).

From an immunopathological standpoint, sarcoidosis is viewed as a T-cell-mediated inflammatory response to unknown antigenic stimulation (Kataria and Holter, 1997; Tajima et al., 1997). Nerve granulomas and multinucleated giant cells found in sarcoidosis are similar to those encountered in tuberculoid leprosy and in the reversal upgrade reaction of leprosy during treatment of multibacillar leprosy, which are both characteristic of a cell-mediated immune response (Said, 2001). Demonstration of granulomas in the muscle specimen is helpful in order to exclude tuberculoid

Fig. 3 Teased fibre preparations. Top: Patient 10. Teased preparation of the endoneurial content after osmication, showing a granuloma (arrow) surrounding an endoneurial blood vessel. The neighbouring myelinated fibres show irregularity of the myelin sheath. Scale bar = 50 μm. Bottom: Patient 4. Group of osmicated teased fibres showing a mixture of axonal degeneration and segmental demyelination–remyelination (arrows). Scale bar = 100 μm.

Fig. 4 Lesions of endoneurial capillaries. Left: Patient 4. Electron photomicrograph of an endoneurial capillary the lumen of which (star) is occluded by white cells. Scale bar = 2 μm. Uranyl acetate and lead citrate. Right: Patient 8. Electron photomicrograph showing an endoneurial capillary surrounded by an inflammatory infiltrate consisting of mononuclear cells. Note that the lumen of the capillary is also occluded (arrow). Scale bar = 2 μm.
leprosy in patients at risk of leprosy, since leprous granulomas do not affect muscles. Granulomas express a cell-mediated immune response to Mycobacterium leprae antigens in leprosy and to unknown antigens in sarcoidosis. In these settings, memory T cells recruit and activate macrophages which become epithelioid cells and may fuse to multinucleated giant cells. In the meantime they gain secretory capabilities (Adams and Hamilton, 1988) and release noxious secretory products, including proteolytic enzymes, which can induce demyelination or axonal degeneration of neighbouring fibres (Said and Hontebeyrie-Joskowicz, 1992). When the granulomatous infiltrate is located in the epineurium, there is little or no nerve fibre damage. The granuloma may thus remain asymptomatic. The granuloma may become seriously damaged. Infiltration of the vessel wall can lead to fibrinoid necrosis, probably as the result of damage of the vessel wall by secretory products of activated macrophages (Said and Hontebeyrie-Joskowicz, 1992). Necrotizing arteritis can in turn induce ischaemic nerve lesions with axonal degeneration, which appear in addition to those secondary to endoneurial inflammation.

The present series illustrates the wide clinical and pathological spectrum of sarcoid neuropathy. We also show the high frequency of necrotizing vasculitis associated with granulomatous infiltration of peripheral nerves and a potential role for ischaemic nerve lesions in this condition. Treatment with corticosteroids is often efficient but the long-term prognosis of non-cranial sarcoid neuropathy remains uncertain.

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References


