Prospective study of the usefulness of sural nerve biopsy

C M Gabriel, R Howard, N Kinsella, S Lucas, I McColl, G Saldanha, S M Hall, R A C Hughes

Abstract

Objective—This study aimed to determine the usefulness of sural nerve biopsy in neurological practice.

Methods—The first prospective study of sural nerve biopsy in 50 consecutive patients was undertaken. The investigating neurologist declared the prebiopsy diagnosis and management plan and after 3 months an independent neurologist evaluated the contribution of the biopsy to diagnosis and management. An independent audit officer sought information from the patient about the adverse effects and value of the biopsy after 6 weeks and 6 months.

Results—In seven cases the nerve biopsy changed the diagnosis, in 35 cases the biopsy confirmed the suspected diagnosis, and in eight cases the biopsy was non-contributory. The biopsy either changed or was helpful in guiding patient management in 60%, especially those with demyelinating neuropathy and multiple mononeuropathy. Seven patients reported having had infection and 10 reported increased pain at the biopsy site 6 months later.

Conclusion—In a consecutive series of 50 cases, sural nerve biopsy altered the diagnosis in 14%, affected management in 60%, and caused persistent increased pain at the biopsy site in 33%.

Keywords: nerve biopsy; peripheral neuropathy; diagnosis; side effects

Despite publication of expert opinion and guidelines1 2 there is wide variation in the use of nerve biopsy in the diagnosis of peripheral neuropathy. Its diagnostic value has to be balanced against the persistent deficit, paraesthesiae, and pain in the territory of the biopsied nerve, which have been reported in both retrospective and prospective studies.1 4 Retrospective studies risk introducing bias in the assessment of diagnostic usefulness. To overcome this problem we have studied prospectively the cases of 50 consecutive patients undergoing sural nerve biopsy in a neurology department with a special interest in peripheral neuropathy.

Methods

We started a prospective study in December 1994 of patients referred to one of us (RACH) and subjected to nerve biopsy. On each occasion, the investigating neurologist (RACH) was required to declare in advance the preferred diagnosis and management plan in the absence of biopsy information. Patients were classified according to their clinical features and the opinion of an experienced clinical neurophysiologist (Dr JA Payan) as having multiple mononeuropathy, axonal neuropathy or demyelinating neuropathy. For a diagnosis of demyelinating neuropathy the presence of evidence of denervation or axonal dropout was permitted but the patients had to show evidence of partial conduction block or marked slowing of conduction in at least two nerve segments not attributable to local compression. A sural nerve biopsy was performed if the patient had a clinically significant neuropathy of unclear pathogenesis in which a biopsy might disclose a treatable cause. The presence of sensory deficit, preferably dense, in the territory of the sural nerve to be biopsied was an additional factor influencing the decision in favour of biopsy. All biopsies were undertaken as diagnostic procedures. Before attendance at hospital for the biopsy the patient was given a written information sheet describing the procedure and explaining the risk of postoperative pain and wound infection. At the time of hospital attendance the patient received a further oral explanation and signed a form of consent.

The sural nerve biopsy was performed by one surgeon (IMcC) under local anaesthetic (10 ml 1% lignocaine). A 3 cm longitudinal incision was made between the anterior border of the Achilles tendon and the posterior aspect of the fibula so that the lower end of the incision was 6 cm above the lateral malleolus. Care was taken to avoid touching the nerve as it was dissected free from the short saphenous vein. In removing a 3 cm length of nerve it was grasped only at its proximal end and this piece of nerve was discarded. In 3% of cases it proved difficult to anaesthetise the nerve. The incision was closed with continuous nylon. The biopsy was processed for light and electron microscopy using standard techniques as reported previously from our laboratory.1 One portion of the biopsy was fixed in formal saline, processed, and embedded in paraffin for preparation of longitudinal and transverse sections stained with haematoxylin and eosin, Martius scarlet blue for collagen, fibrin and fibrinoid material, solochrome cyanin for myelin, Glems’ for axons, Perl’s iron stain, and Congo red. Teased fibre studies were undertaken on selected cases.

Selected biopsies were examined immuno-histochemically for macrophages (CD68+), B

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cells (CD20+), and T cells (CD3+). Another portion was fixed in phosphate buffered glutaraldehyde and processed into TTAAB resin for preparation of 1 µm sections stained with thionin and acridine orange. Ultrathin sections were cut from selected blocks, contrasted with uranyl acetate and lead citrate, and examined with a Hitachi H7000 electron microscope. The nerve biopsies were interpreted by a pathologist (SL), the investigating neurologist (RACH), and in cases of doubt by a third investigator (SMH). A biopsy was considered to show demyelinating neuropathy when more than five demyelinated or demyelinating nerve fibres were detected in any of the sections. Axonal neuropathy was diagnosed when the myelinated nerve fibre density was considered reduced and an excess of degenerating axons or regenerating sprouts was present. Cases with evidence of both demyelinating and axonal pathology were classified as demyelinating. Morphometry and teased fibre preparations were undertaken in cases of doubt but not routinely. In cases of disagreement the interpretation was achieved by consensus.

Three months after the biopsy, the investigating neurologist declared the “postbiopsy” diagnosis and gave an opinion on a standard form as to whether the biopsy had contributed to the diagnosis and to the management of the patient. A neurologist with an independent practice working in the same medical school but a different hospital (RH) also reviewed all the case notes after 3 months and evaluated the contribution of the biopsies to diagnosis and management.

Six weeks and again 6 months after the biopsy, the patients received a postal questionnaire about side effects and value of the biopsy from an audit officer not involved in their previous care. Patients were assured that their comments would not be made available to the neurologist directing their clinical care. Non-responders were sent two further invitations to reply.

Results

CLINICAL FEATURES

Fifty consecutive biopsies were performed between December 1994 and December 1996 on 30 male and 20 female patients whose ages ranged from 10 to 82 years. These biopsies included 38 from patients who were investigated after assessment in a neuromuscular disease clinic and represented 26% of 146 new inpatients, including four in our intensive care unit with Guillain-Barré syndrome, and two patients transferred directly from another hospital specifically for sural nerve biopsy.

Patients were referred for biopsy at widely varying times after the onset of neuropathic symptoms. There were 26 patients with axonal neuropathy who had had symptoms for a median of 3 years (range 1 week-17 years), 15 patients with demyelinating neuropathy who had had symptoms for a median of 1.6 years (range 1 week-40 years), and nine with multiple mononeuropathy who had had symptoms for a median of 1 year (range 5 weeks-9 years).

DIAGNOSTIC VALUE

In seven cases the investigating and independent neurologists agreed that the nerve biopsy had changed the preferred diagnosis (table 1). In three patients, including one with mild diabetes mellitus, non-specific axonal neuropathy had been expected, but the biopsy demonstrated vasculitis (fig 1). In another three patients, all of whom had an IgM paraproteinaemia, biopsy findings could not have been predicted. The first of these had a demyelinating neuropathy and anti-myelin associated glycoprotein antibodies but the nerve biopsy showed unexpected extensive lymphocytic infiltration of the endoneurium and perineurium diagnosed as lymphomatous neuropathy (fig 2). Another patient with an IgM paraproteinaemia, demyelinating neuropathy, and anti-myelin associated glycoprotein antibodies had widely spaced myelin as expected but the biopsy also showed demyelinated nerve fibres and macrophage infiltration diagnostic of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). In a third patient with IgM paraproteinaemia nerve conduction studies showed an axonal neuropathy, but the nerve biopsy showed occasional demyelinated nerve fibres and 10% of myelinated fibres had widely spaced myelin characteristic of IgM paraproteinaemic demyelinating neuropathy associated with antibodies to myelin associated glycoprotein which were subsequently found in the serum (fig 3). In an adolescent who we have previously reported with an acute motor and sensory neuropathy and inexcitable nerves, the favoured diagnosis before biopsy was acute motor and sensory axonal neuropathy, but the biopsy showed florid active demyelination diagnostic of inflammatory demyelinating polyradiculoneuropathy. The patient subsequently improved rapidly.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Duration of symptoms</th>
<th>Prebiopsy diagnosis</th>
<th>Postbiopsy diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>M</td>
<td>1 year</td>
<td>Idiopathic sensory neuropathy</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>F</td>
<td>3 years</td>
<td>IgM paraproteinaemic neuropathy</td>
<td>CIDP and widely spaced myelin</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>M</td>
<td>40 years</td>
<td>IgM paraproteinaemic neuropathy</td>
<td>Lymphomatous neuropathy</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>M</td>
<td>3 years</td>
<td>IgM axonal neuropathy</td>
<td>Widely spaced myelin</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>M</td>
<td>1 week</td>
<td>AMSAN</td>
<td>AIDP</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>M</td>
<td>9 months</td>
<td>Panacloplastic</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>F</td>
<td>18 months</td>
<td>Diabetes</td>
<td>Vasculitis</td>
</tr>
</tbody>
</table>

AMSAN=acute motor and sensory axonal neuropathy; AIDP=acute inflammatory demyelinating polyradiculoneuropathy; CIDP=chronic inflammatory demyelinating polyradiculoneuropathy.
In 35 cases the independent neurologist judged that the biopsy had contributed by confirming a diagnosis which had already been suspected. In eight cases the independent neurologist considered that the biopsy did not contribute to the diagnosis. In six of these cases it merely confirmed the presence of an idiopathic axonal neuropathy. In one case the nerve biopsy was normal but the patient retained the diagnosis of treatment resistant, predominantly motor, chronic inflammatory demyelinating polyradiculoneuropathy. In the remaining case no nerve tissue was present in the biopsy.

MANAGEMENT VALUE
The independent neurologist considered that the biopsy either changed or had been helpful in guiding the patient’s management in 60% of cases. This proportion was slightly less in those with axonal neuropathy (14/26), than in those with demyelinating neuropathy (11/15) and multiple mononeuropathy (5/9) (table 2). Although not encountered in this series, the investigators have personal experience of cases in which the diagnosis of leprosy, especially pure neural leprosy, was confirmed and sometimes first made by nerve biopsy.

Table 2  Number of patients (%) with different types of neuropathy in whom management was agreed to have been altered or not altered by the biopsy

<table>
<thead>
<tr>
<th>Type of neuropathy (total number of patients)</th>
<th>Altered (%)</th>
<th>Not altered (%)</th>
<th>Disagreed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axonal (26)</td>
<td>14 (54)</td>
<td>10 (38)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Demyelinating (15)</td>
<td>11 (73)</td>
<td>3 (20)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Multiple mononeuropathy (9)</td>
<td>5 (55)</td>
<td>3 (33)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>All (50)</td>
<td>30 (60)</td>
<td>16 (28)</td>
<td>4 (8)</td>
</tr>
</tbody>
</table>

SIDE EFFECTS
Thirty nine patients completed the questionnaire after 6 weeks, 30 after 6 months: 29 returned both questionnaires. Six (15% of responders) reported infection and 21 (67%) increased pain at 6 weeks. Seven (18%) reported having had infection and 10 (33%) increased pain at 6 months. There was no significant difference in the incidence of side effects between different types of neuropathy.

Patient satisfaction
Thirty one (79%) of the 39 patients who responded after 6 weeks and 19 (63%) out of 30 who responded after 6 months were very or fairly pleased that they had had the biopsy. Almost all of those who declared that they were “slightly” or “very unhappy” (five out of the remaining eight at six weeks and nine out of 11 at 6 months) had idiopathic axonal neuropathy.
nerve biopsy contributed to the diagnosis in 38% of 53 patients. In another, Neundorfer et al. considered that the biopsy was “crucial” for establishment of the diagnosis in 27% of 36 patients and confirmed a previously suspected diagnosis in 37%. In the largest retrospective study Oh et al. reported helpful or relevant information in 45% of 385 biopsies. In a study of 100 patients over the age of 65 years with disabling neuropathy, studied retrospectively, more than one third had a vasculitic neuropathy, and a further 25% had either CIDP or dysglobulinaemic neuropathy.

**FACTORS WHICH AFFECT DIAGNOSTIC YIELD**

In one retrospective study nerve biopsy was more likely to be useful in diagnosis if the clinical presentation was with multiple mononeuropathies or if neurophysiological tests showed that motor nerve conduction velocities were markedly slowed. In our own study the percentages of patients in whom the diagnosis was altered by the biopsy was somewhat less in the axonal than the demyelinating and multiple mononeuropathy subgroups but the difference was not significant.

**MANAGEMENT VALUE**

To be of real value to the patient an investigation should not only change the diagnosis but should also alter the management and lead to an improved outcome. In our study an independent neurologist considered that management had been affected by the biopsy in 60% of patients. This percentage included patients in whom new treatments were instituted, those in whom treatment was being considered but was not introduced as a result of the biopsy, and those in whom other aspects of care were affected. There was no significant difference in the proportions of patients with demyelinating neuropathies, axonal neuropathies, or multiple mononeuropathies whose management was altered. Argov et al. found a management effect in half of their 120 patients.

**COMPLICATIONS**

The incidence of side effects after biopsy is significant. Two thirds of our patients who answered a questionnaire reported increased pain at 6 weeks and one third reported increased pain at 6 months. It is possible that those with side effects were more likely to respond than those without side effects. Persisting pain or dysesthesia has previously been reported in 11%-58%, although at 5 years all patients have been found to have non-troublesome mild dysesthetic symptoms only. If possible, we perform sural nerve biopsy in patients in whom the sural nerve territory is already anaesthetic in the belief that troublesome postoperative sensory loss and pain will be less. Our results showed that the incidence of numbness perceived as a problem was significantly greater in patients in whom the sural SAP had been detectable before biopsy. There was also a trend for pain at the biopsy site to be more likely in these patients.

**PERSPECTIVE STUDY OF THE USEFULNESS OF SURAL NERVE BIOPSY**

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**DIAGNOSTIC VALUE**

The greatest diagnostic value of an investigation comes from the demonstration of a diagnosis which was not previously suspected or, at least, was not the preferred diagnosis. This happened in seven (14%) of the nerve biopsies in this series. Of lesser value is an investigation which establishes a diagnosis which was previously the preferred diagnosis, as in 35 (70%) of our cases, as it could be argued that the management could have proceeded based on the previous diagnostic preference. Of least value were the eight (16%) biopsies which showed either a non-specific axonal neuropathy or no information. The results of this prospective study have disclosed greater diagnostic usefulness than previous retrospective studies. In a retrospective study of our own biopsies we had noted a change in diagnosis in 17% of 36 patients. In one retrospective study Argov et al. considered that the biopsy was “crucial” for establishment of the diagnosis in 27% of 36 patients and confirmed a previously suspected diagnosis in 37%. In the largest retrospective study Oh et al. reported helpful or relevant information in 45% of 385 biopsies. In a study of 100 patients over the age of 65 years with disabling neuropathy, studied retrospectively, more than one third had a vasculitic neuropathy, and a further 25% had either CIDP or dysglobulinaemic neuropathy.

**RELATION OF SIDE EFFECTS TO SURAL NERVE ACTION POTENTIALS AND TYPE OF BIOPSY**

In 27 patients the sural nerve sensory action potential (SAP) had been absent on the side of the biopsy, in 12 it was less than 5 µV, and in 11 greater than 5 µV. The relative risk of a report of new numbness in patients with a detectable sural SAP was twice that in those with an absent SAP (p<0.05, 95% CI 1.08–3.97). The relative risk of pain was 1.72, although this did not reach statistical significance (95% CI 0.94–3.15). Twenty four patients had full thickness biopsies, usually because of the possibility of vasculitis, and 26 had fascicular biopsies. The proportion of patients with pain was similar in those who had full thickness and fascicular nerve biopsies.

**DISCUSSION**

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Despite the reports of side effects at 6 months after the biopsy, almost two thirds of our patients were pleased they had had the procedure. However, nearly a fifth reported that they were slightly or very unhappy. The explanations given by the patients for their unhappiness included negative results, absence of treatment, and increased numbness or pain. These comments suggest that the patients had higher expectations of the procedure despite previous oral and written explanations.

PRACTICAL ISSUES
The practice of fascicular nerve biopsy was introduced in an attempt to reduce the neurological deficit and chronic dysesthesia arising from biopsy of the whole nerve. However, a longer term study has challenged this, demonstrating similar restoration of sensation after both procedures and no significant difference between the groups after at least 5 years. This last study suggested that by cutting interfascicular branches and damaging the vasa vasorum during fascicular biopsy, more fascicles may be damaged than anticipated. In our practice, biopsy of the whole nerve was reserved for those patients in whom an interstitial process was suspected (and three cases of unexpected vasculitis were discovered). Our study did not show a significant difference in incidence of painful paraesthesiae or other complications after full thickness compared with fascicular biopsy although the sample sizes were insufficient to exclude major differences. Most patients already had significant deficits or pain in the territory of the sural nerve, which complicated the interpretation of this analysis.

Conclusions
In this series sural nerve biopsy altered the diagnosis in 14% and affected management in 60% of 50 consecutive patients. Six months after the biopsy 63% of respondents were pleased to have had the procedure but 33% reported increased pain at the biopsy site. These findings are consistent with published retrospective studies. Consequently, although sural nerve biopsy can be a useful diagnostic procedure in selected cases, patients should be warned of the infection and discomfort which may follow nerve biopsy as well as the diagnostic and management benefits. We prefer to recommend nerve biopsy only in patients with significant, distressing, progressive symptoms, dense sensory loss in the territory of the nerve being biopsied, and failure to achieve a diagnosis by less painful means.

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