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ORIGINAL ARTICLE

Sural nerve biopsy in peripheral neuropathies: 30-year experience from a single center

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Abstract

Introduction Nerve biopsy has been widely used to investigate patients with peripheral neuropathy, and in many centers, it is still a useful diagnostic tool in this setting. In this study, we reviewed the histopathological spectrum of the nerve biopsies performed in our center in a 30-year period and we analyzed their relevance in the clinical setting.

Materials and methods Retrospective analysis of the retrieved data was done for cases of nerve biopsies performed in our institute between 1988 and 2018. Surgical technique and histopathological analysis were done accordingly to standard protocol.

Results Complete clinical and pathological data were available only for 717 cases. The procedure was generally safe, with only 0.3% superimposed infection. Main pathological results were "unspecific" axonal polyneuropathy (49.8%), vasculitis neuropathy (9.3%), acquired demyelinating neuropathy (8.9%), and Charcot-Marie-Tooth (8.2%). Considering clinical-neurophysiological suspicion of vasculitis, nerve biopsy confirmed the diagnosis in 60.9% of cases.

Discussion In conclusion, for inherited neuropathies, we do not recommend this invasive procedure, but we strongly suggest a genetic test. Conversely, in vasculitic neuropathies or in dysimmune neuropathies not clearly confirmed by neurophysiological examination, nerve biopsy continues to represent a useful and irreplaceable tool.

Keywords Nerve biopsy · Neuropathy · Amyloid · Vasculitis · CIDP · CMT · IgM-related neuropathy

Introduction

Nerve biopsy has been largely used in past decades for the diagnosis of peripheral nerve diseases. Its usefulness in the past was principally based on the presence in many neuropathies of peculiar lesions that make the diagnosis simple in some cases. Finding in a pathological specimen amyloid deposits or cell infiltrations, or identifying the pattern of axonal loss (i.e., whether it is homogeneous or not among fascicles), sometimes is crucial for the diagnosis of amyloidosis, vasculitis, or immune nerve diseases [1]. Moreover, some lesions are so specific, such as the presence of very large axons in giant axonal neuropathy [2], or myelin outfoldings in Charcot-Marie-Tooth 4B [3], that nerve biopsy could be conclusive for the final diagnosis. In addition, other technics and instruments, such as immunohistochemistry and electronic microscopy, could improve the possibility of nerve biopsy to clarify many doubts in diagnosis and clinical management [4–6].

On the other hand, nerve biopsy has low sensibility in most of the diseases that could be easily identified: amyloid was found in 13 of 19 patients in a report including AL patients [7], and pathological evidences of nerve vasculitis are present in a variable

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percentage (20–58%) in different papers [8, 9]. Moreover, diagnosis in many neuropathies is based principally on clinical and neurophysiological features, or on genetic tests, indicating nerve biopsy only as a supportive criterion [10, 11].

Another problem is that in literature there are few shared guidelines about technical and evaluation procedures and they are based on short cases: generally, the interpretation of nerve biopsy is limited to a small number of expert pathologists and/or neurologists [12].

Peripheral Nerve Society guidelines restricted the use of nerve biopsy to few specific cases: nerve vasculitis, infectious neuritis (i.e., for leprosy), neuropathies for metabolic or storage deposits (amyloidosis, glycogenosis), chronic inflammatory neuropathies, primary or secondary neoplasia, and some genetic diseases with peculiar lesions (i.e., MTMR2 with myelin out-foldings) [12].

In this paper, we reviewed the histopathological spectrum of the nerve biopsies performed in our center in a 30-year period and we analyzed their relevance in the clinical setting.

Methods

Surgical procedure

All patients had their biopsies performed in our institution under local anesthesia, between 1988 and 2018. Nerve biopsies were taken from the sural nerve, posterior to the lateral malleolus. Approximately 4–5 cm of nerve were resected. Skin closure was done using 5–7 interrupted nylon sutures. A pressure bandage was applied post-operatively, and patients were instructed to rest as much as possible for 48 hours after surgery. Sutures were removed by the surgeon 10–14 days post-operatively.

Nerve analysis

After removal, the nerve specimen was prepared without delay. Routinely, we divided it into two specimens [13]. The first specimen was frozen, then stained with hematoxylin and eosin for study of interstitial tissue, vessels, or presence of inflammatory cells; when necessary, other stainings were performed (i.e., Congo red for detecting amyloid) or direct immunofluorescence was carried out to confirm or characterize inflammatory cells (i.e., CD4 or CD8) or protein deposits (i.e., amyloid or light chains) [13, 14]. The second one was fixed in 2.5% glutaraldehyde in 0.05 M sodium cacodylate buffer for 1–3 hours, then post-fixed in 1% osmium tetroxide and embedded in a resin (epoxy resin) and in LR-white (London-resin white) for immuno-electron microscopy [13]. In order to visualize nerve fiber alterations (i.e., axonal degeneration, loss of small- and large-diameter fibers, axonal sprouts, demyelinating fibers, onion-bulb formations), transverse semi-thin sections were stained with toluidine blue then examined under a light microscope. If necessary, after staining with uranyl acetate and lead citrate, ultrathin sections were examined by electron microscopy (EM) [13]: ultrastructural examination was valuable for a thorough study of a peripheral nerve and was usually carried out on cross sections, sometimes on longitudinal sections to study specific structures, such as nodes of Ranvier, intra-axonal mitochondria, etc. Nerve myelinated fiber density (on semi-thin sections) and unmyelinated fiber density (on ultrathin sections) were evaluated [13]. Teased nerve fiber analysis (dissociation of individual myelinated nerve fibers) was also performed when necessary [13].

Statistical analysis

Fisher's exact test was used for comparing frequencies. The significance level was set at $p < 0.05$.

Results

Surgical procedure

Sural nerve biopsy was performed in 932 patients in the examined period. Complete clinical and pathological data were available only for 717 cases: 434 were male (60.5%) with a mean age at procedure of 54.9 years, and 283 were female (39.5%) with a mean age at procedure of 54.5 years. Only 5 biopsies (0.7%) were technically not satisfying because no fascicle was identified into.

In the first 16 years (1988–2003), 482 biopsies (67.2%) were performed, while the remaining 235 (32.8%) were done in the following 15 years (2004–2018): a great proportion (388 cases, 54.1%) of patients underwent biopsy in a 8-year period (1998–2005) (Fig. 1).

Age at biopsy varied consistently during the observation period (Table 1): generally, a high proportion of patients with young age underwent nerve biopsy in the 1988–2004 period (Table 1).

Nerve biopsy was generally a safe procedure: only in 2/717 (0.3%) patients we experienced a superimposed infection treated with antibiotic therapy. Reduced sensation in the distribution of the sural nerve, compared with the contralateral leg, was reported by 132/717 (18.4%) patients examined, although this was variable; only 72/717 (10%) reported pain.

Nerve analysis

Major pathological findings are summarized in Table 2. Sural nerve biopsy was diagnostic for a defined neuropathy in about a third of cases (235/717, 32.8%): main biopsy results are summarized in Table 3.

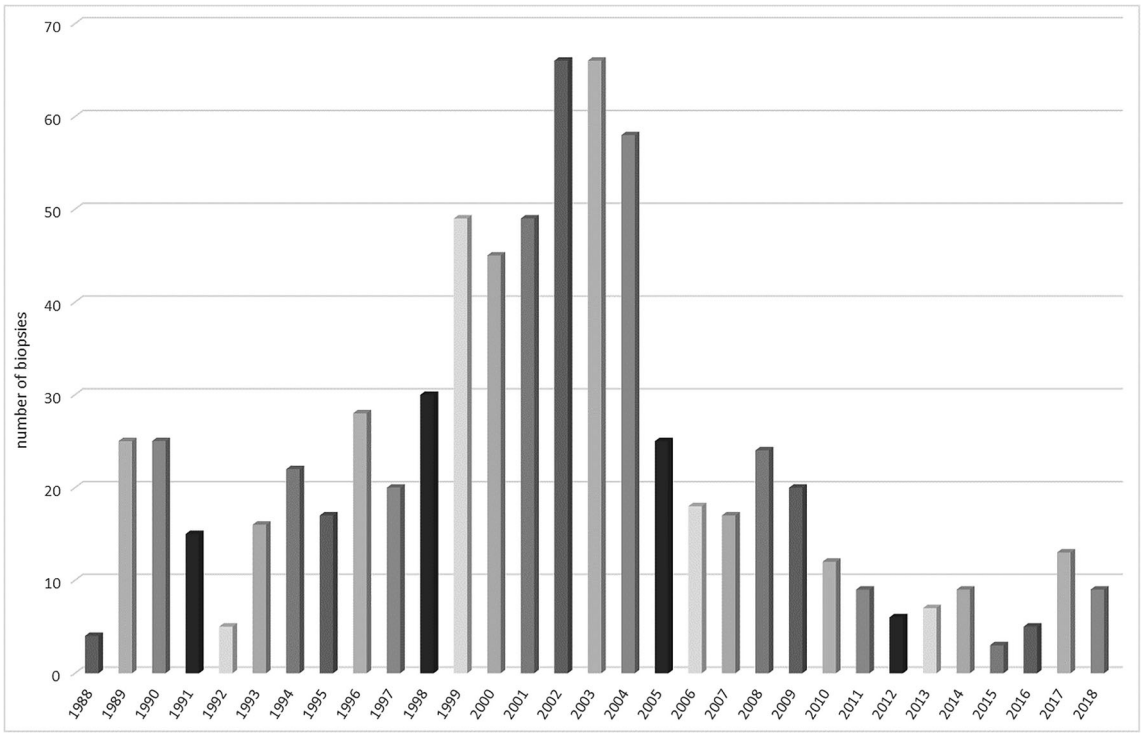

Fig. 1 Histogram of nerve biopsies during the observation period

Considering a specific clinical suspicion, we observed a confirmation of clinical-neurophysiological diagnosis (or highly supportive information) for different conditions in the following proportion:

– Vasculitic neuropathy: 67/110 (60.9%). Pathological findings were pathognomonic (fibrinoid necrosis with inflammatory infiltrates) or supportive (inflammatory infiltrates, asymmetrical axonal loss, sub-endoneurial edema, perineural microfasciculation). Direct immunofluorescence to characterize infiltrates was performed in 34/67 (50.7%) [15, 16] (Supplementary Fig. 1).

Table 1 Age distribution at nerve biopsy

Age range	Nerve biopsies (percentage)					
	Period 1988–2004			Period 2005–2018		
	Male	Female	Total	Male	Female	Total
0–10	14	5	19 (3.5%)	0	0	0 (0%)
11–20	20	14	34 (6.3%)	2	0	2 (1.1%)
21–30	18	10	28 (5.2%)	3	4	7 (4.0%)
31–40	35	23	58 (10.7%)	9	5	14 (7.9%)
41–50	47	36	83 (15.4%)	11	6	17 (9.6%)
51–60	49	42	91 (16.9%)	18	15	33 (18.6%)
61–70	81	47	128 (23.7%)	31	17	48 (27.1%)
71–80	55	32	87 (16.1%)	30	19	49 (27.7%)
81–90	7	5	12 (2.2%)	4	3	7 (4.0%)

Table 2 Main pathological results of nerve biopsies

Pathological findings	Abnormal biopsies (%)
Axonal loss	566/717 (78.9)
Mild	97/566 (17.1)
Moderate	161/566 (28.5)
Severe	248/566 (43.8)
Asymmetric	60/566 (10.6)
Regeneration clusters	140/717 (19.5)
Wallerian degeneration	271/717 (37.8)
Onion bulbs	121/717 (16.9)
Amyloid deposits (Congo red positive)	17/99 (17.2)
Inflammatory infiltrates	74/717 (10.3)
Teased fiber analysis (Dyck classification)	
Stage A	201/514 (39.1)
Stage B	11/514 (2.2)
Stage C	71/514 (13.8)
Stage D	56/514 (10.9)
Stage E	49/514 (9.5)
Stage F	44/514 (8.6)
Stage G	13/514 (2.5)
Stage H	56/514 (10.9)
Stage I	13/514 (2.5)

Table 3 Sural nerve biopsy conclusions

Nerve biopsy conclusion	Total number of cases (%)	Number of cases, 1988–2004 (%)	Number of cases, 2005–2018 (%)	*p* value
Not evaluable	5/717 (0.7)	3/540 (0.6)	2/177 (1.1)	n.s.
Normal	120/717 (16.7)	113/540 (20.9)	7/177 (4.0)	< 0.0001
"Unspecific" axonal neuropathy	357/717 (49.8)	272/540 (50.4)	85/177 (48.0)	n.s.
Vasculitic neuropathy	67/717 (9.3)	30/540 (5.6)	37/177 (20.9)	< 0.0001
Acquired demyelinating neuropathy	64/717 (8.9)	45/540 (8.3)	19/177 (10.8)	n.s.
CIDP	43/717 (6.0)	36/540 (6.6)	7/177 (4.0)	n.s.
Anti-MAG neuropathy	21/717 (2.9)	9/540 (1.7)	12/177 (6.8)	0.0013
CMT	59/717 (8.2)	51/540 (9.4)	8/177 (4.5)	0.0403
Amyloidosis or protein deposits	19/717 (2.7)	8/540 (1.5)	11/177 (6.2)	0.0018
TTR	16/717 (2.2)	8/540 (1.5)	8/177 (4.5)	0.0340
AL	1/717 (0.2)	0/540 (0)	1/177 (0.6)	n.s.
Light chain deposition	2/717 (0.3)	0/540 (0)	2/177 (1.1)	n.s.
HNPP	15/717 (2.1)	11/540 (2.0)	4/177 (2.3)	n.s.
Diabetic neuropathy	6/717 (0.8)	4/540 (0.7)	2/177 (1.1)	n.s.
Lymphoma of peripheral nerve	2/717 (0.3)	0/540 (0)	2/177 (1.1)	n.s.
AIDP	2/717 (0.3)	2/540 (0.4)	0/177 (0)	n.s.
GAN	1/717 (0.2)	1/540 (0.2)	0/177 (0)	n.s.

Abbreviations: *n.s.* not significant, *CIDP* chronic inflammatory demyelinating polyneuropathy, *MAG* myelin-associated glycoprotein, *CMT* Charcot-Marie-Tooth, *TTR* transtiretin, *HNPP* hereditary neuropathy with liability to pressure palsies, *AIDP* acute inflammatory demyelinating polyneuropathy, *GAN* giant axonal neuropathy

- Amyloidotic neuropathy: 17/43 (39.5%). Pathological findings revealed amyloid deposits with positive Congo red staining. Direct immunofluorescence with anti-TTR or anti-light-chain (kappa and lambda) antibodies was available for 8/17 (47.0%), confirming TTR deposits in 7 cases and AL in the remaining one [17, 18] (Supplementary Fig. 2).
- Chronic inflammatory demyelinating polyneuropathy (CIDP): 43/139 (30.9%). Pathological findings were heterogeneous, including axonal loss (with symmetric distribution or not), onion bulbs, inflammatory infiltrates, fibers with thin myelin sheath, and segmental demyelinations [10] (Supplementary Fig. 3).
- Anti-MAG-associated neuropathy: 21/25 (84.0%). Pathological findings were heterogeneous, including variable degree of axonal loss, myelin out-foldings, widening myelin lamellae, and IgM deposition on the myelin sheath [14] (Supplementary Fig. 4).

In single cases, nerve biopsy showed specific clues for final diagnosis, namely giant axonal neuropathy [2], hereditary neuropathy with liability to pressure palsies [19], Charcot-Marie-Tooth 4B [3], Charcot-Marie-Tooth 2E [20], light-chain deposition disease [21], and isolated lymphoma of the peripheral nerve [22].

Discussion

Sural nerve biopsy has been widely used in our center in the last 30 years as a useful tool to diagnose peripheral neuropathy [14, 16–25]. The surgical procedure has been confirmed to be safe with only 0.3% of cases reporting serious side effects. In about 20% of patients, a different degree of hypoesthesia along the sural nerve sensory distribution was reported: probably, this low percentage is influenced by the underlying peripheral neuropathy that could affect the contralateral sural nerve too. Furthermore, pain that could worsen quality of life was reported by only 10% of the patients [26].

Considering the total amount of biopsies, a great proportion (67.2%) was done in the first 16 years; in our opinion, this data was influenced by the changing of indications during the years. Furthermore, about half of the biopsies was done only in 8 years (1998–2005), when the biopsy technique was diffuse and easy to perform, and the indications were wider.

Between 1988 and 2004, 25.7% of patients were 40 years old or younger compared with only 13.0% in the following period ($p = 0.004$): obviously, this result is explained by patients with inherited neuropathy that, before the diffusion of genetic tests, almost always underwent nerve biopsy [27]. Furthermore, also the number of biopsies diagnostic for CMT was significantly slightly higher in this period (1988–

2004) if compared with the following one (2005–2018), confirming our hypothesis (Table 3).

Considering pathology, about 18% of the samples were found to be unremarkable or not evaluable, and the main conclusion (about 50%) was "unspecific" axonal neuropathy: this "diagnosis" showed a similar frequency in both periods examined (1988–2004 vs 2005–2018); conversely, "normal" pathological findings were less frequently observed in the last years (Table 3), probably indicating a more strict indication for the procedure.

However, similarly to other studies [28], we reached a pathological diagnosis in a quarter of cases. The most frequent diagnosis was vasculitis (9.3%), confirming this strong indication for nerve biopsy [29, 30]. Conversely, amyloidosis, which is also considered as a possible indication, was not so frequently found (2.7%): in the last years, even if this diagnosis for the genetic form was slightly more frequent if compared with that of the past (Table 3), we understood that negative biopsies are quite common in late-onset amyloidosis and do not exclude the diagnosis [17].

Considering the utility of nerve biopsy in confirming a clinical-electrophysiological suspicion, the highest rate of success was observed for vasculitis (60.9%); however, also in this condition, negative pathological findings do not exclude the diagnosis [15]. Diagnosis of vasculitis was also more frequent in the last years (Table 3), further confirming a more strict indication for nerve biopsy.

Regarding other inflammatory/dysimmune neuropathies, CIDP was diagnosed in about 30% of cases: pathological aspects of this disease are heterogeneous and could explain the data [31]. Considering all cases with pathological diagnosis of CIDP, in about a third of these (13/43, 30.2%), neurophysiological results were uncertain, so nerve biopsy turned out to be a crucial tool to confirm diagnosis; conversely, cerebrospinal fluid examination was available only for half of the patients (22/43, 51.2%), and it showed an increase of proteins in only a third of cases (7/22, 31.8%).

On the other hand, 84% of biopsies showed pathological findings confirmatory for anti-MAG neuropathy, but in these cases, the titer of antibodies led to the diagnosis [32]. Anti-MAG neuropathy was more frequently diagnosed in the last period (Table 3), considering the utility of nerve biopsy to detect uncommon mechanisms of nerve damage [14].

Finally, for single cases of rare diseases, nerve biopsy determined the diagnosis and therefore was the main diagnostic tool [33–39].

In conclusion, also in our cohort, we confirmed that sural nerve biopsy is a safe procedure. However, under suspicion of a genetic disease, such as CMT or amyloidosis, we do not recommend this invasive procedure, but we strongly suggest genetic tests directly. Conversely, in inflammatory neuropathies, such as vasculitis, or in dysimmune neuropathies not clearly confirmed by neurophysiological examination, nerve biopsy continues to represent a useful and irreplaceable tool.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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