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Original articles

Nerve biopsy : indications and contribution to the diagnosis of peripheral neuropathy

The experience of the Born Bunge Foundation University of Antwerp and University of Liege between 1987 and 1997

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Abstract

We reviewed 355 nerve biopsies analysed at the Laboratories of Neuropathology of the Born-Bunge Foundation/University of Antwerp (BBF/UIA) and University of Liège (ULg) between 1987 and 1997. We examined the indications for nerve biopsy, the yield of the procedure, and the influence of clinical and neuropathological parameters. Contributory biopsies accounted for 35.5% and 47.3% respectively at ULg and BBF/UIA laboratories : of these, one third showed specific histological findings, the majority being informative only when combined with the relevant clinical data. The profile of indications for nerve biopsy was roughly comparable in both laboratories. The search for an inflammatory neuropathy prompted 35-40% of all biopsies with more than 50% of specimens being informative in this indication. The lowest yield (20%) was obtained among the nerve biopsies performed in the absence of any presumptive aetiology. These accounted for 22-33% of all cases. Inadequate surgical resection, delays in transport or processing errors precluded histological study of 4% (BBF/UIA) to 8% (ULg) of the specimens. We conclude that nerve biopsies should be performed by experienced surgeons and handled in specialised laboratories. Only a relatively small number of causes of neuropathy can be diagnosed on the basis of histology alone. More often, contributory biopsies will result from the combination of non-specific suggestive histological features with relevant clinical information. The diagnostic yield of nerve biopsy is function of careful patient selection and close collaboration between the clinician and the neuropathologist.

Key words : Neuropathy ; nerve biopsy ; CIDP ; indication ; vasculitis.

Introduction

Peripheral neuropathy is a common disease in the Western world. Recent surveys from Italy and France have estimated the prevalence of peripheral neuropathy at 3.4-3.5% in the elderly (Hessel *et al.*, 1986 ; The Italian General Practitioner Study Group (IGPSG), 1995, while the incidence of polyneuropathy in the USA is 40/100.000 (Kurtzke, 1982). In a majority of cases, the neuropathy only results in minor discomfort such as limited paresthesia or hypoesthesia, or occasional muscle cramps, and patients do not seek further medical attention. In these cases, the aetiology is most often metabolic, toxic or nutritional with diabetes mellitus and alcoholism as predominant causes (IGPSG, 1995). However, in a subset of patients, peripheral neuropathy manifests as a disabling and/or painful condition motivating neurological consultation. In selected series from hospitals, metabolic, toxic and nutritional causes still represent 50% of aetiologies. Other causes include : inflammatory neuropathy (10-20%), inherited disease (10-20%), and associated neoplasm (5-10%) (Hessel *et al.*, 1986 ; Bouche *et al.*, 1992 and 1998).

It is generally admitted that in 10-20% of cases, no aetiology is found despite extensive investigation (McLeod *et al.*, 1984 ; Vallat *et al.*, 1984 ; Argov *et al.*, 1989 ; Corvoisier *et al.*, 1987 ; Graham *et al.*, 1991). Among these patients with cryptogenic neuropathy, those who are affected by a disabling and/or painful disease of recent onset or progression are potential candidates for a nerve biopsy. For any patient, the decision to undertake a nerve biopsy will have to weigh the potential benefit of histological examination and the possibility of subsequent treatment or genetic counselling against the post-operative sequelae. As there is no international consensus on the indications for nerve biopsy, clinicians often have to rely on the various and sometimes discordant guidelines published in the recent literature (Oh 1990 ; Dyck *et al.*, 1992 and 1996 ; Rappaport *et al.*, 1993 ; Midroni and Bilbao, 1995b ; Chia *et al.*, 1996 ; Bouche *et al.*, 1998 ; Schröder, 1998).

Reviewing the collections of nerve biopsies analysed at the laboratories of neuropathology of Born-Bunge Foundation/University of Antwerp (BBF/UIA) and University of Liège (ULg) between 1987 and 1997, we selected 355 nerve

biopsies from patients over 12 years of age with sufficient clinical information to determine : a) the indications for nerve biopsy, b) the yield of the procedure, and the influence of clinical and neuropathological parameters (Deprez *et al.*, 2000).

Indications to the nerve biopsy

The annual number of nerve biopsies analysed at the laboratories of ULg and BBF/UIA has gradually increased between 1987 and 1998 as shown in Figure 1. This may seem unexpected given the continuous development of alternative procedures for the diagnosis of neuropathies. This is particularly true for hereditary conditions such as hereditary motor and sensory neuropathies (HMSN), hereditary neuropathy with liability to pressure palsies (HNPP) and various metabolic inherited diseases for which molecular genetic analysis of lymphocytes, biochemical screening and alternative sites of biopsy are now the procedures of choice (Bouche *et al.*, 1992 ; McCarthy et al ., 1995 ; Midroni and Bilbao, 1995b ; Martin *et al.*, 1996 ; Ceuterick-de Groote *et al.*, 1998 ; Schröder, 1998).

The profile of indications for nerve biopsy, roughly comparable in both laboratories during the period studied, provides some insights into the causes of the increased use of this procedure (Table 1, columns 1, 2 and 3).

a) The most frequent indication was the absence of any presumptive aetiology at the time of biopsy (22-33% of cases). This loosely refers to the category of cryptogenic neuropathies although this term obviously encompasses different subgroups according to the extent of pre-operative investigation (Matthews, 1952 ; Dyck *et al.*, 1981 ; Fagius, 1983 ; McLeod *et al.*, 1984 ; Vallat *et al.*, 1984 ; Hessel *et al.*, 1986 ; Corvoisier *et al.*, 1987 ; Graham *et al.*, 1991 ; Notermans *et al.*, 1993). In this study, 67% of the patients included in this category had clinical and electrophysiological characteristics similar to those described in previous studies on cryptogenic neuropathy : a mean age of 62 years, sensory or sensory-motor polyneuropathy, with a distal and symmetric topography, and electrophysiological findings of predominantly axonal neuropathy (Matthews, 1952 ; Dyck *et al.*, 1981 ; Fagius, 1983 ; Asbury and Gilliatt, 1984 ; McLeod *et al.*, 1984 ; Corvoisier *et al.*, 1987 ; Graham *et al.*, 1991 ; Bouche *et al.*, 1992 ; Notermans *et al.*, 1993).

b) Biopsies undertaken for suspected vasculitis and suspected chronic inflammatory demyelinating polyneuropathy (CIDP) each accounted for about 10% of cases. Moreover, the search for an inflammatory neuropathy was often also part of the differential diagnosis in those patients with multiple potential causes, raising the total frequency to 35-40% of all biopsies analysed. These rather high figures may indicate an increasing clinical awareness of the wide spectrum of presentations of these potentially treatable inflammatory neuropathies (Vincent *et al.*, 1985 ; Harati and Niakan, 1986, Dyck *et al.*, 1987 ; Said *et al.*, 1988 ; Barohn *et al.*, 1989 ; Hawke *et al.*, 1991 ; Azulay *et al.*, 1992 ; Kissel and Mendell, 1992 ; Serratrice *et al.*, 1994 ; Smalland Lovelace, 1994 ; Midroni and Bilbao, 1995c ; Deprez et al, 2000). Accordingly, the benefits of combined muscle and nerve biopsy have been shown in the diagnosis of vasculitis affecting the peripheral nervous system (PNS). However, it should be emphasised that the value of microscopic examination for the diagnosis of CIDP is still a matter of debate due to the lack of specificity of most associated histological findings (Barohn *et al.*, 1989 ; Krendel *et al.*, 1989 ; Gabreels-Festen *et al.*, 1993 ; Small and Lovelace 1994 ; Midroni and Bilbao, 1995b).

c) Clinical suspicion of HMSN motivated 13-15% of the biopsies with 65% of these having been performed before 1992. In the earlier years of the study, a large number of biopsies were performed in suspected HMSN I and HNPP and they often brought contributory information. They were pro-

Table 1

Nerve biopsy : indications and yield (N = 355)

Indication	Frequency		Contributory biopsies	
	BBF	ULg	BBF	ULg
No working Diagnosis	33%	22%	21%	18%
Suspected CIDP	12%	12%	64%	47%
Suspected vasculitis	13%	6%	50%	66%
Multiple potential causes	15%	20%	42%	19%
HMSN	15%	13%	79%	71%
Other metabolic diseases	7%	11%	22%	37%
Substantiate PNP	5%	16%	*	*

BBF : Laboratory of Neuropathology of the Born Bunge Foundation and University of Antwerp. ULg : Laboratory of neuropathology of the University of Liege. CIDP : Chronic Inflammatory Demyelinating Polyneuropathy. PNP : Polyneuropathy. HMSN : Hereditary Motor and Sensory Neuropathy.

* This category was not included in the evaluation of the yield of the nerve biopsy because the type of answer "yes or no" corresponds to a 100% yield.

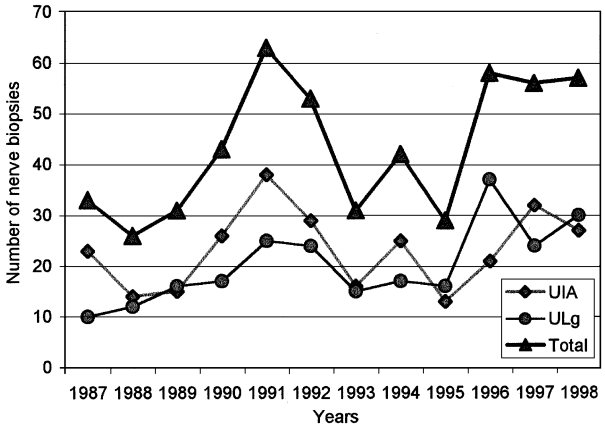

FIG. 1. — Number of nerve biopsies examined at the laboratories of ULg and BBF/UIA between 01/01/1987 and 31/12/1998.

gressively replaced by the less invasive techniques of molecular genetics. Later biopsies were prompted by discordance between clinical and genetic data in cases of HMSN I, or suspected HMSN II and V. In HMSN II, however, histological changes are rather non-specific as they show a predominantly axonal neuropathy with large diameter fibre attrition, numerous regenerative clusters and occasional small onion bulbs.

d) There were significant differences between the two laboratories with respect to the proportion of nerve biopsies performed to substantiate a neuropathic process, with 16% and 5% of cases respectively at ULg and BBF/UIA. This category encompassed a) cases with discordance between the patient's complaint and clinical and/or electrophysiological findings, b) a differential diagnosis between amyotrophic lateral sclerosis (ALS) and genuine polyneuropathy, and rarely, c) between neuropathy and myopathy.

Contribution of nerve biopsy to the final diagnosis

To evaluate the yield of nerve biopsies, we referred to the criteria published by Midroni *et al.* (Midroni and Bilbao, 1995b) and Argov et al (Argov *et al.*, 1989). Contributory biopsies provided information that was either essential or helpful for the patient's management. Essential biopsies showed abnormalities specific or highly suggestive of a definitive diagnosis. Helpful biopsies showed non specific histological changes that proved contributory when related to the clinical data, either by supporting or ruling out a working diagnosis, or by distinguishing among several potential causes, or by showing the presence of inflammatory infiltrates (Deprez *et al.*, 2000). Non contributory biopsies did not influence patient's management other than providing an impression of the severity and activity of the disease.

In our study, contributory biopsies accounted for 35.5% and 47.3% respectively at ULg and BBF/UIA laboratories. These results are roughly similar to those of other authors using similar criteria (Argov *et al.*, 1989 ; Midroni and Bilbao, 1995b ; Chia *et al.*, 1996). Of these biopsies, specific or highly suggestive findings were present in only one third, emphasising the need for a close collaboration between clinicians and neuropathologists.

Inadequate surgical resection, delays in transport or processing errors precluded histological study of 4% (BBF/UIA) to 8% (ULg) of the specimens. Given the propensity of nerve tissue to mechanical and chemical damage, nerve biopsies should always be performed by experienced surgeons and handled in specialised laboratories. The unacceptable figures of specimen loss in this study confirm previous authors' emphasis on the importance of following a specific protocol for nerve biopsy (Dyck *et al.*, 1993 ; Midroni and Bilbao, 1995a ; Bouche *et al.*, 1998 ; Schröder, 1998).

The lowest yield (20%) for nerve biopsy was obtained from patients referred without working diagnosis (table 1). Although in all previously published series, a definite subset of polyneuropathies remain cryptogenic, clinicians should attempt to reduce the proportion of patients in this category by conducting extensive preoperative investigations and repeated examinations. Indeed, several studies have shown that in up to one third of reportedly cryptogenic PNP, long term follow-up would reveal the aetiology by demonstrating a toxic cause or an hereditary condition, or with the emergence of an underlying systemic disease (Dyck *et al.*, 1981 ; McLeod *et al.*, 1984 ; Corvoisier *et al.*, 1987 ; Graham *et al.*, 1991). However, in this study, 9/21 (43%) contributory biopsies demonstrated an unexpected CIDP (7), or microvasculitis (2), confronting the clinicians with the difficult issue of the best timing for nerve biopsy.

The high yield of nerve biopsy associated with hereditary conditions such HMSN has already been discussed above in its historical perspective.

This study also includes information relevant to the diagnosis of inflammatory neuropathies. Nerve biopsies performed in the context of suspected vasculitis were contributory in 50% (BBF/UIA) and 66% (ULg) of cases. Previous studies have shown that the sensitivity of the nerve biopsy in this indication is increased by 15-40% when combined with a muscle biopsy (Vincent *et al.*, 1985 ; Harati and Niakan, 1986 ; Dyck *et al.*, 1987 ; Said *et al.*, 1988). The high yield obtained at ULg for this indication probably reflects the more frequent use of combined nerve-muscle biopsies (Deprez *et al.*, 2000). It is of interest that, in the 18 cases of histologically proven microvasculitis included in our study, only 44% presented with mononeuritis multiplex, the remaining showing symmetrical (33%)

or asymmetrical (22%) distal polyneuropathy. While the onset was acute or subacute in a majority of case, 4 patients presented with a chronic slowly progressive or relapsing neuropathy. Only 28% had manifestations of a systemic disease at the time of biopsy ; biological evidence of an inflammatory syndrome was present in 70%.

The benefit of nerve biopsy in cases with suspected CIDP is a matter of debate. In our study, 47% (ULg) and 64% (BBF/UIA) of biopsies were contributory, most often supporting the preoperative diagnosis. This rather high yield may be inflated by our evaluation criteria. Highly suggestive histological findings such as the association of onion bulbs, ongoing demyelination and endoneurial inflammatory infiltrates were seen in only 22% of the contributory biopsies, while only one nerve showed the characteristic ultrastructural finding of macrophage-mediated myelin stripping. This low sensitivity has also been reported by previous authors (Barohn *et al.*, 1989 ; Krendel *et al.*, 1989 ; Gabreels-Festen *et al.*, 1993 ; Small and Lovelace, 1994 ; Midroni and Bilbao, 1995b ; Molenaar *et al.*, 1998). In the 78% remaining cases, helpful findings were the observation of inflammatory infiltrates in an otherwise established demyelinating neuropathy or the finding of onion bulbs and prominent ongoing demyelination in a previously reported axonal neuropathy. In three cases the diagnosis of CIDP was ruled out by the histological findings of tomacular neuropathy, later genetically confirmed as HNPP, and in one case, by orientating the diagnosis towards a diabetic neuropathy.

The 24 cases of CIDP included in this study also confirmed the wide clinical spectrum of this condition : 50% of patients presented clinically with a chronic distal symmetrical polyneuropathy ; electrophysiological studies supported a predominantly axonal process in 9/24 cases ; 8/24 cases had a normal CSF protein content.

Although our figures parallel those reported by previous authors using similar criteria, a more extensive survey of the previous literature shows considerable variation in the yield of nerve biopsy reported by various laboratories of Neuropathology (Argov *et al.*, 1989 ; Neundorfer *et al.*, 1990 ; Oh, 1990 ; Rappaport *et al.*, 1993 ; Midroni and Bilbao, 1995b ; Chia *et al.*, 1996). When reviewing such data, caution should be exerted to potential bias related to clinical and neuropathological parameters of selection (Deprez *et al.*, 2000).

Conclusions

For any patient, the decision to perform a nerve biopsy should take into consideration :

1. The extent of pre-biopsy investigations, including repeated clinical and electrophysiological examination
2. The specificity and sensitivity of nerve biopsy according to the suspected aetiology
3. The availability of therapy and/or genetic counselling
4. Post-operative sequelae.

Nerve biopsies should be performed by experienced surgeons and handled in specialised laboratories. Only a relatively small number of causes of neuropathy can be diagnosed on the basis of histology alone. More often, contributory biopsies will result from the combination of non-specific suggestive histological features with relevant clinical information. The diagnostic yield of nerve biopsy is function of careful patient selection and close collaboration between the clinician and the neuropathologist. It is hoped that new diagnostic tools generated from in vitro and animal models will increase the diagnostic yield of peripheral nerve biopsy.

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