ORIGINAL ARTICLE

A Continuum of Nerve Biopsies in Peripheral Neuropathy: A Clinicopathological Insight

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ABSTRACT

Background: Peripheral neuropathy is a common neurological disease faced by the neurologists these days. The role of nerve biopsy is ambiguous and the dilemma to identify the underling etiology further adds to the uncertainty. However, ruling out certain etiological causes and confirming specific diagnosis still mandates the procedure. **Aim**: The aim of the study is to evaluate the contribution of nerve biopsy in peripheral neuropathies and study the histomorphological spectrum of these biopsies. **Material and methods**: A retrospective 2-year review of 54 nerve biopsies received in the Department of Pathology was performed at a tertiary care centre. **Results**: A total of 54 nerve biopsies were reviewed during the study period, of which, 6 biopsies (11%) were considered inadequate. Biopsies were broadly divided as biopsies supportive for patient management and biopsies essential for patient management. Biopsies essential for patient management (n=16) comprise vasculitic neuropathy (n=9), lepromatous neuropathy (n=4), hereditary motor sensory neuropathy (n=1) and CIDP (n=2). Biopsies supportive for patient management (n=14) comprise axonal neuropathies (n=6), demyelinating neuropathies (n=5) and mixed neuropathies (predominantly Axonal with secondary demyelinating features, n=3). No diagnostic pathology was identified in 13 cases (24%). **Conclusion**: With the advent of molecular tests and electrophysiologic examinations, nerve biopsy is losing its charm. However, its contribution still hold grounds in specific etiologies like Vasculitic neuropathy, lepromatous neuropathy and to some extent in management of CIDP. Increase in awareness among the pathologists of the histomorphology is essential to aid the physicians managing these patients.

KEY WORDS: Nerve biopsies, Axonal neuropathy, Demyelinating neuropathy, CIDP.

Introduction

Peripheral neuropathy is one of the most common and etiologically diverse group of disease, in dismal, encountered by the neurologists.[1] Although, the prevalence of peripheral neuropathy is about 2-8%,[1] the agony lies in establishing the diagnosis and underlying etiology which remains obscure in nearly 25% of the cases.[2]

Early diagnosis of treatable neuropathies can prevent further worsening of the neuropathic processes, or even allow recovery, hence making the process time sensitive. However, if the diagnosis is delayed and significant axonal loss has occurred, the neurologic deficits may be irreversible. For example, optimising blood glucose in diabetics, correction of vitamin deficiencies, addressing hypothyroidism, urgent intervention in patients with Gullian Barre syndrome improves the quality of patient life significantly.[1,3]

Diagnostic workup of peripheral neuropathy involves detailed evaluation of symptoms, history, examination (motor, sensory, reflexes, gait, autonomic function, cranial nerve examination) and investigation (complete blood count, serum electrolytes, erythrocyte sedimentation rate, fasting blood glucose, vitamin B12, thyroid-stimulating hormone level, CSF). The electrophysiological tests are the cornerstone of evaluation. It differentiates axonal, demyelinating or mixed variety of neuropathies. With the advances in

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neurophysiologic, immunologic, and genetic testing in peripheral neuropathy, the use of nerve biopsy is now primarily limited to patients with possible vasculitic neuropathy, amyloid neuropathy, and atypical forms of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).[3,4] Currently, the search for an etiology is the main indication for nerve biopsy.[5] In the present study, a retrospective review of the performed nerve biopsies is done to evaluate the spectrum of biopsies and evaluate its utility in clinical management.

Material and methods

A 2-year retrospective review of 54 cases of nerve biopsies received in the Department of Pathology was carried out from Jan 2021-Feb 2023. All the patients (inpatient and outpatient) with clinical diagnosis of peripheral neuropathy who underwent nerve biopsy after diagnostic workup to identify the underlying etiology were included. Inadequate and inconclusive biopsies were excluded.

Detailed clinical evaluation, Nerve Conduction Studies/Electromyography and lab investigations (complete blood count, serum electrolytes, erythrocyte sedimentation rate, fasting blood glucose, vitamin B12, thyroid-stimulating hormone level, CSF) were recorded.

All the biopsies were formalin fixed and stained for Hematoxylin-Eosin, Massons Trichrome, Neurofilament, Myelin Basic Protein, Leucocyte Common Antigen and Loyez. AFB (Acid fast bacilli) stain for leprosy was done in suspected cases. All the biopsies were subcategorised into: No diagnostic Pathology, Inadequate and Abnormal-i.e. Biopsies supportive for patient management (axonal and demyelinating neuropathies), Biopsies essential for patient management (vasculitic, hereditary, lepromatous and Chronic Inflammatory Demyelinating Polyneuropathy, CIDP).[5]

Results

In the present study, nerve biopsies of 54 patients were evaluated. The most common nerve excised for biopsy was sural nerve (n=33) followed by peroneal nerve (n=21). The mean age of the patients who underwent nerve biopsy for peripheral neuropathy were 37+/- 4 years and male to female ratio was 2:1. The nerve biopsies were categorized morphologically into Normal/No diagnostic pathology (n=18), Abnormal (n=30), and Inadequate (n=6), after clinical correlation.

Clinically, majority patients (n=19/34, 56%) presented with a chronic course (>8 weeks), 26% patients had subacute (4-8 weeks) course and 18% had acute (4 weeks) course. Motor symptoms predominantly proximal (53%) weakness of the lower limbs (39%) were more common than distal weakness (18%), followed by sensory symptoms (32%). Multifocal neuropathies (56%) were the common presentation, followed by distal symmetric polyneuropathies as demonstrated in Table 1.

Table 1: Clinical profile of the patients presenting withAbnormal biopsies (n=34).

	Clinical presentation		No of Cases (%)
1.	Clinical Course		
		Acute	5 (15%)
		Subacute	9 (26%)
		Chronic	20 (59%)
2.	Weakness		
			11 (32%)
	Proximal	Upper limb	4 (12%)
		Lower limb	7 (20%)
			23 (68%)
	Distal	Upper limb	6 (18%)
		Lower limb	17 (50%)
3.	Sensory loss/sensation loss		10 (29%)
4.	Impairment of vibratory/position sense		6 (18%)
5.	Raynauds phenomena		5 (15%)
6.	Thickened nerves		6 (18%)
7.	Deformity	Clawing of hands	3 (9%)
		Foot drop	2 (6%)
8.	Multifocal neuropathies		18 (53%)

The *Abnormal* group, was further subcategorized into 2 subgroups (Figure 1). *Biopsies essential for patient management (n=16) comprising* vasculitic neuropathy (n=9), lepromatous neuropathy (n=4), hereditary motor sensory neuropathy (n=1) and CIDP (n=2). *Biopsies supportive for patient management* (n=14) comprising axonal neuropathies (n=6), demyelinating neuropathies (n=5) and mixed neuropathies (predominantly Axonal

with secondary demyelinating features, n=3) as illustrated in Table 2.

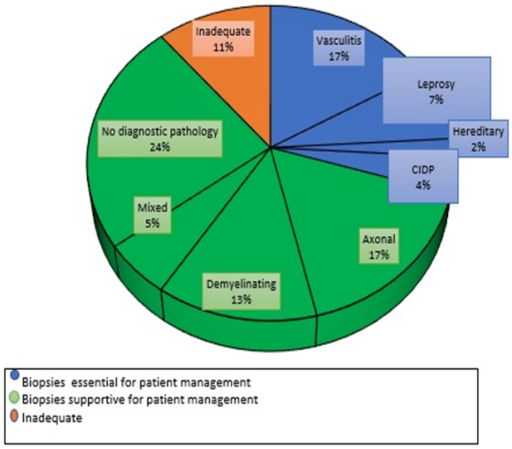

Figure 1: Figure illustrating distribution of the nerve biopsies based on their morphology

Table 2: Demographic characterstics of the patients presenting with peripheral neuropathy

	Male:Female	Mean age	Number of cases (%)
I. Biopsy essential for patient management			
Vasculitic neuropathy	1:1.6	42 years	9 (17%)
Lepromatous neuropathy	3:1	28 years	4 (7%)
Hereditary neuropathies	1:0	23 years	1 (2%)
CIDP	1:1	25 years	2 (4%)
II. Biopsy supportive for patient management			
Axonal	2:1	48 years	9 (17%)
Demyelinating	2:3	37 years	7 (13%)
Mixed	2:1	45 years	3 (5.5%)
No diagnostic pathology	2:1	42 years	13 (24%)
III. Inadequate	6:1	44 years	6 (11%)
Total	**2:1**	**37 years**	**54**

Axonal neuropathies (n=9) had a chronic course (n=7) and distal weakness was common presentation. Patients mostly complained of loss of pain and temperature (n=6). On nerve conduction studies, amplitude was more commonly affected. Histopathology showed features of axonal degeneration (axonal drop out, myelin ovoids) and regeneration (axonal sprouts/regenerating clusters). Neurofilament protein (IHC) also demonstrated axonal atrophy in these cases (Figure 2). The recovery of patients was very slow and the most common underlying etiologies suggested were metabolic and toxic.

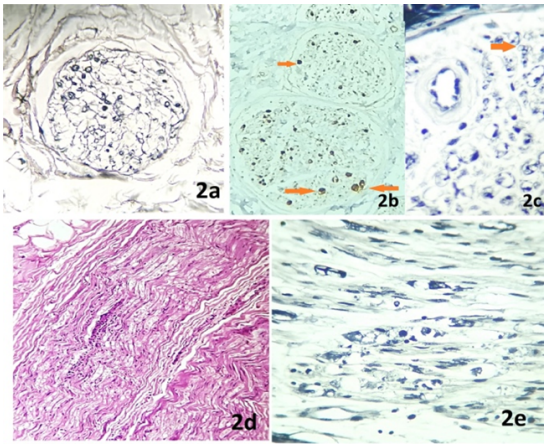

Figure 2: Histopathology demonstrating: a) Marked axonal atrophy (Loyez,80x). b) Variable fiber loss and axonal drop-outs (Neurofilament, 40x). c) Axonal sprouts/regenerating clusters (Loyez,100x). d) Low power view showing myelin ovoids in longitudinal section (HE,20x). e) High power view showing myelin ovoids in longitudinal section (Loyez, 40x)

Demyelinating neuropathies were established in 7 cases. They had acute/subacute onset (n=6) and nearly equal proximal-distal involvement (weakness and paraesthesia's). Four patients presented with loss of vibration and proprioception. On Nerve Conduction studies, velocity was more affected than amplitude. Morphology showed features of demyelination (loss of myelinated fibers, Numerous thinly myelinated fibers, onion bulb and occasional denuded axons) and remyelination (thinly myelinated fibres and Bands of bungner). Loss of myelin was confirmed by myelin basic protein (IHC) or Loyez in all the cases (Figure 3). The recovery of the patients was rapid and the most common etiologies suggested were CIDP (Chronic Inflammatory demyelinating polyneuropathy), DM (Diabetes mellitus) and GBS (Gullian Barre syndrome).

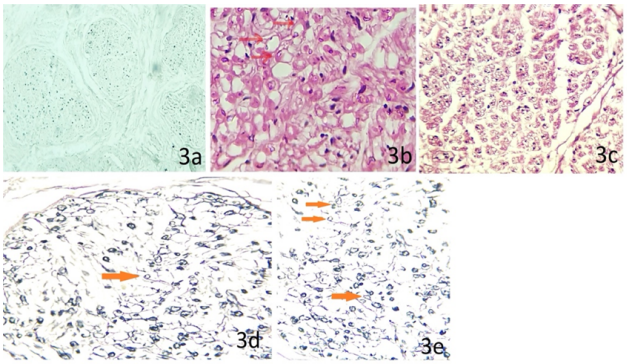

Figure 3: Histopathology demonstrating: a) Variable loss of myelinated fibers (Myelin Basic Protein, 10x). b) Denuded axons (HE, 80x). c) Bands of Bungner (HE,40x). d & e) Thinly myelinated fibers (Loyez, 80x)

Mononeuritis multiplex (6/9) was the most common presentation for patients diagnosed as vasculitic neuropathies. Raynauds phenomenon was seen in 5 cases, and immune work up biopsies were categorised on the basis of Collins criteria[6] into Definite Vasculitis (Active: transmural inflammation, disruption of internal elastic lamina, fibrinoid necrosis on Massons Trichrome as in Figure 4 or thrombus occluding vessel lumen; Chronic: Intimal hyperplasia with luminal narrowing on Massons Trichrome/Van Gieson, neovascularisation and hemosiderin deposition in Perls stain), Probable Vasculitis (perivascular inflammation, endoneural fibrosis on Massons Trichrome and asymmetric nerve fibre loss) and Possible vasculitis (any one feature).

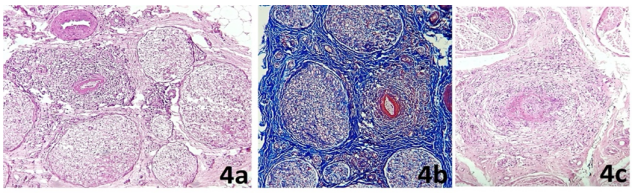

Figure 4: Histopathology demonstrating: a) Fibrinoid necrosis of the vessel wall (HE,20x). b) Fibrinoid necrosis of the vessel wall (MT,20x). c) Transmural inflammation and obliteration of vessel lumen, perivascular inflammatory infiltrate around epineural blood vessels (HE, 40x)

Biopsies diagnosed as CIDP (n=2) presented with symmetrical weakness and ataxia. Nerve conduction study showed variable degree of conduction slowing and even conduction block. Lab investigations reveal raised CSF protein and albuminocytologic dissociation in CSF of both cases. Histology showed onion-bulbs formation suggestive of chronic demyelination and remyelination, endoneurial expansion due to inflammatory cells, perineural edema, and variable fascicular involvement observed in hematoxylin-eosin and Loyez stain.

Hereditary neuropathies include HMSN; CMT (Hereditary motor and sensory neuropathies; Charcot Marie Tooth), HSAN (Hereditary sensory and autonomic neuropathy), HMN (Hereditary motorneuropathy), HNPP (Hereditary neuropathy with liability to pressure palsy) and HNA (Hereditary neuralgic amyotrophy)[7]. On clinical and electrophysiologic correlation, Charcot Marie Tooth disease was suspected in one case, where patient had positive family history (father had similar symptoms), bilateral foot drop and distal weakness.

Lepromatous leprosy was identified in 9 cases. 6 of them had no skin lesions but thickened nerves. Morphologically, variable presentation ranging from perineuritis (n=3), to granulomatous infiltration in the endoneurium (n=5), and burnt out fascicles (n=3) were seen. AFB stain was positive in 4 cases only, as the other 5 cases had either taken treatment or were defaulters.

Discussion

Nerve biopsies are considered as the last resort of investigation used only when the detailed workup for peripheral neuropathy fails to identify the etiology. The role of nerve biopsies is often a matter of debate. In the present study, we referred to Midroni et al.[8], Argov et al.[9] criteria and Pant Iet al.[10]criteria, where the biopsies were categorised as essential for patient management (n=16), supportive for patient management (n=18) and biopsies ruling out/changing the course of treatment in the no diagnostic pathology group (n=13). All these were considered contributory biopsies.

Contributory biopsies in the present study were 87% (n=47). Biopsies essential for patient management constituted 34% of the cases. These findings were concordant to Argov et al.[9] (38%), Deprez et al.[11](20%) and Pant I et al.[10] (30%).

Biopsies supportive of patient management (34%) comprised of 17% Axonal and 13% demyelinating neuropathies. These findings are similar to J Goel et al.[12] (18%, axonal) and I Pant et al.[10](8%, demyelinating). Differentiating demyelinating and

axonal neuropathiesis important as the latter (Wallerian degeneration) is associated with a relatively poor prognosis for recovery.

A considerable decline in the percentage of hereditary neuropathies was observed in our study (n=2%) as observed by Prada et al.[13] (52/1179, 4%) and Pant I et al.[10](3 %) due to the increasing availability of molecular tests like Next generation sequencing.

The number of vasculitic neuropathy cases (17%) identified were relatively high as observed in other studies by Pant I et al.[10] (16%) and J Goel et al.[12] (18%). The male to female ratio in the present study also showed mild female preponderance (1.6:1) as was observed by Prada et al.[13](1.8:1). Localised vasculitic patients (n=6), i.e. restricted to peripheral nervous system were treated either with oral glucocorticoids or a short course of cyclophosphamide. Patients with systemic (n=3) vasculitis (constitutional symptoms and positive immune profile) were aggressively managed with long term immunosuppressive treatment. As is evident in literature, nerve biopsy is the standard procedure of choice for diagnosing Vasculitis, which can be seen in the present study also, as this was the most common indication of biopsy in our study (n=21, 38%).

Nerve biopsies may be performed, in need of supportive evidence for diagnosing CIDP. In view of classical histological findings in correlation with lab investigations, only 2 cases were identified in the present study. Similarly, a single case was diagnosed in the study by Pant I et al.[10]. As emphasised by Deprez et al.[11], most associated histological findings are not specific, thereby questioning the role of microscopy for diagnosing CIDP. This may be the cause of such low prevalence of CIDP in our study, as biopsy was not frequently indicated in the presenting cases due to lack of specificity. Moreover, cases of Gullian Barre syndrome or acute demyelinating polyradiculopathies were excluded, as patients presented with acute flaccid paralysis and were managed by IVIg. While patients having chronic (relapsing and remitting) weakness were managed on steroids, instead of IVIg.

Leprosy is diagnosed based on skin lesions, which can be confirmed with nerve biopsy if required. Nerve biopsy is indicated only in cases with no visible skin lesions or to evaluate the effectiveness of treatment.[14] Biopsy was decisive in 28% cases of leprosy without skin lesions.[15] Although, leprosy is endemic to India, only 7% of the cases were categorised in our study. This is because histopathology of nerves in leprosy is relatively less studied at our center than its cutaneous counterpart. Variable histology was seen. Pure neuritic type was the common presentation. Similar findings were observed by Pant I et al.[10](5.4%), and J Goel et al.[12] (5.3%).

Conclusion

Nerve biopsy is an invasive procedure, only indicated after detailed preliminary evaluation of the peripheral neuropathy. Our study is in concordance with various previous studies, where biopsy has contributed to patient management making its role existent and enduring. Hence, increase awareness of the techniques (stains), and histomorphology is required among the pathologists, in order to assist the neurologists in managing these patients.

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