Original Article

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Pathology Section

Histopathological Study of Peripheral Neuropathies on Nerve Biopsy: A Cross-sectional Study

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ABSTRACT

Introduction: Peripheral neuropathy is common in clinical practice, with a reported prevalence of 2.4% in the general population. There are numerous aetiologies for peripheral neuropathy like diabetes, ischaemia, vasculitis, inflammatory demyelinating disorders, nutritional deficiencies, paraproteinemic disorders, paraneoplastic syndromes, toxic exposures, and hereditary neuropathies. An exhaustive haematological, biochemical, and serological work-up, cerebrospinal fluid evaluation, electrodiagnostic tests, and nerve biopsy are required when overlapping clinical features present a diagnostic challenge.

Aim: To analyse the histopathological characteristics of nerve biopsies in individuals with peripheral neuropathy.

Materials and Methods: This cross-sectional study was conducted in the Department of Pathology at Kasturba Medical College from January 2011 to December 2016. Nerve biopsies received in the Department of Pathology, Kasturba Medical College and Hospitals in the Ambedkar Circle and Attavar area, as well as at Government Wenlock Hospital, Mangaluru, Karnataka, India were studied. Clinical and laboratory data were collected from biopsy requisition forms and patient case records from the aforementioned hospitals. Results were presented in numbers and percentages.

Results: A total of 134 nerve biopsies were included in the study. The age range of all cases studied was 7-86 years, with a mean age of 51.8 years. The study population consisted of 63.4% males and 36.6% females, resulting in a male-to-female ratio of 1.7:1. Vasculitic Neuropathy (VN) accounted for 38.1% cases, followed by chronic inflammatory neuropathies (21.7%) and Diabetic Neuropathy (DN) (12.6%). Other diagnosis included ischaemic neuropathy (6.7%), Hereditary Motor and Sensory Neuropathy (HMSN) (3.7%), subacute inflammatory demyelinating neuropathy (3.0%), as well as two cases each of Hansen's neuritis, amyloid neuropathy, and acute inflammatory demyelinating neuropathy (1.5% each). One case of toxic neuropathy (0.7%) was identified, while 9.0% of cases displayed histological features that were either non specific or not characteristic of any specific diagnosis.

Conclusion: Vasculitic neuropathy was found to be the most common aetiology of peripheral neuropathy, followed by Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and DN. The histopathological examination of nerve biopsies is a useful tool in distinguishing between diseases with overlapping clinical features, confirming or excluding vasculitis, and diagnosing hereditary conditions in settings where genetic testing is unavailable or unaffordable.

Keywords: Chronic inflammatory demyelinating polyneuropathy, Diabetic neuropathy, Nerve biopsy, Peripheral neuropathy, Vasculitic neuropathy

INTRODUCTION

Peripheral neuropathy is common in clinical practice, with a reported prevalence of 2.40% in the general population [1]. More than a hundred aetiologies of peripheral neuropathy have been reported, and a final diagnosis is typically reached after a thorough assessment involving history taking, physical examination, laboratory tests, radiological evaluations, and electrodiagnostic tests. In some cases, cerebrospinal fluid analysis and genetic testing may be necessary. Nerve biopsy, although an invasive procedure, is utilised when there is diagnostic uncertainty despite an exhaustive work-up. In such instances, nerve biopsy can help in reaching a definitive diagnosis and guiding the treatment plan [2,3], particularly in cases of VN, granulomatous neuropathy, Hansen's neuritis, and atypical presentations of CIDP [4,5].

The sural nerve is commonly biopsied [2,3], and paraffin and resin semithin sections are prepared using routine H&E stains, along with additional stains and immunohistochemical testing. Teased fibre preparation, electron microscopy, and genetic testing are employed as needed [6]. There is a dearth of studies on neuropathies that explore the incidence and distribution of various neuropathies across different ages and genders, as well as their aetiologies [7]. This study aims to address this gap by examining the histopathological features of nerve biopsies in patients with peripheral neuropathy.

MATERIALS AND METHODS

This was a cross-sectional study with a retrospective study duration from January 2011 to September 9, 2015, and a prospective study duration from September 10, 2015, to December 2016, conducted in the Department of Pathology, Kasturba Medical College, Mangaluru, Karnataka, India. Institutional Ethical Committee (IEC) clearance was obtained (IEC KMC MLR 09-15/188).

Inclusion criteria: Only inpatients of the institute were included in the study.

Exclusion criteria: Inadequate length of the biopsy (<1 cm), biopsies in which interpretation was limited by excessive stretch, crush, or hyperosmolar artifact, cases in which clinical and Nerve Conduction Study (NCS) findings were inadequate or not available either in the biopsy requisition form or patient record files, and lastly, cases where paraffin blocks and/or slides were unavailable for review.

Sample size: The sample size of this study comprised a total of 157 nerve biopsies received during the study duration, out of which 134 cases were included in the study.

Study Procedure

Nerve biopsies received in the Department of Pathology, Kasturba Medical College, from Kasturba Medical College Hospitals of Ambedkar Circle and Attavar area and Government Wenlock Hospital

were studied. The data were collected from biopsy requisition forms and case record files of patients admitted to the above hospitals.

A nerve biopsy was done for aetiological diagnosis of peripheral neuropathy, received in 2.50% glutaraldehyde or 10% neutral buffered formalin. The nerve biopsy specimen was then sectioned, and part of the biopsy was secondarily fixed in Fleming's solution (1% Osmic acid + 2% Chromic acid + Glacial acetic acid). During subsequent routine tissue processing, 4-5 µm thick sections were stained by Haematoxylin and Eosin (H&E) and Masson's Trichrome (MT) stains. Other histochemical stains such as Congo Red and Perl's Prussian Blue were performed as indicated.

Sections of the biopsy fragment secondarily fixed in Fleming's solution were stained with Kulchitsky Pal (KPal) stain to study the severity of myelinated nerve fibre loss and morphological changes. Deparaffinised sections were placed in KPal solution in a hot air oven at 55-60ºC for 45 minutes. A 0.25% potassium permanganate solution was added for 15-30 seconds, followed by Bleach in 2% Oxalic acid (2 gm Oxalic acid, dihydrate in 100 mL distilled water) for one minute. Counterstaining was done with Eosin for 30 seconds.

The microscopic findings were correlated with clinical features and laboratory investigation results to arrive at the final diagnosis. All the data regarding clinical findings, laboratory investigations, and NCS collected from biopsy requisition forms and case record files of the patients, and histological findings, were recorded in the case record form.

STATISTICAL ANALYSIS

The data were analysed by proportions, tables, and graphs. Statistical Package for the Social Sciences (SPSS) version 17.0 was used. Various morphological features were analysed for their frequency and compared with the final diagnosis using the Chi-square test and Fisher's exact test, wherever appropriate.

RESULTS

A total of 157 nerve biopsies were received during the study period, of which 134 cases were included in this study. Twenty-three cases were excluded based on the exclusion criteria. The peak incidence of peripheral neuropathy was seen in the age group of 40-70 years, and the age range observed was 7-86 years (mean±SD age 51.8±17.30 years). There were 85 (63.4%) males and 49 (36.6%) females (M:F=1.7:1) [Table/Fig-1]. The incidence of peripheral neuropathy was highest in males in all age groups. The male-to-female ratio was 1.2:1 among cases of CIDP and 2.4:1 among cases of DN. The commonest aetiology was VN (51/134, 38.1%), followed by CIDP (29/134, 21.1%) and DN (17/134, 12.7%), with other causes in smaller proportions [Table/Fig-2]. The histological features of the major types of peripheral neuropathies, including CIDP, DN, and VN, have been summarised in [Table/Fig-3].

Age range (years)	No. of cases (%)	Males	Females
<10	1 (0.7)	01	00
11-20	6 (4.5)	04	02
21-30	12 (9.0)	07	05
31-40	15 (11.2)	10	05
41-50	25 (18.7)	16	09
51-60	25 (18.7)	14	11
61-70	31 (23.1)	17	14
71-80	13 (9.7)	10	03
81-90	6 (4.5)	06	00

[Table/Fig-1]: Age and sex distribution of the cases.

Among other investigations, in the cases of VN, 28 cases showed elevated ESR (range 3-98). Serological reports were available for

Aetiology	Number of cases (%)
Vasculitic Neuropathy (VN)	51 (38.1)
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	29 (21.6)
Diabetic Neuropathy (DN)	17 (12.7)
Ischaemic	9 (6.6)
Hereditary Motor and Sensory Neuropathy (HMSN)	5 (3.6)
Hansen's	2 (1.5)
Subacute Inflammatory Demyelinating Neuropathy (SIDP)	4 (3.0)
Acute Inflammatory Demyelinating Polyneuropathy (AIDP)	2 (1.5)
Amyloid neuropathy	2 (1.5)
Toxic neuropathy	1 (0.6)
No diagnosis	12 (9.0)

[Table/Fig-2]: Percentage of cases of different aetiologies of peripheral neuropathy.

Histologic feature	CIDP (n=29)	Diabetic neuropathy (DN) (n=17)	Vasculitic neuropathy (VN) (n=51)
Asymmetric loss of myelinated fibres	29 (100)	17 (100)	51 (100)
a. Mild degree loss	4 (13.8)	2 (11.8)	10 (19.60)
b. Moderate degree	12 (41.40)	8 (47.0)	23 (45.1)
c. Severe degree	13 (44.89)	7 (41.2)	18 (35.3)
Large/small fibre loss			
a. Large>small fibre loss	3 (10.3)	0	1 (2.0)
b. Large=small fibre loss	16 (55.2)	7 (41.2)	32 (62.8)
c. Large<small fibre loss	10 (34.5)	10 (58.8)	18 (35.2)
Onion bulbs	0	0	1 (2.0)
Raynaut bodies	0	0	2 (3.9)
Subperineurial oedema	13 (44.8)	3 (17.6)	17 (33.3)
Hyalinised endoneurial blood vessels	3 (10.3)	7 (41.2)	0
Endoneurial fibrosis	29 (100)	17 (100)	51 (100)
Regenerating clusters	18 (62.1)	9 (52.9)	34 (66.7)
Thinly myelinated fibres	25 (86.2)	9 (52.9)	26 (51.0)
Endoneurial inflammation	17 (58.6)	4 (23.5)	16 (31.3)
Endoneurial oedema	10 (34.5)	3 (17.6)	12 (23.5)
Myelin ovoids	12 (41.4)	0	4 (7.80)
Perineurium unremarkable	27 (93.1)	15 (88.2)	50 (98)
Perineurium inflammation	1 (3.4)	2 (11.8)	1 (2.0)
Epineurial blood vessels unremarkable	7 (24.1)	2 (11.8)	0
Medial hypertrophy	6 (20.7)	5 (29.4)	10 (19.6)
Inflammation	18 (62.1)	14 (82.3)	51 (100)
Neovascularisation	10 (34.5)	8 (47)	34 (66.7)
Subendothelial fibrosis	5 (17.2)	3 (17.6)	11 (21.6)

[Table/Fig-3]: Comparison of histologic features of CIDP, Diabetic Neuropathy (DN) and Vasculitic Neuropathy (VN).

35 cases, out of which 14 were positive for serological markers of vasculitis, including four cases positive for Antinuclear Antibody (ANA), three for ANA, Anti-Neutrophilic Cytoplasmic Antibody (c-ANCA), and Anti-Neutrophilic Perinuclear Antibody (p-ANCA), 1 case for ANA and p-ANCA. One case was positive for Anti-Cyclic Citrullinated Peptide (anti-CCP) and four cases were positive for RA factor. One case was positive for Anti-Sjogren's-Syndrome-Related Antigen (anti-SSA) and anti-SSB antibodies. Among cases of CIDP, CSF examination was done in five cases, out of which 4 (80%) were normal and 1 (20%) showed albuminocytologic dissociation. Among patients with DN, 12 (70.6%) were males and 5 (29.4%) were females, with a

male-to-female ratio of 2.4:1, with an age range of 45-84 years and a mean age of 57.5 years.

Nine cases were of ischaemic neuropathy, all of which showed an asymmetric pattern of loss of myelinated fibres with varying patterns on NCS. Five cases were of HMSN, all of which showed a symmetric pattern of loss of myelinated fibre, with a predominance of sensorimotor axonal neuropathy on NCS. Subacute inflammatory demyelinating neuropathy was seen in four cases with both axonal and demyelinating patterns on NCS, with an asymmetric pattern of loss of small more than large myelinated fibre in three cases. Acute inflammatory demyelinating neuropathy was present in two cases. Both were males aged 26 and 56 years, with sensorimotor axonal and demyelinating patterns on NCS and marked hypergammaglobulinaemia on serum protein electrophoresis in one of the cases. Two cases each were diagnosed as amyloid neuropathy with amyloid deposits around endoneurial capillaries exhibiting apple-green birefringence on polarised microscopy. One of these cases was simultaneously diagnosed with multiple myeloma. Two cases were of Hansen's neuritis, wherein one case had bilateral ulnar and sural nerve thickening and was diagnosed as BB leprosy, and the other one as TT leprosy. One case was diagnosed as toxic neuropathy with a history of liver transplant and was on Tacrolimus. In 9,0% of cases, a definite histological diagnosis could not be made.

Clinical characteristics of peripheral neuropathies are compiled in [Table/Fig-4], with an emphasis on sensorimotor patterns. Asymmetric sensorimotor involvement is seen in 42 instances (82.4%), symmetric sensorimotor involvement is seen in 27 cases (93.10%) of CIDP, and asymmetric involvement was primarily seen in 13 cases (76.5%) of DN. In three cases (33.3%), ischaemic neuropathy exhibits both patterns equally. In all five cases (100%) HMSN has symmetric sensory neuropathy. Whereas amyloid-associated and toxic neuropathies have asymmetric involvement in all cases (100%), inflammatory demyelinating neuropathies present symmetrically. In two cases (100%), symmetric sensorimotor involvement with sensory impairments is the hallmark of Hansen's neuropathy. These results show that different peripheral neuropathies have different clinical characteristics and diagnostic implications. [Table/Fig-5] provides a summary of NCS results for different types of peripheral neuropathies, showcasing unique nerve involvement patterns.

Type of neuropathy	Asymmetric sensorimotor neuropathy	Symmetric sensorimotor neuropathy
Vasculitic Neuropathy (VN)	42/51 (82.4)	9/51 (17.6)
CIDP	2/29 (6.9)	27/29 (93.10)
Diabetic Neuropathy (DN)	13/17 (76.5)	4/17 (23.4)
Ischaemic neuropathy	3/09 (33.3)	3/09 (33.3)
HMSN	-	5/05 (100)
Subacute Inflammatory demyelinating Neuropathy (SIDP)	1/04 (25)	3/04 (75)
Acute Inflammatory Demyelinating Polyneuropathy (AIDP)	-	2/02 (100)
Amyloid associated neuropathy	2/02 (100)	-
Hansens's neuropathy	-	2/02 (100) sensory>motor
Toxic neuropathy	1/01 (100)	-

[Table/Fig-4]: Clinical features of all peripheral neuropathies.

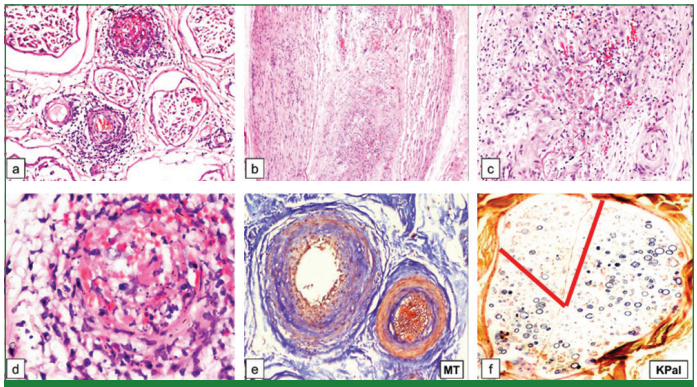
VN typically shows axonal participation, mainly affecting both sensory and motor functions in 22 cases (43.1%), with significant sensory and motor involvement. CIDP displays prominent axonal demyelinating characteristics, especially in sensorimotor nerves in 17 instances (58.6%), suggesting a combination of factors in its pathophysiology. Six cases (35.3%) of DN show various patterns with axonal damage in sensorimotor nerves, while two cases (11.8%) exhibit damage in sensory nerves and five cases (29.4%)

Type of neuropathy	Axonal	Demyelinating	Axonal demyelinating	Mononeuritis multiplex
VN (51 cases)	Sensorimotor 22 (43.1%), Sensory 07 (13.7%), Motor 03 (5.9%)		Sensorimotor 04 (7.8%), Sensory 01 (2.0%)	14 (27.5%)
CIPD (29 cases)	Sensorimotor 04 (13.8%)	Sensorimotor 06 (20.7%)	Sensorimotor 17 (58.6%), Motor 02 (6.9%)	
DN (17 cases)	Sensorimotor 06 (35.3%), Sensory 02 (11.8%)	Sensorimotor 02 (11.8%)	Sensorimotor 05 (29.4%), Motor 01 (5.9%)	01 (5.9%)
HMSN (05 cases)	01/05 (25%) Sensorimotor		04/05 (75%) Sensorimotor	
SIDN(04 cases)	01/04 (25%) Sensory	01/04 (25%) Motor	02/04 (50%) Sensorimotor	
AIDP (02 cases)			02/02 (100%) Sensorimotor	
Amyloid associated neuropathy (02 cases)			02/02 (100%) Sensorimotor	
Hansen's neuropathy (02 cases)				02/02 (100%) Sensory> motor axonopathy
Toxic neuropathy (01 case)	01/01 (100%) Sensorimotor			

[Table/Fig-5]: NCS finding of all peripheral neuropathies.

show axonal demyelination in sensorimotor nerves. HMSN usually shows axonal demyelinating damage in sensorimotor nerves in four instances (75%), setting it apart from other forms. Both AIDP and SIDN present acute inflammation and axonal demyelination in sensorimotor nerves, seen in two cases (100%) and two cases (50%), respectively. In two cases (100%), there was a consistent presence of axonal demyelinating involvement in sensorimotor nerves in both amyloid-associated and toxic neuropathies. Hansen's Neuropathy displays unique axonal demyelination that is sensory-driven in two cases (100%). These discoveries clarify various neuropathic processes and assist in clinical understanding and treatment.

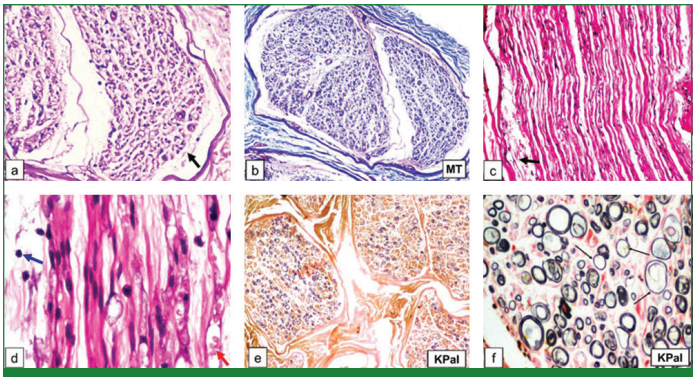
Histopathological analysis of VN, CIDP is depicted in [Table/Fig-6,7]. Various histological features of different peripheral neuropathies were depicted [Table/Fig-8].



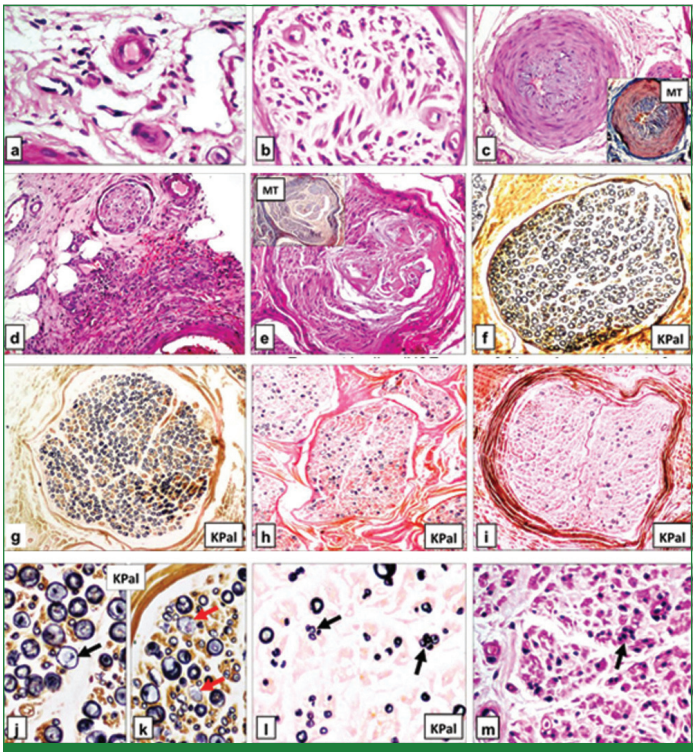
[Table/Fig-6]: Vasculitic Neuropathy (VN): a,b) Epineurial perivascular and transmural inflammation (H&E, x40); c) Epineural perivascular and transmural inflammation (H&E, x100); d) Fibrinoid necrosis and leukocytoclasis (H&E,x400); e) Subendothelial fibrosis and medial hypertrophy (H&E, x400), and f) Severe degree of myelinated fibre loss and sectorial pattern [(sector defined within red lines) KPal, x100].

DISCUSSION

In the present study, various aetiologies of peripheral neuropathy were found affecting a wide age range of patients, with the peak incidence of peripheral neuropathy in the age group of 40-70 years, and the observed age range was 7-86 years (mean±SD



[Table/Fig-7]: CIDP: Subperineurial oedema (black thick arrow) (H&E, x100); b) Endoneuroial fibrosis (MT, x100); c) Endoneurial oedema (H&E, x100); d) Endoneurial lymphocytic infiltrate (blue arrow), myelin ovoids (red arrow) (H&E, x400); e) Asymmetric, moderate degree of loss of myelinated fibres (KPal, x40); f) Thinly myelinated fibre (thin black arrow) (KPal, x400).



[Table/Fig-8]: Histological features of peripheral neuropathies: a) Microvasculitis (Diabetes) (H&E x400); b) Hyalinised blood vessels (Diabetes); c) Arteriosclerosis with medial hypertrophy, subendothelial fibrosis (MT x400); d) Neovascularisation and perivascular inflammation (H&E x400); e) Raynaut bodies (MT x100); f) Normal small and large myelinated nerve fibers (KPal x400); g) Mild myelinated nerve fiber loss (KPal x400); h) Moderate myelinated nerve fiber loss (KPal x100); i) Severe myelinated nerve fiber loss (KPal x100); j) Thinly myelinated fibers (black arrow); k) Degenerating myelin (red arrow) (KPal x400); l) Regenerating clusters (arrow) (KPal x400); m) Bands of Bungner (arrow) (H&E x100).

age 51.8±17.30 years). Collins MP and Periquet MI reported an age range of 13-88 years with a mean age of 59.5 years (SD±15.3 years), with a male-to-female ratio of 1.25:1, in their study on peripheral neuropathy [8].

According to a study in 100 elderly patients undergoing nerve biopsies, the prevalence of peripheral neuropathy rises with age. Most cases (91.30%) had a lower limb onset of symptoms, and 82.60% had a chronic course. Clinical signs included weakness (80%) and muscle wasting (63%), along with sensory complaints such as paresthesias (89%) and decreased feeling (70%). These results demonstrated the substantial impact of peripheral neuropathy in the elderly [9]. Another similar study showed an increased prevalence of peripheral neuropathy with age, as nerve biopsies in 100 elderly patients revealed various neuropathies. Most cases had a chronic onset (79%), with prevalent symptoms such as paresthesias (75%) and impaired sensation (85%), underscoring the significant impact of peripheral neuropathy in older adults [10]. This could be due to the impact of the ageing process on the peripheral system and due to the increase in the prevalence of other co-morbidities like diabetes mellitus [10]. Compiled epidemiologic data on peripheral neuropathy in India is still lacking [7].

The maximum number of cases in the current study were of VN (51/134, 38.1%), followed by CIDP (29/134, 21.6%) and DN (17/134, 12.7%). Other aetiologies comprised a much smaller proportion of cases. In another Indian study, out of 100 cases aged >65 years, most of the cases were attributed to a vasculitic aetiology (46%) [11]. In a study done amongst 225 cases of peripheral neuropathy in Eastern India, the commonest aetiology was found to be GBS (24.80%), followed by DN (11.10%) [11]. In a similar study conducted amongst 284 cases of idiopathic peripheral neuropathy, most cases were finally diagnosed to be of diabetic aetiology (72 patients, 25.35%) [12]. The use of nerve biopsy in the diagnosis of peripheral neuropathy has been found to range from 24 to 94% across various studies [10].

The VN, which comprised the major chunk of cases in the present study, arises due to inflammation of vasa nervorum, leading to ischaemic damage to the involved nerve trunk [5]. In the current study, only one case of VN was seen in the paediatric age group. Vasculitic neuropathies are rare in children, and when present, they are usually associated with SLE [13]. Clinically, the majority of the VN cases had asymmetric sensorimotor neuropathy (82.4%), and the remaining cases had symmetric sensorimotor neuropathy (17.6%), which was similar to an Ohio State University study, wherein asymmetric polyneuropathy was seen in most cases (85%), followed by multifocal neuropathy (13%) and distal symmetric polyneuropathy in 2% of cases [14]. In one of the Indian studies on VN, among 20 cases, mononeuritis multiplex was seen in 16 cases, and the remaining 4 cases showed distal symmetrical sensorimotor polyneuropathy [10].

In the present study, NCS revealed sensorimotor axonal neuropathy (43.1%) in the majority of cases, followed by mononeuritis multiplex (27.4%) and sensory axonal neuropathy (13.7%), with a few cases showing other patterns. NCS in patients with VN in previous studies have shown primarily sensorimotor pathology [15]. In the present study, serological markers were available in 35 cases of VN, and one or more markers of primary vasculitis were positive in 40% (14/35) of cases. This included 11.4% (4/35) of cases which showed positive results with markers like ANA, c-ANCA, and p-ANCA, diagnosed as PSVN. The remaining cases were diagnosed as SSVN and comprised cases with positive results with markers like anti-CCP, RA factor, and anti-SSA/anti-SSB antibodies. ESR was elevated in 55% of cases of VN in this study. Previous study cohorts in VN have shown an incidence of abnormalities in ANA 25%. ANCA has been reported to be commonly associated with SVN [8]. In a study among cases of peripheral neuropathy in the elderly (>65 years), 46 cases were reported as vasculitic on biopsy, and out of those, serological investigations were done in 16 cases. Among them, 25% (4/16) of cases were positive for ANA, and 12.50% (2/16) of cases each were positive for c-ANCA and p-ANCA. Thus, it was suggested that VN should be considered as a differential diagnosis in the elderly who present with distal symmetric polyneuropathy, even when the clinical profile and serological markers for systemic vasculitis are supportive of vasculitis [9].

Among cases of CIDP in the current study, the male-to-female ratio was 1.2:1. In two Indian studies, there were 118 and 12 patients of CIDP, and the male-to-female ratio was 2.8:1 and 3:1, respectively. Though cases of CIDP can be seen at any age [16], Vasanth A et al., have reported electrophysiological evidence of demyelination in all the 12 (100%) cases of CIDP included in their study [17], which was similar to the demyelinating pattern seen in the majority of the cases (86.20%) in this study. Sensorimotor axonal demyelinating neuropathy was the commonest pattern observed in the present study in 56.20% of cases. In a study by Kulkarni GB et al., based on the usefulness of supportive pathologic criteria in the diagnosis of CIDP, a predominantly demyelinating pattern was seen in 65.2%

of cases, an axonal pattern in 8.7% of cases, and a mixed axonal and demyelinating pattern in 26.1% of cases [16]. In the present study, though most of the cases (65.5%) showed a mixed axonal and demyelinating pattern, followed by a pure demyelinating pattern seen in 20.6% of cases and a pure axonal pattern seen in 13.7% of cases.

In the present study, symmetric sensory motor neuropathy was seen in the majority of cases (93.1%), and asymmetric sensory motor neuropathy in the remaining (6.9%) cases. Among patients with DN in the current study, 70.6% were males and 29.4% were females, with a male-to-female ratio of 2.4:1, with an age range of 45-84 years and a mean age of 57.5 years. A previous similar study among cases of DN showed 66% males and 34% females with a male-to-female ratio of 1.97:1 and an age range of 31-95 years, with a mean age of 64.7 years [17]. Distal sensorimotor polyneuropathy was seen in the majority of the cases with the classic glove and stocking pattern of involvement. In a study on Chinese patients with DN, histology revealed perineurial oedema in all cases, with a mild degree of loss of myelinated fibres in 40% of cases, followed by moderate and severe degrees of loss in 20% of cases each. Those cases with severe degrees of loss had increased endoneurial collagen [18]. In the current study, the perineurium was unremarkable in the majority of the cases (88.2%). A moderate degree of loss of myelinated fibre was seen in 47% of cases, severe degree loss in 41.2% of cases, and mild loss in 11.8% of cases. Endoneurial fibrosis was seen in all cases.

Among cases of Hansen's neuritis, both cases included in the current study were males aged between 30-50 years. This was in concordance with previous studies on the same with an age range of 16-69 years and a male-to-female ratio of 1.8:1 [19]. Peripheral nerve thickening has been reported in 32% of cases of pure neuritic leprosy in previous studies, with sensory axonal neuropathy as the commonest pattern on NCS. The majority of cases of pure neuritic leprosy were diagnosed as BT (42.8%), followed by borderline lepromatous (BL-23.9%), polar tuberculoid (TT) in 13%, and mid-borderline (BB) in 10.8% of cases [19]. In the current study, one of the cases had bilateral ulnar and sural nerve thickening and was diagnosed as BB leprosy, whereas the other case was diagnosed as TT leprosy.

In the current study, the two cases reported as amyloid neuropathy presented with asymmetric sensorimotor neuropathy and showed sensorimotor axonal demyelinating neuropathy, with amyloid deposits around the endoneurial capillaries. A previous study by Vital C et al., among six cases of amyloid neuropathy, four were also associated with monoclonal gammopathy, and two patients presented with idiopathic polyneuropathy [20].

CMT cases were found to be associated with a uniform slowing of conduction velocities on NCS. Histologically, onion bulbs are common in CMT1 along with axonal loss, whereas in CMT2, axonal and regenerating clusters without demyelination are commonly seen [21]. In the present study, one case (25%) showed axonal and demyelinating neuropathy, and the remaining four cases (75%) presented with axonal neuropathy. Sixty percent of cases showed thinly myelinated fibre, and one case (25%) showed regenerating clusters.

The current study's nerve biopsies revealed that CIDP, observed in 21.6% of cases and characterised by remarkable histological abnormalities, is a significant cause of peripheral neuropathy. This result was consistent with the research by Agrawal A et al., which found that 7.2% of cases had chronic demyelinating neuropathy. The significance of identifying demyelinating illnesses as important aetiologies of peripheral neuropathy is highlighted by both investigations. Furthermore, it was observed in this study that 29 cases (21.6%) of peripheral neuropathy in this analysis were associated with CIDP, which strongly correlates with the 7.2% of cases in Agrawal A et al.,'s study that were identified as chronic demyelinating neuropathy. These results underscore the ongoing challenges in using nerve biopsies to diagnose these illnesses and the need for further research and advanced diagnostic methods [22].

In the present study, a predominance of male patients (M:F=1.7:1) with peripheral neuropathy was observed, consistent with demographic trends seen in similar studies. The age distribution showed a peak incidence in the 40-70 age group, with a mean age of 51.8 years. This closely aligns with findings reported by Kaur A and Harsh A, where nerve biopsies were also utilised to diagnose various forms of peripheral neuropathy. Both studies emphasised the diagnostic utility of nerve biopsies in identifying conditions such as CIDP and VN, highlighting their critical role in guiding clinical management and treatment strategies [23].

In the present study, both cases diagnosed as AIDP were males aged 26 and 56 years. CSF findings were not available for either of these patients. Previous studies have reported a mean age of onset of 40 years with a slight male predominance and protein elevation and albumin-cytologic dissociation in the CSF [24]. Nerve biopsies are no longer indicated in the diagnosis of AIDP, and hence there is a dearth of recent literature elucidating the microscopic features of the same. The proportion of cases for which an exact aetiological diagnosis could not be made was much less (9.0%) compared to previous studies (46%) [25]. Among these cases, two cases clinically suspected of CIDP did not show supportive histological features. One case was positive for amyloid deposits on abdominal fat but negative for the same in the nerve. Another case suspicious of autonomic neuropathy clinically showed myelinated fibre loss on histology. The current study relied only on light microscopy, and any other cause could not be ascertained for these cases.

Limitation(s)

Lack of immunohistochemistry for inflammatory cells, neurofilament protein for axon density, myelin basic protein for myelin staining, and semithin studies.

CONCLUSION(S)

This study concluded that nerve biopsy can aid in the diagnosis of cases of peripheral neuropathy when considering clinical features, electrodiagnostic tests, and other investigations, especially when the combination of the latter three fails to provide a definite diagnosis. VN was the most common aetiology of peripheral neuropathy, followed by CIDP and DN. The histopathological examination of nerve biopsies is a useful tool in distinguishing between diseases with overlapping clinical features, confirming or excluding vasculitis and diagnosing hereditary diseases in settings where genetic testing is either not available or affordable.

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