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Study of Significance of Sural Nerve Biopsy in Diagnostic Dilemma in Neuropathy from a Tertiary Care Referral Centre in Central India

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ABSTRACT

Sural nerve biopsy is important in diagnosing causes of neuropathy. Peripheral neuropathies are a heterogenous group of disorders with varying etiologies. A systematic approach is required for patient evaluation for cost effective diagnosis. Nerve biopsy has a good diagnostic yield if done in properly selected cases. This is especially so for the asymmetrical neuropathies particularly infectious causes like leprosy, vasculitis and amyloidosis.

Keywords: Sural nerve biosy, peripheral neuropathy.

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INTRODUCTION

Peripheral neuropathies are amongst the most common disorders in patients attending neuropathy clinic. A step wise systematic approach comprising a good clinical history, a thorough neurological and systemic examination, electro diagnostic studies and relevant biochemical tests should be undertaken. Nerve biopsy should only be performed when there is suspicion of certain disorders, particularly amyloidosis, vasculitis, leprosy, and tumor infiltration. Nerve biopsy is rarely necessary for the diagnosis of CIDP and should primarily be used to exclude other etiologies. The yield of nerve biopsy depends on a number of factors, including selection of patients, expertise of the laboratory, and techniques used. A recent prospective study has shown that nerve biopsy improves treatment in an estimated 60% of patients¹, a figure close to that of an earlier retrospective study². With hereditary neuropathies, it is now seldom necessary to perform a morphological study of a nerve biopsy specimen. In multifocal neuropathy, nerve biopsy more often contributes to the diagnosis than in the other patterns of neuropathy. Although sural nerve biopsy has been considered a standard method of diagnosing vasculitic neuropathy, the procedure yields unequivocal evidence of vasculitis in only 20% of patients in whom biopsies are performed for this indication^{3, 4}. A recent multicenter prospective study confirmed the higher yield for performing a biopsy of the superficial peroneal nerve combined with a peroneus brevis muscle biopsy to search for vasculitis because of the higher frequency of involvement of the peroneal nerve in vasculitic neuropathy and the frequent involvement of muscle arteries⁵.

Patients and method

The present study was carried out at a tertiary care 1000 bedded referral hospital in eastern part of India, over a period of 24 months from September 2011 to September 2013. This study was conducted on Seventy Five patients suffering from peripheral neuropathy. These were referred to neurology department for evaluation and included in the study after proper written consent. The neuropathy was considered disabling when sensorimotor deficit of peripheral origin leads to impairment of activity of daily living. Patients suffering from a disabling neuropathy of known origin were included in the study only when uncommon manifestations were present. Initially all patients had been examined by two neurologists separately. Neurological interview and examination was carried out in a standardized manner. A detailed evaluation was performed on all individuals to record the number and distribution of affected nerves. Nerve thickening was ascertained by comparing one nerve with its counterpart on the contralateral side. Sensory impairment, motor deficit, and disability/deformity status were assessed by using standard methods. Individual muscle power was graded according to the method described by the Medical Research Council

(MRC) of London⁶. The distribution of motor and sensory symptoms were recorded as distal symmetrical, distal asymmetrical, or focal or multifocal. A family history of neurological disease, the concurrence of other diseases or possible intoxication (medication, alcohol or other toxic agents) were also recorded. All patients had routine blood tests, biochemical assays and protein electrophoresis. Other tests were performed only when required in the clinical context. Routine electrophysiological tests were carried out in all patients comprising motor and sensory nerve conduction and F waves. The median and ulnar nerves in the upper limbs and the Tibial , Common Peroneal and Sural nerves were evaluated in the upper limbs. In cases of symmetrical neuropathies one upper limb and one lower limb were evaluated while in asymmetrical neuropathies at least three limbs were evaluated .The following variables were measured: distal motor latency, motor and sensory conduction velocity, the amplitude of the compound muscle action potential, F wave and sensory nerve action potential. The variables were considered abnormal when they exceeded the limits of normality by 2 SDs. Normal data were prepared for our laboratory. When required in the clinical context, muscles were examined using concentric needles. Those patients in whom the clinical, electro diagnostic, and the biochemical tests were inconclusive were subjected to a sural nerve biopsy. Sural nerve biopsy was carried out under aseptic precautions after taking a written informed consent. The procedure was done under local anesthesia using 1% lignocaine which was infiltrated behind lateral malleolus. Incision was given along the short saphenous vein. the scarpa's fascia was divided with blunt dissection exposing the nerve and vein which was separated. Nerve was ligated at the proximal end and was cut distal to ligature. A 2.5 cm length of nerve was taken out. Gluteraldeyde/formalin fixed nerve biopsies were processed for paraffin embedding and sectioned in transverse and longitudinal planes. Four-6 micron thick sections were routinely stained with hematoxylin-eoisn (HE) for morphological examination and masson's trichrome (MAT) for collagen. For the Kultshitsky-pal (K-pal) stain for myelin, a small segment of fixed nerve was placed overnight in Fleming's solution and processed the next day for paraffin embedding Final diagnosis was made after biopsy. If diagnosis was not evident then cryptogenic neuropathy was labeled. To evaluate the yield of nerve biopsies, we referred to the criteria published by Midroni et al. and Argov et al . Diagnostic biopsies showed abnormalities specific or highly suggestive of a definitive diagnosis. Contributory biopsies provided information that was either essential or helpful for the patient's management. Non contributory biopsies did not influence patient's management and was not revealed any significant information helping in diagnosis or management of patient. All data entered in SPSS 16.0 version and analyzed. Significant difference between proportions is tested by Fishers's exact probability test.

Table 1: Final diagnosis in nerve biopsy group

S. No	Final diagnosis	No. of patients (%)
1	HD	22(30.13%)
2	Axonopathy	4(5.47%)
3	Vasculitis	21 (28.76%)
4	CIDP	4 (5.47%)
5	Inflammatory neuropathy	4(5.47%)
6	Demylinating	2(2.73%)
7	Diabetic	4 (5.47%)
8	Undiagnosed	12 (16.43%)
	Total	73 (100%)

Most common diagnosis was leprosy in nerve biopsy patients (30.13%) Second most common diagnosis was Vasculitis (28.76%). (16.3%) patients remain undiagnosed after biopsy.

	Diagnostic	Contributory	Noncontributory	Total (%)
No. of patients	15	14	7	36
Clinical presentation				
Multiple Mononeuropathy	11	12	1	24(67)
Polyneuropathy	4	2	6	12(33)
Impaired JP/vibration	10	8	3	21
Diminished DTRs	12	5	2	19
Tingling	14	11	3	28
Numbness	12	13	4	29
Sensory Motor involvement				
Sensory	6	2	5	13
Motor sensory	9	12	2	23
Electrophysiological study finding				
Axonal	12	12	6	30
Demyelinating	3	2	1	6
Duration of illness before biopsy				
<1 year	11	6	3	20
>1 year	4	8	4	16

RESULTS AND DISCUSSION

Out of total 100 patients, 73 patients selected for nerve biopsy. Thirty nine (52%) patients were diagnosed with detailed clinical electrophysiological and routine investigations. The mean age in biopsy group patients was 43.19 ± 22.62 years, range from 8 to 72 years. Patients were dispersed in all age groups with two peaks between 11-30 and 61-80 years age group 36% in each. Male: female were 2.2:1. Total duration of illness before biopsy varied from 1 month to 20 years, median was 12 months. Multiple mononeuropathy was present in 67% and polyneuropathy was found in 33%. Sensorimotor (72.22%) type of neuropathy was most common clinical and electrophysiological diagnosis while predominant sensory presentation

was seen in 27.8% of patients. Sensory symptoms were symmetrical in 14 and asymmetrical in 25 patients. Weakness was present in 34(94%) of patients, which was symmetrical in 44% and asymmetrical in 56% patients. Other results are depicted in table no. 2. Final diagnosis could be made in 80% of patients. Diagnosis was Hansen's disease in 30%, Vasculitis in 29%, CIDP in 5.5% and diabetes in 5%. In fifteen cases the neurologists agreed that the nerve biopsy had changed the preferred diagnosis or gave diagnosis otherwise even not suspected. This group called as biopsy importance point of view as 'Diagnostic'. In 14 cases the neurologists judged that the biopsy had contributed by confirming a diagnosis which had already been suspected. This group called as 'Contributory'. In seven cases the neurologists considered that the biopsy did not contribute to the diagnosis and those were remaining undiagnosed and called 'Idiopathic'. These termed as 'Noncontributory'. Out of these 'Idiopathic' cases, one case was suspected cryoglobulinemic vasculitic neuropathy secondary to Hepatitis C infection. Another patient suspected to have B12 deficiency neuropathy, but remained unproved after investigation. This patient responded well to parenteral B12 treatment during 6 month follow up. Out of eighteen leprosy patients nerve biopsy revealed epithelioid granuloma in 39%, AFB positive in 28% and inflammatory infiltrate in 78% patients. A correlation between the clinical and electro diagnostic findings with the nerve biopsy revealed that that impaired joint position and vibration was more in group of patients in which biopsy proved useful (Diagnostic as well as contributory), but p value was not significant. Similarly diminished DTRs were statistically non significant more in useful group. Tingling was statistically more significant in biopsy favoring group than in noncontributory group (p 0.03). Biopsy was more helpful in patients with multiple mononeuropathy group than polyneuropathy (p 0.003). Similarly patients presenting with predominant or pure sensory complains were less likely to be diagnosed by biopsy than patients with mixed presentation (p 0.04). Pattern of electrophysiological involvement either axonal or demyelinating and duration of illness before biopsy had no correlation with the outcome of biopsy. This was a prospective study of 100 consecutive patients of peripheral neuropathy who referred to us and were undiagnosed after evaluation by physicians. Only seventy three of them underwent sural nerve biopsy for a disabling neuropathy. Most evident straightforward causes like Diabetes, alcohol, drug induced etc were not included. Probable hereditary neuropathy patents were not considered for biopsy rather they went for genetic evaluation. Thus mainly the treatable cases which remained undiagnosed/ inconclusive after clinical, electro diagnostic and biochemical evaluation were considered. In thirty (41%) of the patients nerve biopsies were diagnostic. In another 28 cases (39%) patients nerve biopsy proved to be contributory. It thus helped in confirming diagnosis or excluded other causes of

neuropathy thus ending the controversy. Thus in about 29 cases (80%), performing nerve biopsy proved to be worth while. Of least value were the seven (20%) biopsies which showed either a non-specific axonal neuropathy or no information. An important point to be noted here is a detailed clinical history and meticulous neurological examination with first line routine investigation, proved to be sufficient in 39 patients (52%) who were referred to us. In a prospective study by Gabriel C M *et al* (2000) (1) found that the greatest diagnostic value in 14%, of lesser value 70% and of least value were in 16%. These results revealed that 84% patients got advantage from nerve biopsy which is closer to our results. In a retrospective study of by Hughes *et al* they also noted a change in diagnosis in 17% of 36 patients⁷. In one retrospective study Argov *et al*⁸ considered that nerve biopsy contributed to the diagnosis in 38% of 53 patients. In another, Neundorfer *et al*⁹ considered that the biopsy was “crucial” for establishment of the diagnosis in 27% of 56 patients and confirmed a previously suspected diagnosis in 37%. In the largest retrospective study Oh¹⁰ 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 neuropathy¹¹. In our series leprosy neuropathy was found most common (50%) cause of undiagnosed peripheral neuropathy. This is highly different from other studies from western world. This indicates that leprosy is still most common cause of treatable peripheral neuropathy. These results also depict that leprosy is still endemic in India despite of all efforts by Government of India and WHO. Leprosy neuropathy almost always occurs in conjunction with a certain type of skin lesion. The presence of nerve deficit in patients from endemic areas who did not have skin lesions is considered sufficient reason for a PNL diagnosis^{12, 13, 14}. In the presence of dense neuropathic sensory loss and dark skin colored people it is not always possible to make out anesthetic patch over skin so there should be a high index of suspicion. The proportion of leprosy patients with PNL will ultimately depend on the population in question, as, for example, in India, where its incidence has been reported to range from 5.5 to 17.7% of all leprosy cases¹⁵. Nerve biopsy findings are well according to previous studies. Vasculitic neuropathy was demonstrated in 8 patients, out of them in 5 patients it was associated with necrotizing arteritis and it was found very likely in 3 patients, accounting for a total of 22% of the cases. This is similar than that found in other studies^{16,17,18,19}. (Huang, 1981; Hessel *et al.*, 1986; George and Twomey 1986; Barach, 1989; Wertman *et al.*, 1988). A correlation of biopsy with the clinical features revealed that in the patients with the clinical pattern of multiple mononeuropathy, nerve biopsy proved beneficial than polyneuropathy group (P 0.003). Similarly in patients with sensorimotor symptoms nerve biopsy was more valuable (P

0.04). A significant correlation was found in presence or absence of tingling. Biopsy proved more diagnostic when tingling was there than absence of it (P 0.03). These results are expected in the case of multiple mononeuropathy.

CONCLUSIONS

Thus in carefully selected patient group nerve biopsy is a useful aid for etiological diagnosis and management of patients, more so in patients with mononeuropathy multiplex group. In this prospective planned study sural nerve biopsy altered the diagnosis in 41% and overall contributed in 80% in 36 consecutive patients. Hansen's disease was the commonest cause of neuropathy in our series and being one of the commonest treatable causes of neuropathy in an endemic country like India, one must have a high index of suspicion so that early can be started and long term complications prevented.

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