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Clinicopathologic Analysis of 124 Biopsy-Proven Peripheral Nerve Diseases

We reviewed clinical, histological and ultrastructural findings of 124 cases of sural nerve biopsy specimens to delineate the trends of peripheral nerve diseases in our institute. Eighty-one were men and 43 were women. We categorized them into five groups: specific diagnosis (66 cases, 53.2%), axonal degeneration type (47 cases, 37.9%), demyelinating type (4 cases, 3.2%), mixed axonal degeneration-demyelinating type (6 cases, 4.8%) and normal (1 case, 0.9%). Cases with specific diagnosis included 21 inflammatory demyelinating polyneuropathy (15 chronic inflammatory demyelinating polyradiculoneuropathy, 6 Guillain-Barré disease), 13 hereditary motor and sensory neuropathy (7 Charcot-Marie-Tooth type I, 6 Charcot-Marie-Tooth type II), 10 vasculitis, 6 toxic neuropathy, 4 leprosy, 3 diabetic neuropathy, 2 alcoholic neuropathy, 1 Fabry's disease and other specific diseases (5 cases). In our cases, the proportion of specific diagnoses was higher, while the proportion of demyelinating peripheral neuropathies and normal were lower than those of Western series. The results of this study indicate that 1) a close clinicopathologic correlation is important to make a precise diagnosis of peripheral nerve biopsy, 2) Biopsy under strict indication may reduce unnecessary histologic examination, 3) There is no difference in disease pattern of peripheral neuropathy between Western people and Koreans.

Key Words: *Microscopy, Electron; Peripheral Nervous System Diseases; Nerve, Sural; Biopsy*

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INTRODUCTION

Peripheral neuropathy is a common clinical problem in neurology. The aims of histopathological investigation of peripheral nerve, usually sural nerve, are identification of characteristic changes, or reaction patterns allowing diagnosis and defining the acuity, progression and degree of peripheral neuropathies or of the extent of regeneration and restitution (1).

There have been several reports on the analysis of nerve biopsies in Western people (1-3). Common diseases of peripheral nerve biopsies in Western countries include Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), hereditary motor and sensory neuropathy (HMSN), leprosy, diabetic neuropathy/microangiopathy, amyloidosis, tomaculous neuropathy and paraprotein neuropathy in descending order (2). However, to the best of our knowledge, there has been no report done on the analysis of sural nerve biopsies from Koreans. Therefore, we reviewed clinicopathologic and ultrastructural studies on optimally processed 124 cases of sural nerve biopsy specimens from Koreans.

MATERIALS AND METHODS

One hundred twenty-four cases of sural nerve biopsy specimens from the files of Department of Pathology of Asan Medical Center from 1989 to 1999 were reviewed. Eighty-one were male (mean age at biopsy: 42 years) and 43 were female (mean age at biopsy: 41 years). Pathology reports and clinical data were reviewed to record clinical histories, including symptoms and signs, family histories, duration of symptoms and results of nerve stimulation tests (nerve conduction velocity, NCV) and electromyographic studies (EMG).

All available glass slides and stored ultrastructural pictures were also reviewed. We categorized them after clinicopathologic reviews into five groups: specific diagnoses, axonal degeneration type, demyelinating type, mixed axonal degeneration-demyelinating type and normal peripheral nerve.

When the patients showed typical symptoms and signs with compatible NCV and EMG features, family histories representing neuropathy and pathognomonic or characteristic histologic features of sural nerve biopsy, we designated them as having a specific diagnosis.

Axonal degeneration type was designated when the biopsy revealed decreased numbers of myelinated or unmyelinated axons, breakdown of axons and myelin sheaths, persistence of columns of empty Schwann cells (collagen pockets) and basement membranes and increased amounts of endoneurial connective tissue.

Demyelinating type was designated when the biopsy displayed features of demyelinated axons, demyelination and/or remyelination with disproportionally thin-myelinated axons and Schwann cell proliferation. When the biopsy showed increased numbers of replicating Schwann cells forming concentric circles alternating with collagen layers around the axon resulting in an onion-bulb formation, we categorized it as chronic demyelinating type.

When the biopsy revealed features of mixed degeneration of axons and demyelination and/or remyelination, we called it mixed axonal degeneration-demyelination type. When the biopsy showed features of normal peripheral nerve, we categorized it as normal.

RESULTS

Diagnoses of the 124 cases were summarized in Table 1. Sixty-six cases were diagnosed as having specific entities (53.2%). Axonal degeneration type was seen in 47 cases (37.9%) (Fig. 1). There were six cases (4.8%) of mixed axonal degeneration-demyelinating type and four cases of (3.2%) nonspecific demyelinating type. Only one case (0.9%) showed normal histologic and ultrastructural findings.

Table 1. Analysis of 124 cases of sural nerve biopsy specimens

Categories of diseases	Number of cases	Percentage
Specific diagnosis	66	53.2%
Axonal degeneration	47	37.9%
Mixed axonal degeneration & demyelination	6	4.8%
Demyelination	4	3.2%
Normal	1	0.9%
Total	124	100%

The diagnoses of 66 cases with specific entities were summarized in Table 2. Among these 66 cases, 21 cases revealed inflammatory demyelinating polyneuropathy (15 CIDP, 6 Guillain-Barré syndrome). Thirteen cases of HMSN consisted of seven type I (Charcot-Marrie-Tooth disease) (Fig. 2) and six type II (neuronal type). Vasculitis was seen in 10 cases, which were composed of five polyarteritis nodosa, two rheumatoid arthritis (Fig. 3), one necrotizing vasculitis, one Churg-Strauss syndrome and one Sjögren's syndrome. Toxic neuropathy was demonstrated in six cases among which two cases were due to intoxication of trichloro-dibenzoparadioxin, one organophosphate intoxication, one chloropromazine intoxication

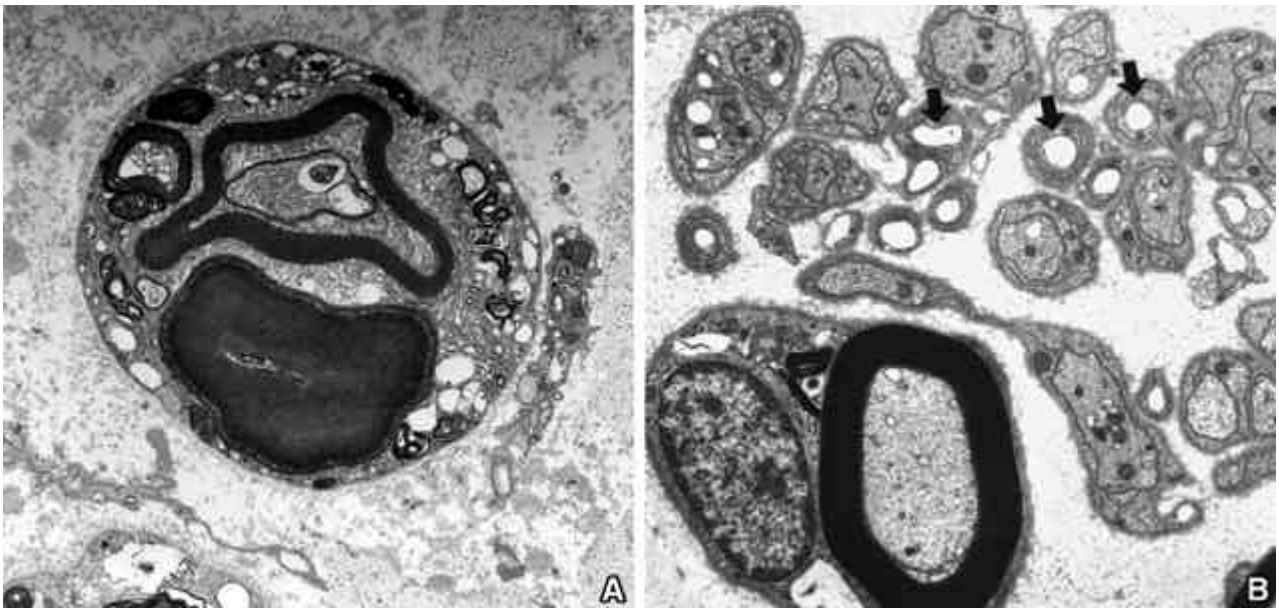

Fig. 1. A: Axonal degeneration showing disintegration of axoplasm and myelin figures is observed. There is a marked loss of nerve fibers with increased amounts of endoneurial connective tissue (uranyl acetate and lead citrate stain, ×2,000). **B:** Axonal neuropathy: There are numerous collagen pockets (arrows) in the Schwann cells suggesting loss of unmyelinated nerve fibers (uranyl acetate and lead citrate stain, ×3,000).

Table 2. Specific diagnoses among 124 sural nerve biopsies

Diagnosis	Number of cases
CIDP	15
HMSN	13
Vasculitis	10
Guillain-Barré syndrome	6
Toxic neuropathy	6
Leprosy	4
Diabetic neuropathy/microangiopathy	3
Alcoholic polyneuropathy	2
Fabry's disease	1
Adrenoleukodystrophy	1
Amyloidosis	1
Folate deficiency	1
Hereditary sensory and autonomic neuropathy	1
Small fiber neuropathy	1
Total	66

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; HMSN, hereditary motor and sensory neuropathy

and two unknown agents. There were four cases of leprosy (Fig. 4), three diabetic neuropathy/microangiopathy and two alcoholic polyneuropathy. The remainder consisted of one case of amyloidosis, adrenoleukodystrophy, Fabry's disease (Fig. 5), small fiber neuropathy (Fig. 6), hereditary sensory and autonomic neuropathy and folate deficiency.

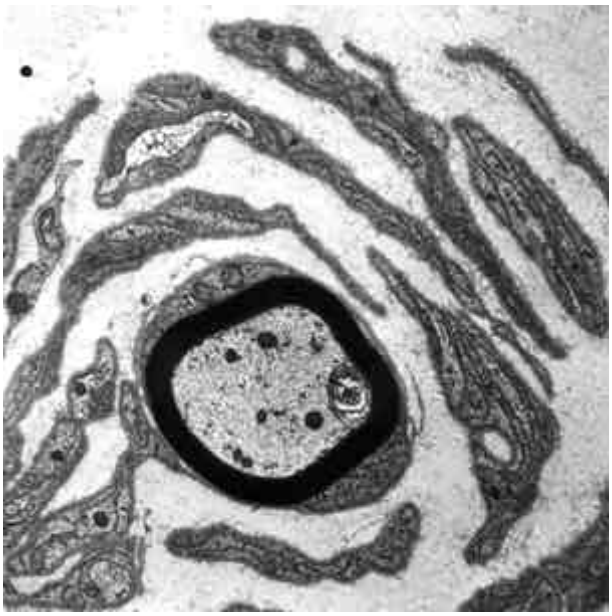

Fig. 2. Charcot Marie Tooth disease type I: Replication of Schwann cells forming concentric circles alternating with collagen layers results in onion-bulb formation and hypertrophic nerve fibers (uranyl acetate and lead citrate stain, ×3,000).

DISCUSSION

Nerve biopsies in peripheral neuropathies are employed to establish a diagnosis, treatment plan and prognosis and to provide information for genetic consul-

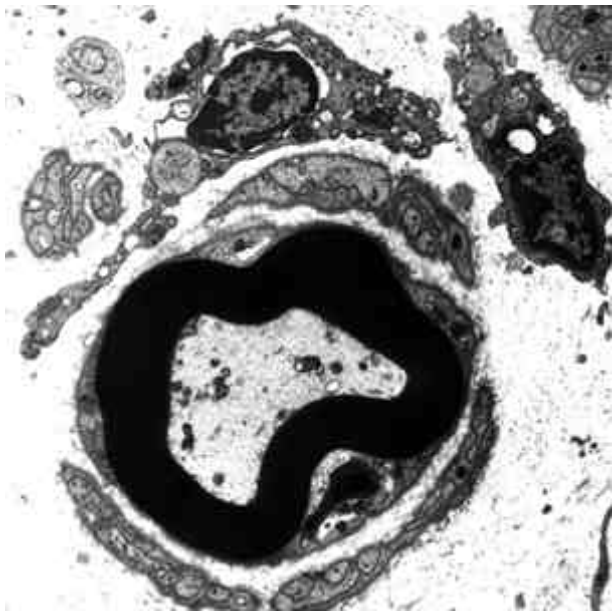

Fig. 3. Rheumatoid arthritis: Small onion-bulb formations with endoneurial lymphocytic infiltration are present (uranyl acetate and lead citrate stain, ×4,000).

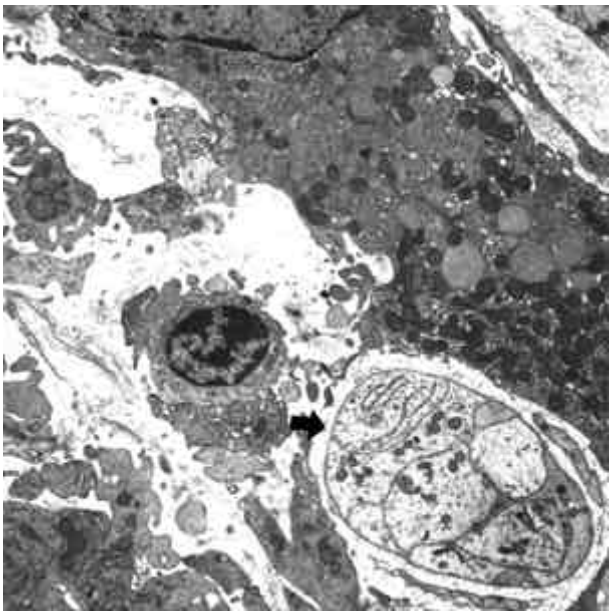

Fig. 4. Leprosy: Endoneurium is infiltrated by lymphohistiocytes. Loss of nerve fibers and swollen Schwann cell processes (arrow) surrounded by external lamina are seen (uranyl acetate and lead citrate stain, ×2,000).

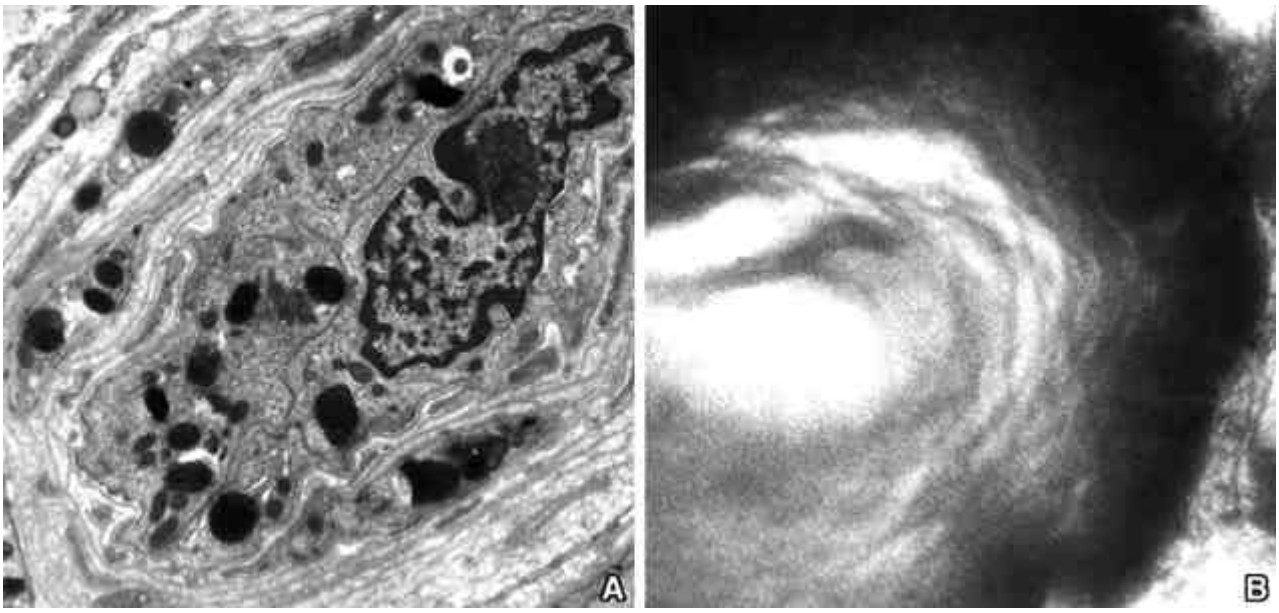

Fig. 5. **A:** Fabry's disease: Several lipid storage inclusions in the endothelial cells and pericytes (uranyl acetate and lead citrate stain, ×5,000). **B:** High power view of a storage inclusion shows a periodic lamellar appearance (uranyl acetate and lead citrate stain, ×50,000).

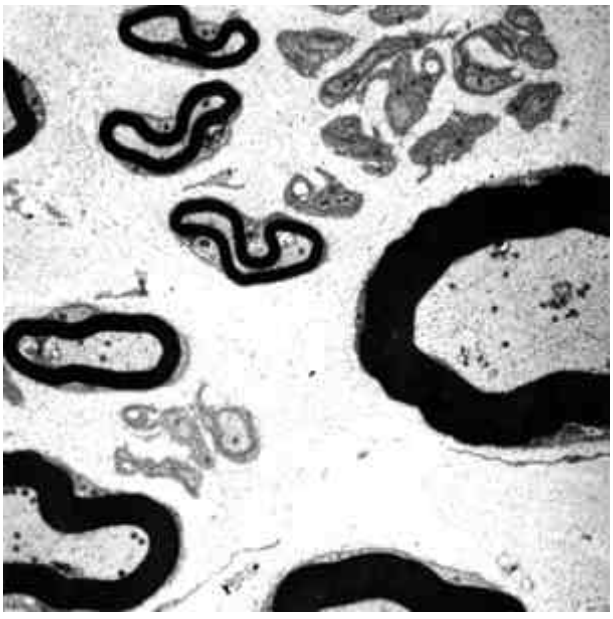

Fig. 6. Small fiber neuropathy shows selective loss of small nerve fibers with shrunken Schwann cell-process and remaining collagen pockets while the myelinated nerve fibers are intact (uranyl acetate and lead citrate stain, ×3,000).

tation (4). They are particularly useful for identifying interstitial abnormalities and for documenting the extent and chronicity of axonal and Schwann cell involvement in diffuse polyneuropathies (5).

There are several candidates for peripheral nerve biopsies, including sural nerve, superficial peroneal nerve, skin branches of peroneal nerve, saphenous nerve, superficial radial nerve and major auricular nerve. Among these nerves, sural nerve is most frequently used for diagnostic purposes due to available data on its composition, lack of motor function and minimal postoperative deficit (6). In our study, we also used sural nerve for the diagnosis because of the above mentioned advantages.

To evaluate peripheral nerve biopsies, five methods are most commonly used including routine paraffin embedded hematoxylin-eosin (H&E) staining, frozen sections, resin embedding-semithin sections, electron microscopic study and teased fiber analysis. Each method has been known to offer different types of information (6). Routine H&E staining is used for identifying interstitial lesions, such as endoneurial inflammatory cell infiltration, vasculitis, granulomas, fibrosis and amyloid deposits. Frozen sections are useful in evaluating vasculitis and metabolic disorders and to permit subsequent special stains and/or immunohistochemical studies. Resin-embedded sections are known to provide good information on the populations of both large- and small-diameter myelinated nerve fibers, to allow assessment of amount of myelin and its thickness relative to axon caliber, to permit identification of onion bulbs and allow electron microscopy if necessary. Electron microscopy is the most useful tool in examining unmyelinated nerve fibers, cytoplasmic organelles and storage materials. Teased fiber analysis is used to differentiate between demyelinating neuropathy and axonal neuropathy because demyelinating and hypomyelinating segments and axonal destruction are easily seen. In our

study, we used routine H&E staining, resin embedding and electron microscopy.

There are several patterns on the interpretation of the peripheral nerve biopsies (6, 7). Axonal degeneration and regeneration were known to be the most common pathologic findings in peripheral nerve biopsies. They often occur in combination. In H&E stained longitudinal sections, the features of axonal degeneration are chains of eosinophilic globular bodies with vacuolated spaces in more than 6 segments in length which have been called "myelin ovoids". In the early stage of axonal degeneration, myelin debris are arranged as irregular clusters within the original axon, and in the later stage, small clear vacuoles are detected within the phagocytic cells.

The features of chronic axonopathies include decreased number of axons per cross-sectional diameter and collagen deposition in endoneurial spaces. Axonal regeneration is considered when the diameter of small unmyelinated or myelinated axons are below the lower limit of the diameter of unmyelinated or small myelinated nerve fibers. The regenerating nerve fibers are proportional in ratio to myelin/axon thickness. They could be clustered close together in resin-embedded sections.

The features of axonal degeneration such as selective depletion of small myelinated and unmyelinated fibers have been observed in amyloidosis, diabetes, Fabry's disease, Tangier disease, chronic idiopathic anhydrosis and hereditary sensory and autonomic neuropathies (2).

Demyelination is referred as a selective degeneration or loss of myelin sheaths with intact axons. On resin-embedded sections, the axons have inappropriately thin myelin sheaths. When repetitive episodes of demyelination involve the same internodes, the proliferation of Schwann cells creates concentrically oriented layers of Schwann cell processes forming "onion bulbs". Segmental demyelination has been described in demyelinating diseases such as Guillain-Barré syndrome (2), CIDP, Charcot-Marie-Tooth disease type I, Loussy-Levy syndrome and Dejerine-Sotta's disease.

Several reports of peripheral nerve biopsies in Western people (2, 3) have been done. In one report (2), specific diagnosis was possible in 28.7% (196 of 683 cases). Peripheral neuropathy with axonal degeneration was 43.5% (297 of 683cases). Mixed axonal degeneration-demyelinating type was 8.6% (59 of 683 cases). Focal chronic inflammation and axonal degeneration type was 6.3% (43 of 683 cases). Normal or minimal change was 12.9% (88 of 683 cases). Whereas in Schroder's study (3), peripheral neuropathy of the axonal type was 29.9% among 5,266 cases, that of the demyelinating type was 15.7%, that of the neuronal type was 14.3% and that of specific diagnosis was 38.7%. Normal peripheral nerve was seen in 1.4%.

In our study, specific diagnosis was made in 66 of 124 cases (53.2%), which is higher than that of Western studies. The proportion of axonal degeneration type (37.9%) was similar to that of Western reports, but the proportion of normal (0.9%), demyelinating (3.2%) and mixed axonal degeneration-demyelinating (4.8%) types was lower in this study than that of Western studies. Higher proportion of specific diagnosis in our study may indicate that a close clinicopathologic correlation, including patients' history, family history, laboratory data, electromyographic study and nerve conduction test, is important to make a precise diagnosis in peripheral nerve biopsies.

The leading causes of specific diagnosis of peripheral neuropathy in our institute were CIDP, HMSN, vasculitis, Guillain-Barré syndrome and toxic neuropathy in descending order. Whereas, the common causes of peripheral neuropathy in Bilbao's report were Guillain-Barré syndrome, CIDP, vasculitis, HMSN, leprosy and diabetic neuropathy-angiopathy in descending order. The frequent causes of peripheral neuropathy in Schroder's report included vasculitis, HMSN, amyotrophic lateral sclerosis, neuropathy in mitochondrial myopathy, hypertrophic neuropathy, tomaculous neuropathy and diabetic neuropathy in descending order. However, the relative frequency of individual disease in specific diagnosis group in our study was similar to that of Bilbao's result, showing that there is no different disease pattern in peripheral neuropathy between Western people and Koreans.

Among six toxic neuropathy, two cases were intoxication of trichloro-dibenzoparadioxin, one each of chloropromazine intoxication and organophosphate intoxication and two cases of unknown agent. The proportion of normal or minimal change of sural nerve was extremely rare in our study. Sural nerve biopsy under strict biopsy indication may reduce noncontributory negative biopsy findings.

The diagnostic utility of the peripheral nerve biopsy is tremendous. However, in many occasions, despite apparent pathologic changes, they can be nonspecific (2). Although the proportion of specific diagnosis of our study was much higher than Western studies, the remaining 46.8% remained as nonspecific pathologies. Although these nonspecific axonopathies and/or myelinopathies comprised a reasonable proportion like other reports, better diagnostic skills need to be developed.

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