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Selective Loss of Small Myelinated and Unmyelinated Fibers in Shy-Drager Syndrome

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Summary. The number and sizes of myelinated and unmyelinated fibers in biopsied sural nerves in cases with Shy-Drager syndrome were studied in comparison with cases with olivopontocerebellar degeneration not having autonomic dysfunction. In Shy-Drager syndrome, there was a tendency for both small myelinated and unmyelinated fiber densities to be reduced in comparison with cases with olivopontocerebellar degeneration. Unmyelinated fibers more than 0.5 μm in diameter were significantly reduced in Shy-Drager syndrome, a fact suggesting unmyelinated fiber degeneration. Multilamellated Schwann cell processes, isolated Schwann cell processes, and collagen pockets were more numerous and conspicuous in cases with Shy-Drager syndrome. It was concluded that unmyelinated fibers and small myelinated fibers in the peripheral nerves were involved selectively in Shy-Drager syndrome. The significance of the findings was discussed in terms of autonomic dysfunction observed clinically.

Key words: Shy-Drager syndrome – Sural nerve – Umyelinated fiber loss – Small myelinated fiber loss – Autonomic dysfunction

Introduction

The Shy-Drager syndrome is a form of system atrophy of the nervous system. Its clinical manifestations include various autonomic symptoms, such as orthostatic hypotension, anhidrosis, impotence, and in some cases signs of more generalized neurologic disease, particularly of the extrapyramidal system.

Some morphological substrata of autonomic dysfunction in the Shy-Drager syndrome have been reported. Almost all autopsied cases so far reported have shown degeneration of melanin-containing brainstem nuclei and of central preganglionic autonomic neurons, such as dorsal vagal nuclei and intermedio-lateral column cells. Also, in some cases cell loss, axonal swelling, or Lewy bodies have been described in autonomic ganglia [20, 22, 23, 25].

However, it still remains unknown whether there are morphological changes in the peripheral autonomic nerves in Shy-Drager syndrome. The purpose of this paper is to quantify the number and size of myelinated and unmyelinated fibers in biopsied sural nerves from cases with Shy-Drager syndrome in comparison with those from cases with olivopontocerebellar degeneration not having autonomic symptoms.

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Material and Methods

Materials consisted of three cases with olivopontocerebellar atrophy (OPCA) without autonomic dysfunction (cases 1, 2, and 3), and three cases with Shy-Drager syndrome (cases 4, 5, and 6). Patients in both groups were in the same age range (from 56 – 71 years). All three cases with Shy-Drager syndrome had severe postural hypotension with frequent syncopal episodes. Anhidrosis and impotence were noted in two cases.

To assess the sensitivity to catecholamine, 0.7 mg of freshly prepared epinephrine was injected s.c. in three cases with Shy-Drager syndrome. Systolic blood pressure was increased by 56 – 102 mm Hg (normal values: < 30 mm Hg), and the heart rate was increased remarkably in case 4 (by 61/min) and case 5 (by 49/min) (normal values: < 30/min). Thus, all patients with Shy-Drager syndrome showed marked hypersensitivity to epinephrine.

Case 5 died 1 year after biopsy. Neuropathologic examination revealed typical findings of olivopontocerebellar degeneration in association with degeneration of dorsal vagal nuclei, intermediolateral column cells, and sympathetic ganglia.

Biopsied sural nerves were fixed in 2.5 % glutaraldehyde buffered with 0.1 M phosphate, pH 7.4, at 4° C for 2 h, postfixed in 1 % osmium tetroxide, dehydrated, and embedded in Epon 812. For light-microscopic observation, transverse section, 1 μm thick, were stained with toluidine blue. The density and the diameters of myelinated fibers were measured in two or three fascicles on photographs with a final magnification of 1,000. For electron microscopic study, ultrathin transverse sections were stained with uranyl acetate and lead citrate. The density and the diameters of unmyelinated fibers were measured over the gross area of about 50,000 μm^2 on photographs with a final magnification of 10,000.

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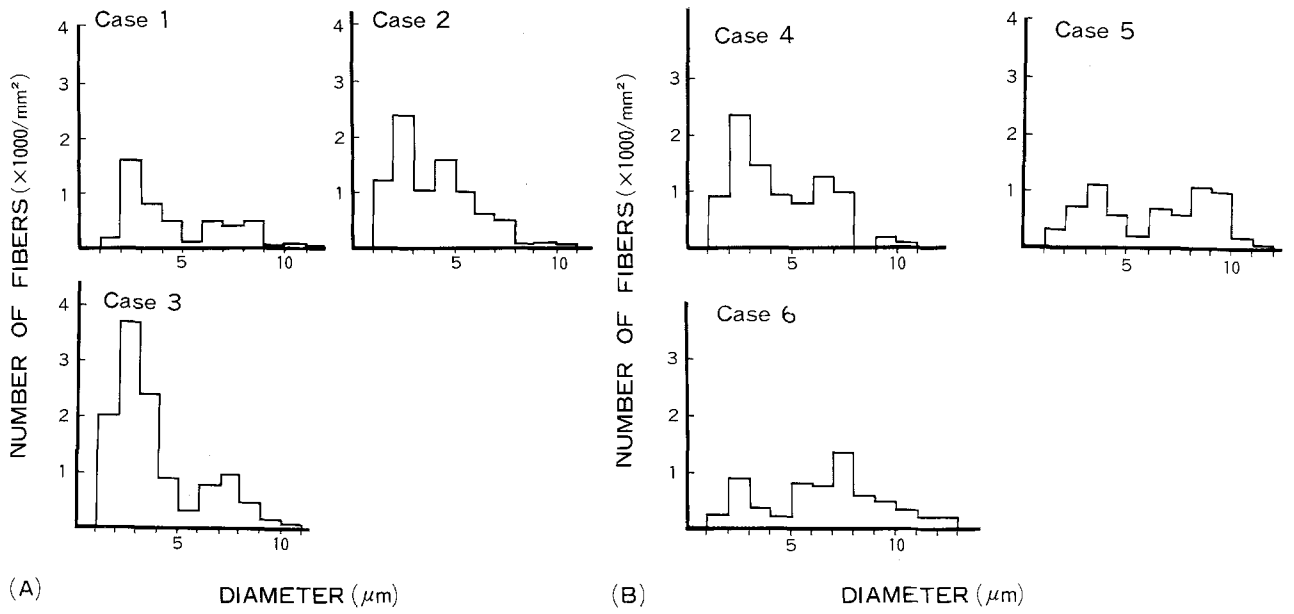

Fig. 1. Size-frequency histograms for myelinated fibers in patients with olivopontocerebellar atrophy without orthostatic hypotension (**A**) and in patients with Shy-Drager syndrome (**B**)

Results

Myelinated Fibers

Figure 1A shows the histograms of the diameters of myelinated fibers in cases with olivopontocerebellar atrophy not associated with autonomic dysfunction. Histograms of cases 1 and 3 show a normal bimodal distribution, with the peak at small diameter being greater than the peak at large diameters. As compared to these results, Fig. 1B shows the fiber diameter histograms of myelinated fibers in cases with Shy-Drager syndrome. The histogram of case 4 is normal. Cases 5 and 6 show histograms with bimodal distribution, but the peak of small diameter fibers was reduced in height as compared to that in cases with olivopontocerebellar atrophy without autonomic disorders.

Large myelinated fibers were more than 5 μm in diameter, small myelinated fibers less than 5 μm. The density of large myelinated fibers in cases with Shy-Drager syndrome was not decreased in comparison with that in cases with olivopontocerebellar atrophy without autonomic dysfunction. The density of small myelinated fibers ranged from 3.210 to 9.016/mm^2 with the average of 6.194/mm^2 in cases with olivopontocerebellar atrophy without autonomic failures. In comparison with these, the small myelinated fiber density was reduced in two of three cases (cases 5 and 6) with Shy-Drager syndrome (5,653/mm^2 in case 4, 2,870/mm^2 in case 5, and 2,031/mm^2 in case 6 with the average of 3,518/mm^2) though the difference in the average values was not significant. There was no remarkable difference between the two groups of patients in the density of total myelinated fibers.

Unmyelinated Fibers

Figure 2A shows the histograms of the diameters of unmyelinated fibers in three cases with olivopontocerebellar atrophy without autonomic dysfunction. The peak is at 0.6 – 0.8 μm in case 1. In case 2 the fiber diameters are distributed from 0.2 – 0.8 μm with almost equal frequencies. In case 3 the peak is shifted to 0.3 – 0.4 μm, but the number of fibers more than 0.5 μm in diameter does not appear to be reduced. In cases with Shy-Drager syndrome (Fig. 2B), the size frequency histograms of unmyelinated fibers is distorted by decreased numbers of large axons with diameters more than 0.5 μm.

There were unmyelinated fibers of more than 0.5 μm in diameter, and unmyelinated fibers of less than 0.5 μm in diameter. The density of total unmyelinated fibers range from 26,568/mm^2 to 44,258/mm^2 in cases with olivopontocerebellar atrophy without autonomic disturbance. When cases with Shy-Drager syndrome were compared with these cases, the total unmyelinated fiber density was normal in case 4 (28,138/mm^2), decreased slightly in cases 5 and 6 (19,670/mm^2 and 14,113/mm^2, respectively). The decrease of total unmyelinated fibers was not due to the decrease of fibers less than 0.5 μm in diameter, but mainly due to the decrease of fibers with diameters more than 0.5 μm. The density of unmyelinated fibers more than 0.5 μm in diameter was signif-

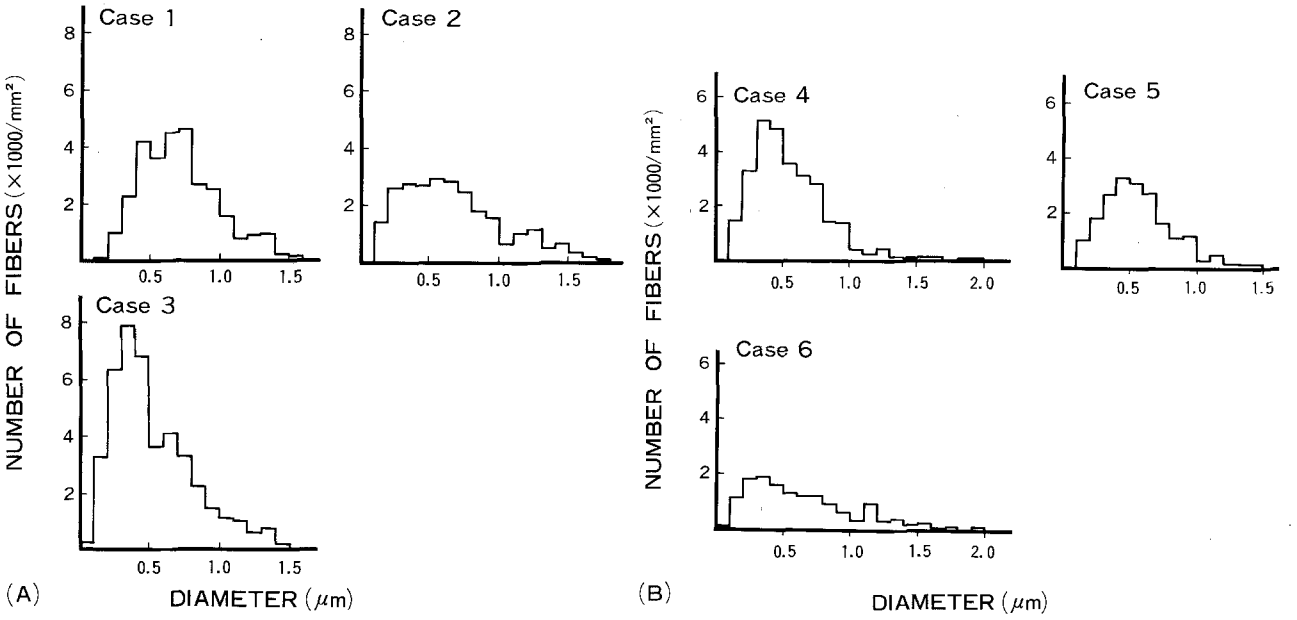

Fig. 2. Size-frequency histograms for unmyelinated fibers in patients with olivopontocerebellar atrophy without orthostatic hypotension (**A**) and in patients with Shy-Drager syndrome (**B**)

icantly reduced in cases with Shy-Drager syndrome (7,703 – 13,512/mm^2, average: 10,691/mm^2) compared to that in cases with olivopontocerebellar atrophy without autonomic dysfunction (17,057 – 21,842/mm^2: average: 19,517/mm^2) ($P < 0.01$).

Electron-microscopic observations on the sural nerves from patients with Shy-Drager syndrome revealed a number of multilamellated Schwann cell processes, small isolated Schwann cell projections, and collagen pockets, all of which are evidence of degeneration of unmyelinated fibers (Fig. 3). These findings were also observed in cases with olivopontocerebellar atrophy not associated with autonomic disturbance, but were far more numerous and conspicuous in cases with Shy-Drager syndrome.

Discussion

This study revealed various degrees of loss of small myelinated and unmyelinated fibers in the sural nerves from patients with Shy-Drager syndrome.

The density of unmyelinated fibers in normal sural nerves varies considerably in previous reports. For subjects younger than 52 years, values of 21,755 – 33,859/mm^2 [14, 15], 32,179 – 66,813/mm^2 [7, 8], 19,000 – 56,900/mm^2 [3], and 41,130 – 49,730/mm^2 [26] have been reported. The age of the patients in the present series ranges from 56 – 71 years. Although the available data for older population are still insufficient, the density of unmyelinated fibers seems to be decreased in the aged: 25,018/mm^2 (59 years old) [14, 15], 19,447/mm^2 (66 years old) [8], 17,868/mm^2 (83 years old) [21], and 23,128/mm^2 (88 years old) [21]. Therefore, the density of unmyelinated fibers seems to be about 20,000 – 25,000/mm^2 in the age range of the present subjects. In this regard, the unmyelinated fiber density in all cases with olivopontocerebellar atrophy without autonomic symptoms was within normal range, while it was decreased in two of three cases with Shy-Drager syndrome. It has been known that, when unmyelinated fibers undergo degeneration and regeneration, the histogram of unmyelinated fiber diameters is distorted by the shift of the peak to smaller diameters [2, 8, 10], or shows a bimodal distribution with an additional peak at small diameters consequent upon regenerating sprout [14, 15, 16]. The quantitative data and abnormal findings in Schwann cell processes in the present study suggest that degeneration of unmyelinated fibers has occurred in cases with Shy-Drager syndrome.

Peripheral autonomic nerves consist largely of unmyelinated fibers and a small proportion of myelinated fibers with small diameter [11]. In the sural nerve these autonomic fibers are considered to coexist and intermingle with somatic sensory fibers conducting pain and temperature sensation. Although cases with Shy-Drager syndrome in the present series did not show sensory disturbance on neurologic examination, it cannot be determined whether the decrease of small myelinated fibers and unmyelinated fibers implies the selective involvement of autonomic fibers, because the possibility remains that reduction of afferent nerve potentials may be shown by physiologic investigations. However, it can be assumed that autonomic fibers

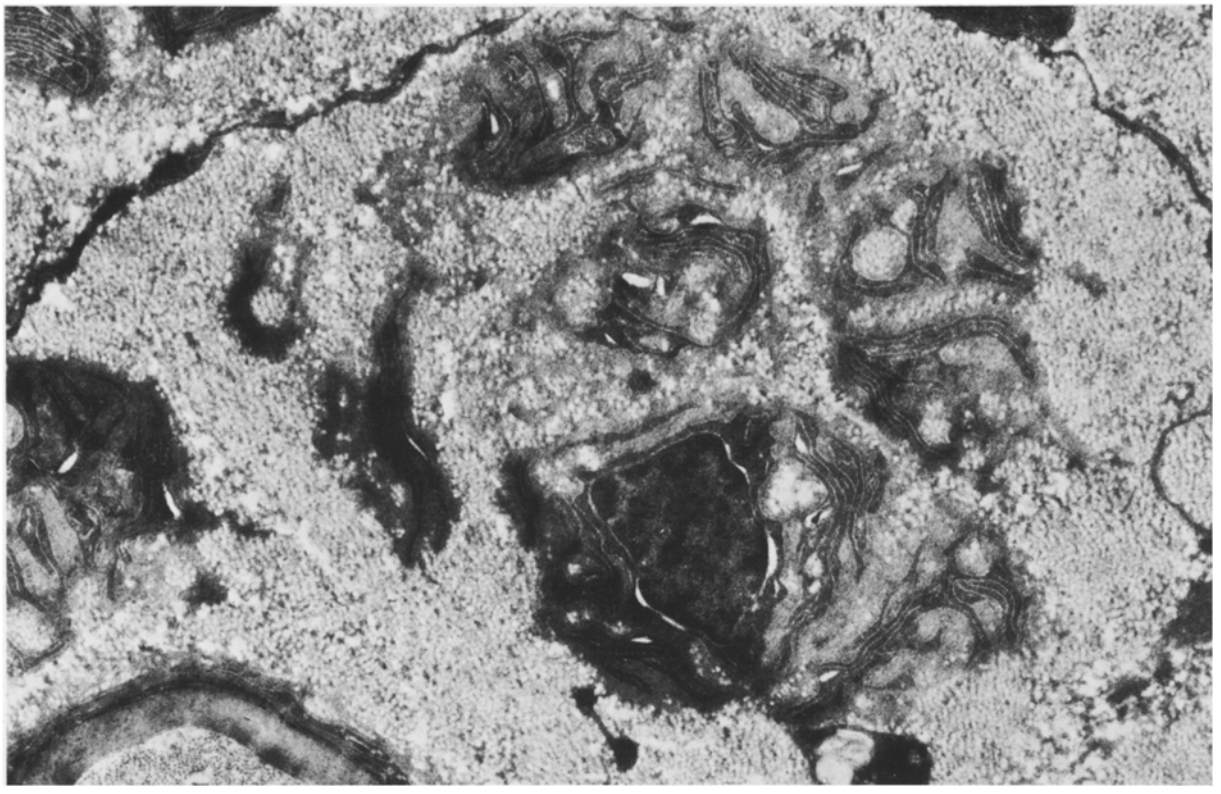

Fig. 3. Electron-microscopic findings of the sural nerve from a case with Shy-Drager syndrome (case 6). There are a number of multilamellated Schwann cell processes and collagen pockets. ×8,900

constitute a large proportion of degenerated fibers, when clinical symptoms are considered. If this assumption is correct, such relatively selective involvement of peripheral autonomic fibers is more likely to be secondary to changes in autonomic ganglion cells rather than primary.

Although systematic morphological studies on the sympathetic ganglia in Shy-Drager syndrome are still insufficient, some reports have indicated cell loss [12, 24], axonal swelling [13, 19, 27], and Lewy bodies [13, 19] in autopsied cases. The sympathetic ganglia from case 5 in the present series showed marked cell loss and chromatolysis. Biochemical studies have demonstrated that plasma norepinephrine levels in patients with Shy-Drager syndrome are lower than in control subjects in recumbency [4] or on assumption of the upright posture [28]. Recently, Petito and Black [18] found morphological abnormalities in the sympathetic ganglia from patients with idiopathic orthostatic hypotension (IOH) and a significant decrease of dopamine-β-hydroxylase activity and normal choline acetyltransferase activity in the sympathetic ganglia from IOH patients. All three cases with Shy-Drager syndrome in the present study showed denervation hypersensitivity to epinephrine. The present results in the sural nerves are consistent with these facts.

Previous reports have indicated that there are two groups of patients with orthostatic hypotension and other autonomic dysfunction. Ziegler et al. [28] suggested that in contrast to the patients with isolated autonomic insufficiency, patients with CNS involvement appeared to have an intact peripheral sympathetic nervous system. Davison and Morgan [5] and Hughes et al. [12] showed that the prognosis of IOH is much better in patients who do not develop generalized neurologic disease than in patients with degenerative changes in the nervous system. In the present study, the quantitative changes in the sural nerves were greatest in case 6, and were less severe in cases 4 and 5. At the time of biopsy, case 6 was still independent, while case 4 was already bedridden and case 5 was using a wheelchair. Therefore, it appears that peripheral autonomic nerves are less affected in cases with severe degeneration of the CNS.

Selective involvement of small myelinated nerves and unmyelinated fibers in the peripheral nerves has been reported in relatively rare conditions, such as amyloid neuropathy [6], hereditary sensory neuropathy

[9], Riley-Day syndrome [1, 17], and congenital insensitivity to pain with anhidrosis [24]. These diseases are associated with symptoms of autonomic dysfunction, such as orthostatic hypotension, anhidrosis, disturbance of bladder control and bowel motility, and perforating ulcers in the legs. The present results suggest that Shy-Drager syndrome can be included in the group of relatively rare diseases where peripheral nerves are involved in a similar fashion.

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