Spinal Autonomic Neurons in Werdnig-Hoffmann Disease, Mannosidosis, and Hurler’s Syndrome: Distribution of Autonomic Neurons in the Sacral Spinal Cord

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Abstract. In Werdnig-Hoffmann disease, mannosidosis, and Hurler’s syndrome, two groups of neurons (the Onuf’s and intermediomedial nuclei) in the ventral horn of the mid-sacral region are found to share common selective sparing or vulnerability with the intermediolateral nuclei of the thoracolumbar and sacral regions of the spinal cord. This finding confirms the previous observations on the characteristic involvement or sparing in Fabry’s disease (14), Shy-Drager syndrome (17), amyotrophic lateral sclerosis, anterior poliomyelitis, and neuronal intranuclear hyaline inclusion disease (15), and supports the assumption that the Onuf’s and intermediomedial nuclei in the ventral horn represent autonomic neurons much as the thoracolumbar and sacral intermediolateral nuclei.

INTRODUCTION

There has been accumulating evidence that autonomic neurons in the sacral spinal cord of man are located not only in the intermediolateral region between the ventral and dorsal horns but also in the ventral horn (5–7, 12–15, 17). The intermediolateral nucleus of the sacral cord has generally been regarded as autonomic neurons much as that of the thoracolumbar region. There has, however, been no uniformity of opinion as to the autonomic nature of the Onuf’s nucleus (11), the “colonne en torsade” of Laruelle (7), and the “medial myoeiotic nucleus” of Massazza (10) or the “nucleus sympatheticus medialis inferior s. lumbosacralis” of Jacobsohn (5, 6), all of which are located in the ventral horn. The Onuf’s nucleus, which is located mainly in the second sacral segment, has been considered to be an autonomic center by some (5–7, 12), while others have regarded its cells as motor neurons (4, 8, 9, 11). The “colonne en torsade,” which is located in the second and third sacral segments and includes the Onuf’s nucleus, was regarded as a parasympathetic center by Laruelle (7). Rexed (13) subsequently described a cell column in cat sacral spinal cords, which he believed to be homologous to the “colonne en torsade” in man, and asserted that it represents autonomic neurons. The “nucleus sympatheticus medialis inferior s. lumbosacralis” or the “medial myoeiotic nucleus,” which is also said to include the Onuf’s nucleus, was regarded as autonomic cells by Jacobsohn (5, 6) and Massazza (10). In the recent reports by Sung (14, 15), three groups of sacral neurons which were designated as the intermedioventral, intermediomedial, and intermediolateral nuclei were assumed to be autonomic neurons. The first two nuclei corresponded to the
"colonne en torsade" of Laruelle (7), while the last is the nucleus which is generally well recognized as autonomic cells. The assumption was solely based on neuropathological evidence that the three nuclei share common selective vulnerability or sparing with the well-known thoracolumbar autonomic cells (intermediolateral nucleus or cell column) in diverse neurological disorders (14, 15, 17). In light of the previous studies, selective sparing or vulnerability of the three sacral nuclei in Werdnig-Hoffmann disease, mannosidosis, and Hurler's syndrome has been studied to learn further whether they are indeed of the same type representing autonomic neurons, as has been assumed.

MATERIALS AND METHODS

Included in this study were three patients with Werdnig-Hoffmann disease, mannosidosis, and Hurler's syndrome, respectively, as shown in Table 1.

Werdnig-Hoffmann disease (infantile spinal muscular atrophy) is generally believed to be a heredofamilial disease of infants, which affects chiefly, if not only, the lower motor neurons. Iwata and Hirano (4) have recently described characteristic sparing of the Onuf's nucleus in contrast to severe diffuse loss of motor neurons in the sacral spinal cord in three patients with the disease.

Mannosidosis is a deficiency of α-mannosidase A and B, which leads to intracellular storage of mannose-rich oligosaccharides in various tissues (2). In the central nervous system, neurons are almost universally affected by storage of oligosaccharides, but the degree of the storage varies considerably in different types of neurons. In the spinal cord, neurons of the intermediolateral nucleus in Clarke's cell column are more severely affected than motor neurons of the ventral horn (16).

Hurler's syndrome is a deficiency of β-galactosidase, which leads to storage of mucopolysaccharides in various tissues (3). In the central nervous system, almost all types of neurons are affected by lipid storage, but the degree of ballooning of neurons varies in different types of neurons. In the spinal cord of the present patient, ventral horn motor neurons are more strikingly ballooned than neurons of the intermediolateral nucleus and Clarke's cell column.

Multiple transverse sections at various levels of the spinal cord above the sacral cord were sampled for histological examination. In the sacral cord, each segment was identified by way of the ventral nerve roots and was sectioned at every 2- to 3-mm interval. Every section was blocked in paraffin, and from each block, 8 μ semiserial histological sections were made. The sections were stained with hematoxylin and eosin (HE), periodic acid Schiff (PAS), Nissl, and Bielschowsky's silver stains.

OBSERVATIONS

Werdnig-Hoffmann disease: In the thoracolumbar region of the spinal cord, motor neurons of the ventral horn were diffusely lost, and the cell loss was

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patients Included in the Study</th>
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<tbody>
<tr>
<td>Diseases</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Werdnig-Hoffmann disease</td>
<td>1</td>
</tr>
<tr>
<td>Mannosidosis</td>
<td>1</td>
</tr>
<tr>
<td>Hurler's syndrome</td>
<td>1</td>
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</tbody>
</table>
Fig. 1. Twelfth thoracic segment (A, B) and second sacral segment (C, D). A & B: Clarke's cell column (c) and intermediolateral nucleus (i) are well preserved, while motor neurons are diffusely lost (v). C & D: Motor neurons in anterior (a) and posterior (p) lateral groups are diffusely lost, while neurons in Onuf's nucleus (arrows) and medial myeloeic nucleus (m) are well preserved. Hematoxylin and eosin stain. ×30 (A, B, C) and ×48 (D).
Fig. 2. Third sacral segment, rostral (A, B) and caudal (C, D) levels. Motor neurons in posterior lateral group (p) are severely lost, while neurons of Onuf's nucleus (o) and intermediodermal nucleus (arrows) are well preserved. Hematoxylin and eosin stain. ×30.
accompanied by mild fibrous astrogliosis. Occasional persisting neurons showed central chromatolysis. These changes were most striking in the lumbar segments. In the Clarke's cell column, occasional neurons also showed central chromatolysis, but the neurons were otherwise relatively well preserved (Fig. 1A, B). Neurons of the intermediolateral nucleus were remarkably spared (Fig. 1A, B). In the sacral cord, loss of motor neurons accompanied by fibrous astrogliosis in the ventral horn similar to that in the lumbar segments was observed at all levels (Fig. 1C, D). Neurons of the Onuf's nucleus in the second and third segments were, however, remarkably well preserved (Fig. 1C, D). Also spared were neurons of the intermediomedial nucleus in the third segment (Fig. 2) and those of the intermediolateral nucleus in the fourth segment (Fig. 3). Rare neurons of the Onuf's nucleus showed central chromatolysis. Also well preserved were small neurons scattered in the dorsal and medial parts of the ventral horn in both the lumbar and sacral regions (Fig. 1D) and in the ventral horn of the fourth sacral segment (Fig. 3B). These small neurons in the former two regions corresponded to the "intermediomedial nucleus" of Bok (1) and the "medial myoleiotic nucleus" of Massazza (10) or the "nucleus sympathethicus medialis inferior s. lumbosacralis" of Jacobsohn (5, 6).

Mannosidosis: In the thoracolumbar region of the spinal cord all types of neurons showed vacuolation of the cytoplasm due to storage of the adventitial material. The change was, however, most striking in neurons of the inter-
mediolateral nucleus (Fig. 4). In the sacral cord, neurons of the Onuf's and intermediolateral nuclei were again more severely affected than motor neurons of the ventral horn (Fig. 5). Neurons of the intermediomedial nucleus were also affected, but they were not readily distinguished from scattered small neurons so affected in the neighborhood and in the medial part of the ventral horn.
Hurler's syndrome: In the thoracolumbar region of the spinal cord, motor neurons of the ventral horn as well as neurons of the intermediolateral nucleus showed marked lipid storage, but the former were comparatively more severely ballooned than the latter neurons (Fig. 6). Neurons of Clarke's cell column were mildly affected. Neurons in the dorsal and medial regions of the ventral horn, which corresponded to the "intermediomedial nucleus" of Bok (1) and the "medial myoleiotic nucleus" of Massazza (10) in the lumbar segment, were also affected by lipid storage. In the sacral cord, all neurons in the gray horns showed marked lipid storage. Because of lipid storage and ballooning of the perikaryon of neurons, neuronal grouping was more readily recognized than usual. The Onuf's and intermediolateral nuclei were easily distinguished from other nuclei because of the cell size and compact aggregation of neurons (Figs. 6 and 7B). The intermediomedial nucleus, on the other hand, was less well defined (Fig. 7A) and varied considerably from section to section. It was attenuated or had disappeared in one section, but reappeared in the next. All three, the Onuf's, intermediomedial, and intermediolateral nuclei, were not always observed together on both sides in a given section. Among the three, the Onuf's nucleus occurred most often on both sides symmetrically. The intermediomedial nucleus was frequently masked by similar small neurons in the dorsal and medial regions of the sacral segment (Fig. 7A). Similar cells were scattered in the ventral horn of the fourth segment, in which the medial group of large motor neurons was readily seen (Fig. 7B). Small neurons in the medial region of the ventral horn were seen more clearly than usual in the sacral segment (Fig. 6), as in the lumbar segment. They appeared to correspond to the
Fig. 6. First (A) and second (B, C) sacral segments. Small neurons in myoleiotic nucleus (m) and Onuf's nucleus (o) are distinct from anterior (a) and posterior (p) lateral group motor neurons, though all are affected by lipid storage. Periodic acid Schiff stain. ×30 (A, B) and ×120 (C).

"nucleus sympathetic medialis inferior s. lumbosacralis" of Jacobsohn (5, 6) or the "medial myoleiotic nucleus" of Massazza (10).

COMMENT

The present investigation confirms the previous observations (14, 15, 17) that selective vulnerability varies among different types of spinal neurons in diverse
neurological disorders (Table 2) and that less well-known types of spinal neurons may be recognized with better-known groups of neurons by virtue of common selective vulnerability.

In Werdnig-Hoffmann disease, neurons of the Onuf's, intermediomedial, and intermediolateral nuclei of the sacral region are spared, much as is the thoracolumbar intermediolateral nucleus. It is, therefore, reasonable to assume

**TABLE 2**
Selective Vulnerability of Various Groups of Spinal Neurons in Diverse Neurological Disorders: Affected Severely (+ +), Mildly (+), and Spared (−)

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Ventral horn motor neurons</th>
<th>Thoracolumbar intermediolateral nucleus</th>
<th>Onuf's, intermediomedial and intermediolateral nuclei of sacral cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>Werdnig-Hoffmann</td>
<td>++</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Mannosidosis</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Hurler's syndrome</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Fabry's (14)</td>
<td>−</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>A.L.S. (15)</td>
<td>++</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Shy-Drager syndrome (17)</td>
<td>+ or ++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>
that the sacral neurons are similar to the thoracolumbar neurons, which are believed to be autonomic cells. Our observation generally confirms the reports describing the Onuf's nucleus as being spared in Werdnig-Hoffmann disease and anterior poliomyelitis by Iwata and Hirano (4) and in amyotrophic lateral sclerosis by Mannen et al. (8, 9). However, these authors asserted that the nucleus represents motor neurons, but offered no explanation as to why the nucleus is spared.

In mannosidosis, the Onuf's and intermediolateral nuclei of the sacral cord and the thoracolumbar intermediolateral nucleus share common selective vulnerability, and they are more severely affected than motor neurons of the ventral horn. Neurons of the intermediomedial nucleus appear to respond very much like those of the Onuf's and intermediolateral nuclei, but they do not form a discrete, compact group and are thus not readily distinguished from scattered neurons in the neighborhood which are similarly affected.

In Hurler's syndrome, in contrast to the two other disorders, almost all types of spinal neurons are universally affected by lipid storage. Large motor neurons are, however, comparatively more ballooned than other neurons and neurons of the sacral nuclei in question are readily distinguished from them because of a remarkable difference in size. The Onuf's and intermediolateral nuclei are easily distinguished from other groups of small neurons such as the "intermediomedial nucleus" of Bok (1) and the "medial myoeiotic nucleus" of Massazza (10) because of their distinct locations and the relatively compact aggregation of their neurons. The intermediomedial nucleus, on the other hand, is usually composed of clusters of a few neurons deep in the ventral horn, and it is not readily identified as a distinct nucleus because of scattered small neurons similarly affected by lipid storage in the same area and in the "intermediomedial nucleus" of Bok and the "medial myoeiotic nucleus" of Massazza.

On the basis of the foregoing observations in Werdnig-Hoffmann disease, mannosidosis, and Hurler's syndrome, when taken together with the previous findings in other neurological disorders (Table 2), it seems logical to assume that neurons of the Onuf's, intermediomedial, and intermediolateral nuclei of the sacral cord represent autonomic cells, much as do those of the thoracolumbar intermediolateral nucleus.

REFERENCES

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