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Pursuit of the origin of the large myelinated fibers of the anterolateral funiculus in the spinal cord in humans in relation to the pathomechanism in amyotrophic lateral sclerosis

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Abstract To determine the origin of the large myelinated fibers in the anterolateral funiculus (ALF) in the spinal cord of humans, myelinated fibers in the ALF of the mid-cervical spinal cord were examined quantitatively. Five groups of subjects were examined, consisting of control subjects, patients with cerebral lesions and showing complete degeneration of the unilateral/bilateral pyramis of the medulla oblongata, those with lesions of the pontine tegmentum, those with lesions of the lower cervical spinal cord, and those with thoracic/lumbar lesions. The results indicate that the large myelinated fibers in the ALF of the mid-cervical spinal cord of humans originate from the tegmentum of the brain stem and the lower cervical spinal cord, and not from the cerebrum, or the thoracic or lumbar spinal cord. Thus, they are descending fibers from the brain stem tegmentum and ascending fibers from the lower cervical cord, and not corticospinal tracts or long-ascending fibers from the thoracic or lumbar spinal cord. The origin of the large myelinated fibers in the ALF of the spinal cord in humans, the number of which was severely decreased in patients with amyotrophic lateral sclerosis, is considered to be the long-descending neurons in the brain stem tegmentum and the propriospinal neurons in the spinal cord.

Key words Amyotrophic lateral sclerosis · Anterolateral funiculus · Morphometry · Propriospinal fiber · Reticulospinal fiber

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Introduction

The white matter of the spinal cord contains bundles of various nerve fiber tracts. It has been reported that the anterolateral funiculus (ALF), which is the ventral part of the lateral funiculus [24], contains, as long-descending tracts, the ventral pyramidal tract (human [4]), corticospinal tracts (human [23]), reticulospinal tracts (cat, opossum and human [11, 12, 17, 24, 25, 29]), the vestibulospinal tract (cat and human [29, 32, 33]), and raphe spinal tracts (opossum [18]). In addition, the ALF contains, as long-ascending tracts, the spinothalamic tract (human [15, 29, 34, 35]), the spinoreticular tract (human [29]), the spinocerebellar tract (human [15, 29]), and Helweg's triangular tract (human [37]). Propriospinal fibers (cat and human [1, 7, 29]) have also been observed.

In the white matter of most patients with sporadic amyotrophic lateral sclerosis (ALS), the ALF degenerates along with the lateral and anterior corticospinal tracts [9–11, 16, 28, 36]. We have reported previously that: (1) the fiber-size distribution of the myelinated fibers in the ALF and lateral corticospinal tract (LCS) of the control subjects exhibited a peak at 2 μm, (2) there were marked and significant losses of large myelinated fibers in the ALF and LCS of ALS patients, (3) the patients who required respirator support showed more severe degeneration of the ALF than those who required none, and (4) the degree of myelinated fiber loss in the LCS did not correlate with either the duration of their illness or their history of respirator use [28].

The neurons originating in the reticulospinal tract, the neurons in the spinal cord [11], and the propriospinal neurons [26, 27] have been proposed as the origins of the degenerated fibers observed in the ALF of patients with ALS. In the present study, to determine the origin of the large myelinated fibers in the ALF of the human spinal cord, the number of which is severely reduced in patients with ALS, myelinated fibers in the ALF of the mid-cervical spinal cord were examined quantitatively in five groups of subjects, including control subjects. The disease

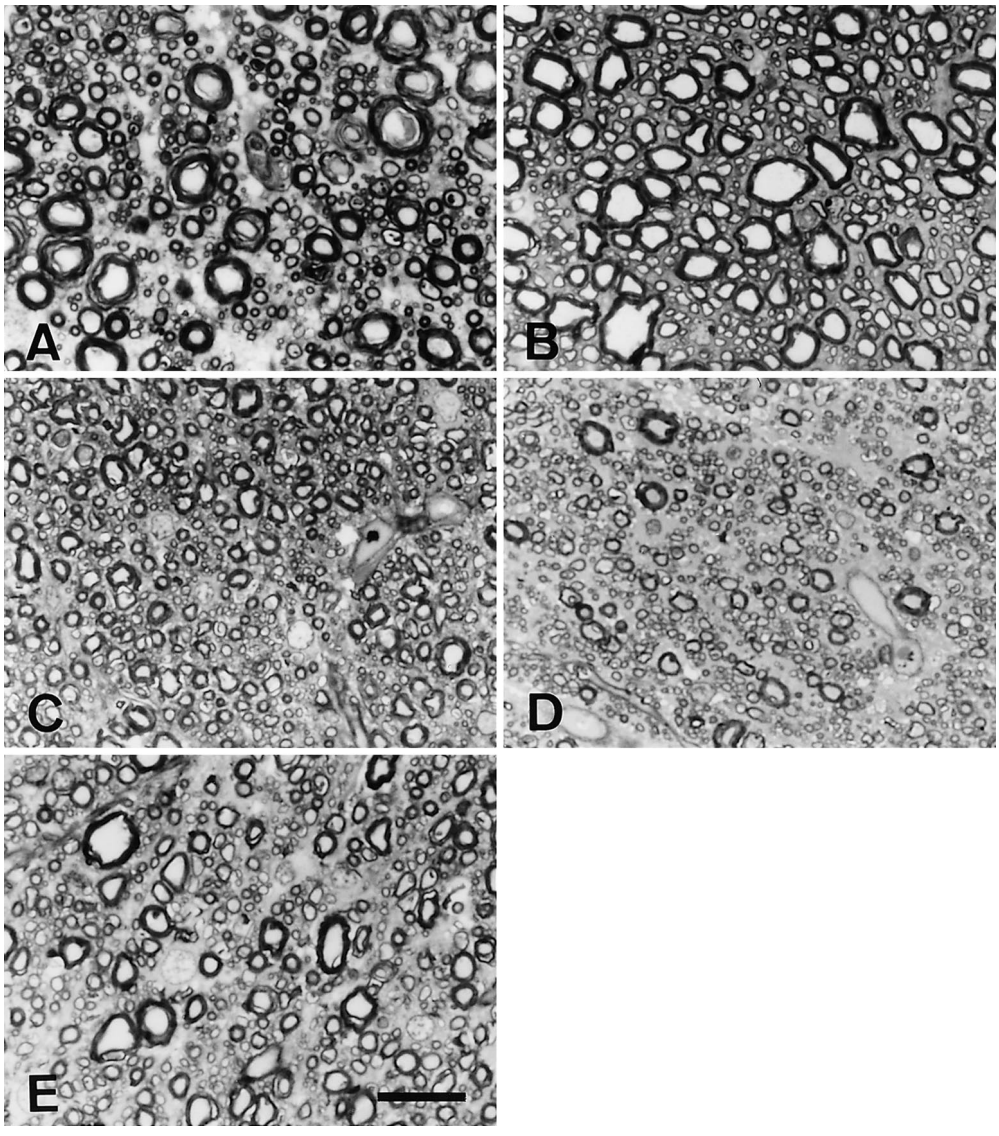

Fig. 1 A–E Light micrographs of the ALF. **A** Group I: In a control subject, large myelinated fibers are observed admixed with small and medium-sized myelinated fibers. **B** Group II: In a patient with cerebral lesions, large myelinated fibers, and small and medium-sized myelinated fibers are observed. **C** Group III: All patients with lesions of the pontine tegmentum exhibit a small number of large myelinated fibers, and a relatively large number of small myelinated fibers. **D** Group IV: In a patient with lesions of the lower cervical cord, a small number of large myelinated fibers is observed. **E** Group V: In a patient with transverse myelopathy of the thoracic spinal cord, many large myelinated fibers are observed admixed with small and medium-sized myelinated fibers (*ALF* anterolateral funiculus). **A–E** Toluidine blue preparation. *Bar* 20 μm

groups that were examined included patients with cerebral lesions showing complete degeneration of the unilateral/bilateral pyramis of the medulla oblongata, those with lesions of the pontine tegmentum, those with lesions of the lower cervical spinal cord, and those with thoracic/lumbar lesions.

Materials and methods

The subjects (controls and patients) were divided into five groups for postmortem examination. Group I: Five control subjects (aged 62–87 years; mean ± SD 74.4 ± 9.9 years); group II: four patients with cerebral lesions, such as cerebral hemorrhage and/or cerebral infarct, showing unilateral/bilateral complete degeneration of the pyramis (aged 53–77 years; mean ± SD 69.3 ± 11.0 years); group III: five patients with lesions of the pontine tegmentum, such as pontine infarct or pontine glioma (aged 25–75 years, mean ± SD 48.8 ± 20.0 years); group IV: five patients with lower cervical involvement, such as cervical spondylosis or vertebral metastasis of cancer (aged 59–72 years, mean ± SD 65.8 ± 6.3 years); and group V: four patients with thoracic/lumbar spinal cord lesions, such as transverse myelopathy or poliomyelitis (aged 17–82 years, mean ± SD 57.3 ± 29.7 years). These 18 patients and 5 control subjects were Japanese, and none of them had had cardiac arrest, hypoglycemic episodes, or severe liver dysfunction. The interval between death and autopsy was 3–5 h.

The methods used in the present study were essentially similar to those reported previously [28]. The fourth or fifth cervical segments of the spinal cord were fixed in 20% formalin in 0.1 M phosphate buffer (PB; pH 7.3). The duration of fixation was 3–8 years. Each segment was then fixed in 1% osmium tetroxide in 0.1 M PB, followed by dehydration through a graded ethanol series and embedding in Epon 812. Sections (1 μm thick) were cut, stained with toluidine blue, and then examined with the aid of a light microscope.

The myelinated fibers in the ALF were quantitatively examined bilaterally in control subjects and in patients with cerebral lesions. Since there was no difference in number between the myelinated fibers in the right and left side, those in the right side of the ALF were examined in other groups. The ALF was divided into three equal parts anteriorly from the medial to the lateral margins of the anterior horn and photographs of the mid-medial, mid-lateral and lateral portions were taken (× 200 magnification). The large bundles of myelinated fibers with diameters of 10–12 μm, at which was thought to be the intramedullary portion of the anterior spinal root, crossing the ALF were avoided when taking these photographs. Enlarged prints (× 2285 magnification) were made and the mean diameter of the myelinated fibers was obtained, using a

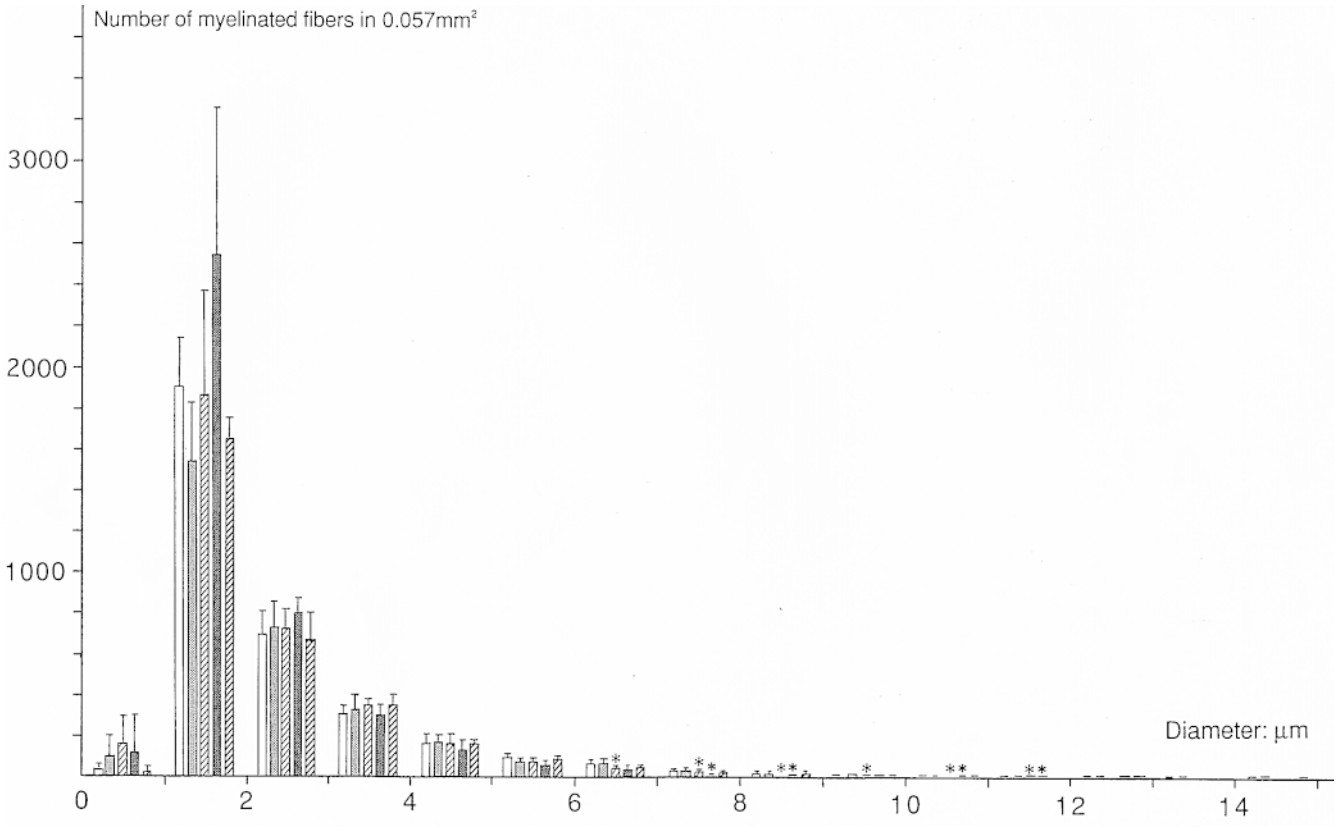

Fig. 2 Fiber-size distribution of the myelinated fibers in the ALF. □ Group I: the fiber-size distribution of the control subjects exhibits a prominent sharp peak at 2 μm. ▒ Group II: the fiber-size distribution of the myelinated fibers is similar to that of the control subjects. ▨ Groups III and ■ IV: the basic pattern of the fiber-size distribution of the myelinated fibers is similar to that observed for the control subjects, however, the number of myelinated fibers with a diameter of over 6 μm is significantly lower in this group. ▨ Group V: the fiber-size distribution of the myelinated fibers is similar to that of the control subjects. The total area of each ALF of each patient examined is 0.057 mm^2. Values indicated are means and SD. *Asterisks* $P < 0.05$

digitizer, by averaging the longest and shortest diameters (the latter being perpendicular to the former).

The data for the three areas in the ALF of each patient and control subject were summed and the frequency distribution of the myelinated fiber diameters, in 1-μm increments, was determined and represented on bar charts as $\pi r^2 \times N$ (where r is half the mean diameter of the myelinated fibers and N is the number of myelinated fibers), to show that the large myelinated fibers, although fewer in number, cover a wider area. The total area of each ALF of each patient examined was 0.057 mm^2.

Statistical evaluation was performed using the Mann-Whitney U test to compare the numbers of myelinated fibers in 1-μm increments, with diameters of less than 3 μm (small), 3–6 μm (medium-sized), and over 6 μm (large), between each group.

Results

Group I

Light microscopic examination of the ALF of the control subjects revealed large myelinated fibers admixed with small and medium-sized myelinated fibers (Fig. 1A). The fiber-size distribution of the myelinated fibers in the control subjects showed a prominent peak at 2 μm in the ALF (Figs. 2, 3). The distribution pattern was similar to that of the myelinated fibers in the control subjects from whom the ALF had been fixed in 3% glutaraldehyde-1% paraformaldehyde in 0.1 M PB, reported previously [28]. There was no significant difference between the numbers of myelinated fibers in the right and left side (Table 1). The number of myelinated fibers with a diameter of over 3 μm was relatively small, whereas the number of myelinated fibers with a diameter of less than 3 μm was relatively large, as compared with those fixed in 3% glutaraldehyde-1% paraformaldehyde [28] (Table 2).

Group II

Light microscopic findings of the ALF from patients with cerebral lesions showed small, medium-sized and large myelinated fibers (Fig. 1B). The fiber-size distribution of the myelinated fibers was similar to that of the control subjects (Figs. 2, 3). There was no significant difference between the numbers of myelinated fibers in the right and left side of these subjects (Table 1). The numbers of the large, medium-sized and small myelinated fibers were not significantly different from those of the controls (Table 2).

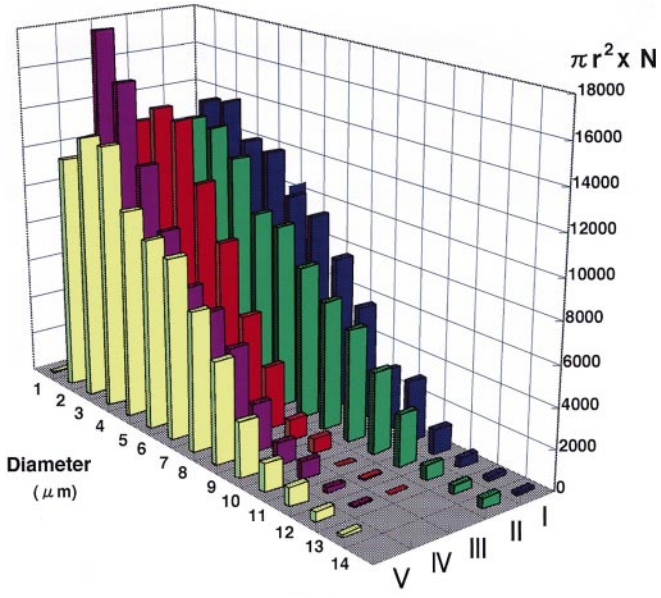

Fig. 3 Fiber-size distribution of the myelinated fibers in the ALF. The averages in the control subjects and the data of each patient are represented on bar charts as $\pi r^2 \times N$ (where *r* is half the mean diameter of the myelinated fibers and *N* is the number of myelinated fibers), to show that the large myelinated fibers, although fewer in number, cover a wider area. The total area of each ALF of each patient examined is 0.057 mm^2. The averages of the data for the control subjects (group I) are shown in *dark blue*, the data for patients with cerebral lesions (group II) are shown in *green*, the data for patients with lesions of the pontine tegmentum (group III) are shown in *red*, the data for patients with lesions in the lower cervical spinal cord (group IV) are shown in *purple*, and the data for patients with lesions in the thoracic/lumbar spinal cord (group V) are shown in *yellow*. In groups III and IV, the number of myelinated fibers with a diameter of over 6 μm appear to have decreased, although they are preserved in groups II and V

Group III

Light microscopic findings of the ALF from patients with lesions of the pontine tegmentum showed a small number of the large myelinated fibers and a relatively large number of small myelinated fibers (Fig. 1C). The basic pattern of the fiber-size distribution of the myelinated fibers was similar to that in the control subjects; however, the number of myelinated fibers with a diameter of over 6 μm was significantly lower (Figs. 2, 3, and Table 2).

Group IV

Light microscopic findings of the ALF from patients with lesions of the lower cervical cord showed a small number of large myelinated fibers (Fig. 1D). The basic pattern of the fiber-size distribution of the myelinated fibers was similar to that of the control subjects, however, the number of myelinated fibers with a diameter of over 6 μm was significantly reduced (Figs. 2, 3, and Table 2).

Table 1 The myelinated fibers in the ALF were quantitatively examined bilaterally in control subjects (group I) and in patients with cerebral lesions (group II). Statistical evaluation was performed using the Mann-Whitney U test to compare the numbers of myelinated fibers in 1-μm increments and with diameters of less than 3 μm (small), 3–6 μm (medium-sized), and over 6 μm (large), between each group. There was no significant difference between the numbers of myelinated fibers in the right and left side in the control subjects (group I) and in patients with cerebral lesions (group II). The total area examined was 0.057 mm^2 (*ALF* anterolateral funiculus)

	Diameter		
	< 3.0 μm	3–6 μm	> 6 μm
I. Control			
Right side (*n*=5)	2645.2 ± 247.6	605.2 ± 62.8	158.4 ± 11.6
Left side (*n*=5)	2615.8 ± 193.1	633.3 ± 83.2	162.3 ± 30.8
II. Cerebral lesions			
Right side (*n*=4)	2335.5 ± 400.9	627.0 ± 83.6	183.0 ± 91.6
Left side (*n*=4)	2437.5 ± 413.1	650.0 ± 81.7	167.5 ± 59.1

Group V

Light microscopic examination of the ALF from patients with thoracic/lumbar lesions revealed large myelinated fibers admixed with small and medium-sized myelinated fibers (Fig. 1E). The fiber-size distribution of the myelinated fibers was similar to that of the control subjects (Figs. 2, 3). The numbers of large, medium-sized and small myelinated fibers were similar to those noted for the controls (Table 2).

Discussion

In the present study, the number of large and medium-sized myelinated fibers in the control subjects was relatively small, and the number of small myelinated fibers was relatively large as compared with those of control cases fixed with 3% glutaraldehyde-1% paraformaldehyde, previously reported [28]. This suggests that slight shrinkage of the myelinated fibers fixed in 20% formalin in 0.1 M PB had occurred compared with those fixed in 3% glutaraldehyde-1% paraformaldehyde in 0.1 M PB.

The results of the present study have revealed that: (1) large myelinated fibers in the ALF of the mid-cervical spinal cord originate from the tegmentum of the brain stem and from the lower cervical spinal cord, (2) large and medium-sized myelinated fibers in the ALF of the mid-cervical spinal cord are not corticospinal tracts, (3) nor are these fibers long-ascending tracts from the thoracic and lumbar spinal cord.

A histological and quantitative study has revealed neither degenerative fibers, loss of myelinated fibers, nor atrophy of the ALF in patients with hemispherectomy [40]. The finding concurs with the results of the present study.

The number of large and medium-sized myelinated fibers in the ALF of the mid-cervical spinal cord in patients with complete transverse myelopathy at the thoracic level was not reduced. This indicates that the long-as-

Table 2 The number of myelinated fibers in the ALF. The mean ± SD of the values are indicated. The examined area is 0.057 mm^2 in each subject or patient. Statistical evaluation was performed using the Mann-Whitney U test to compare the numbers of myelinated fibers with diameters of less than 3 μm, 3–6 μm and over 6 μm. In the patients with lesions of the pontine tegmentum (group III) and with lesions of the lower cervical cord (group IV), the number of myelinated fibers with a diameter of over 6 μm had decreased significantly

		Diameter		
		< 3.0 μm	3–6 μm	> 6 μm
I. Control	(*n*=5)	2645.2 ± 247.6	605.2 ± 62.8	158.4 ± 11.6
II. Cerebral lesions	(*n*=4)	2335.5 ± 400.9	627.0 ± 83.6	183.0 ± 91.6 *
III. pontine tegmentum lesions	(*n*=5)	2745.4 ± 607.6	620.2 ± 54.5	56.4 ± 19.3 *
IV. Lower cervical lesions	(*n*=5)	3472.4 ± 802.8	519.2 ± 117.9	88.6 ± 23.6
V. Thoracic/lumbar lesions	(*n*=4)	2403.0 ± 83.2	607.0 ± 91.6	147.0 ± 25.6

* $P<0.01$

cending tracts, such as the spinothalamic [15, 29, 34, 35], spinoreticular [29], spinocerebellar [15, 29], and Helweg's triangular [37] tracts are either not composed of large or medium-sized myelinated fibers, or else do not pass through the areas investigated in the present study.

The results presented here show that a proportion of the large myelinated fibers in the ALF of the mid-cervical spinal cord originate from the lower cervical cord, and that the large myelinated fibers in the ALF are not long-ascending fibers from the thoracic and lumbar spinal cord. This finding suggests that the large myelinated fibers reduced in number in patients with lower cervical involvement are not long-ascending fibers, but propriospinal fibers connecting neighboring segments. The present study has also revealed that the large myelinated fibers in the ALF of the mid-cervical segment originate from the tegmentum of the brain stem and the lower cervical spinal cord, and their origins are considered to be reticulo-, vestibulo- and/or raphe-spinal neurons, and propriospinal neurons.

In advanced ALS patients who require the long-term use of a respirator, an extensive reduction in the number of neurons other than motor neurons has been observed, in addition to complete loss of the anterior horn cells [8, 20]. It has also been noted that the tegmentum of the brain stem and the intermediate zone of the spinal cord exhibit extremely severe atrophy and neuronal loss, and that the ALF degenerates markedly in these ALS patients [8, 20]. Bunina bodies and ubiquitin-immunopositive inclusions have been observed in the neurons of the reticular formation of the medulla oblongata in patients with ALS [5, 22]. This indicates that an ALS-specific disease process exists in the neurons in the reticular formation.

Spinocerebellar neurons as well as the neurons of Clarke's column have been shown to degenerate in the spinal cord of ALS patients [2, 38, 41], and the number of neurons in the intermediolateral nucleus and Onuf's nucleus is reduced [6, 13, 14, 39]. The occurrence of a sequential degeneration of the neurons in the intermediate zone (Rexed's [31] laminae V–VIII) of the spinal cord are a result of loss of anterior horn cells (Rexed's lamina IX) has been reported in patients with ALS [26, 27]. Long-ascending neurons [29], internuncial neurons [29], and propriospinal neurons [1, 21] have been shown to occur in the intermediate zone of the spinal cord.

It has been shown that propriospinal neurons at the cervical segment are located in laminae V–VII (cat and monkey [21]) of Rexed [31], and that these neurons play roles in movement control and sensorimotor integration of the extremities [19, 30]. The reticulospinal and propriospinal tracts terminate in laminae V–VIII in the cervical cord (cat [3]). Thus, the reticulospinal neurons in the brain stem and propriospinal neurons in the spinal cord are considered to be closely linked. Further studies are necessary to elucidate whether or not such a linkage of degenerating mechanisms exists between the propriospinal neurons in the spinal cord and the neurons in the brain stem tegmentum in patients with ALS.

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