ALF in classic ALS.

## MECHANISM OF THE MIDDLE ROOT ZONE DEGENERATION IN FAMILIAL ALS

Some patients of familial ALS with or without SOD-1 gene mutation show degeneration of the posterior funiculus, that is "middle root zone degeneration" (Fig. 11a) (Makifuchi and Ikuta 1977, Takahashi et al. 1994). The pattern is quite different from that of the Wallerian degeneration of the transverse myelopathy, or the subacute myelo-optico-neuropathy (SMON), an intoxication of clioquinol (hydoxyquinoline), which primaly involves the spinal ganglia and the axons (Tateishi J et al. 1972, 1973) (Fig, 11b). On the pathomechanism of the middle root zone degeneration, Ikuta et al. (1982) reported a retrograde trans-synaptic degeneration of the afferent fibers to the degenerated Clarke's column, based on the findings of marked loss of neurons in the Clarke's column at the severely degenerated left-side of the posterior funiculus (Fig. 11a).

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LEGENDS

Table 1. 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. Cited from ref. Oyanagi et al. 1999.

Fig. 1. Cervical cord of a control subject (A) and a patient with classic ALS (B). Asterisks indicate ALF. Klüver-Barrera preparation.

Fig. 2. Photographs were taken at three points in both the anterolateral funiculusu (ALF) and lateral corticospinal tract (l-CST). For further details, see text. Cited from ref. Oyanagi et al. 1995.

Fig. 3. In the present study, in order 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 (Group I). The disease groups that were examined included patients with cerebral lesions showing complete degeneration of the unilateral/bilateral pyramis of the medulla oblongata (Group II), those with lesions of the pontine tegmentum (Group III), those with lesions of the lower cervical spinal cord (Group IV), and those with

thoracic/lumbar lesions (Group V).

Fig. 4. Size distribution of neurons in the cervical gray matter of a control subject. Large neurons, with a nuclear area greater than 151 $\mu m^2$, are located in lamina IX; middle sized neurons, 71 to 120 $\mu m^2$, in lamina IV-VIII; and numerous small neurons are distributed in lamina II, III and VII. This pattern of distribution seems to correspond to the laminar cell architecture of the cat reported by Rexed (1954). Cited from ref. Oyanagi et al. 1983.

Fig, 5. Size distribution of neurons in the cervical gray matter of an advanced ALS patient. The large neurons in lamina IX disappear almost completely. The middle-sized neurons located in laminae VI, VII, and VIII decrease markedly. However, the distribution of the small neurons appears the same as in the control subjects in all parts of the spinal gray matter. Cited from ref. Oyanagi et al. 1983.

Fig. 6. Size distribution of the neurons in the cervical gray matter of a ALS patient, whose muscular strength was fairly well preserved up to death. The large neurons, with a nuclear area greater than 151 $\mu m^2$, are severely decreased in Rexed's lamina IX. However, the degree of decrease of the neurons is not equal to that of advanced ALS patients. The neurons in the intermediate zone and posterior horn are quite well preserved. Cited from ref. Oyanagi et al. 1989.

Fig. 7. Progression pattern of neuronal loss in the spinal gray matter of ALS. The findings indicate that the primary degeneration may occur in the anterior horn cells and the neurons in the intermediate zone degenerate sequentially in the spinal gray matter in ALS.

Fig. 8. An ALS patient with relative preserved AHCs (asterisks) but severe degeneration of the l-CST (A). An ALS patient with marked loss of AHCs (asterisks) but relatively slight degeneration of the l-CST (B). Cervical cord. Klüver-Barrera preparation.

Fig. 9. ALS patients showing asymmetry of the spinal white matter. Volume of the left anterior CST (a) is large, and that of right anterior CST (b) is small, but left lateral CST (b') is large, and right lateral CST (a') is small. This finding indicates a + a' = b + b'. A: cervical, B; thoracic of a different patient. Klüver-Barrera preparation.

Fig. 10. Evaluation of the ratio for the decrease in numbers of large myelinated fibers between the ALF and l-CST. Open circle; control subject, solid circle; ALS patient without respirator support, solid square; ALS patient with respirator support. Numbers indicate the duration of illness. Patients who required respirator support showed more severe degeneration of the ALF in the ALS than those who required none, and the degree of myelinated fiber loss in the l-CST did not correspond with either the illness duration or the history of respirator use. Cited from ref. Oyanagi et al. 1995.

Fig. 11. A familial ALS patient with SOD-1 gene mutation showing a degeneration of the left middle root zone (A). The 12th thoracic segment. Mid-thoracic cord of a patient with SMON (B). Klüver-Barrera preparation.

| | | Diameter | | |
|---|---|---|---|---|
| | | < 3.0 μm | 3-6 μm | > 6.0 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 | 148.0 +/- 25.6 |

* $P < 0.01$

**Table 1. Oyanagi et al.**

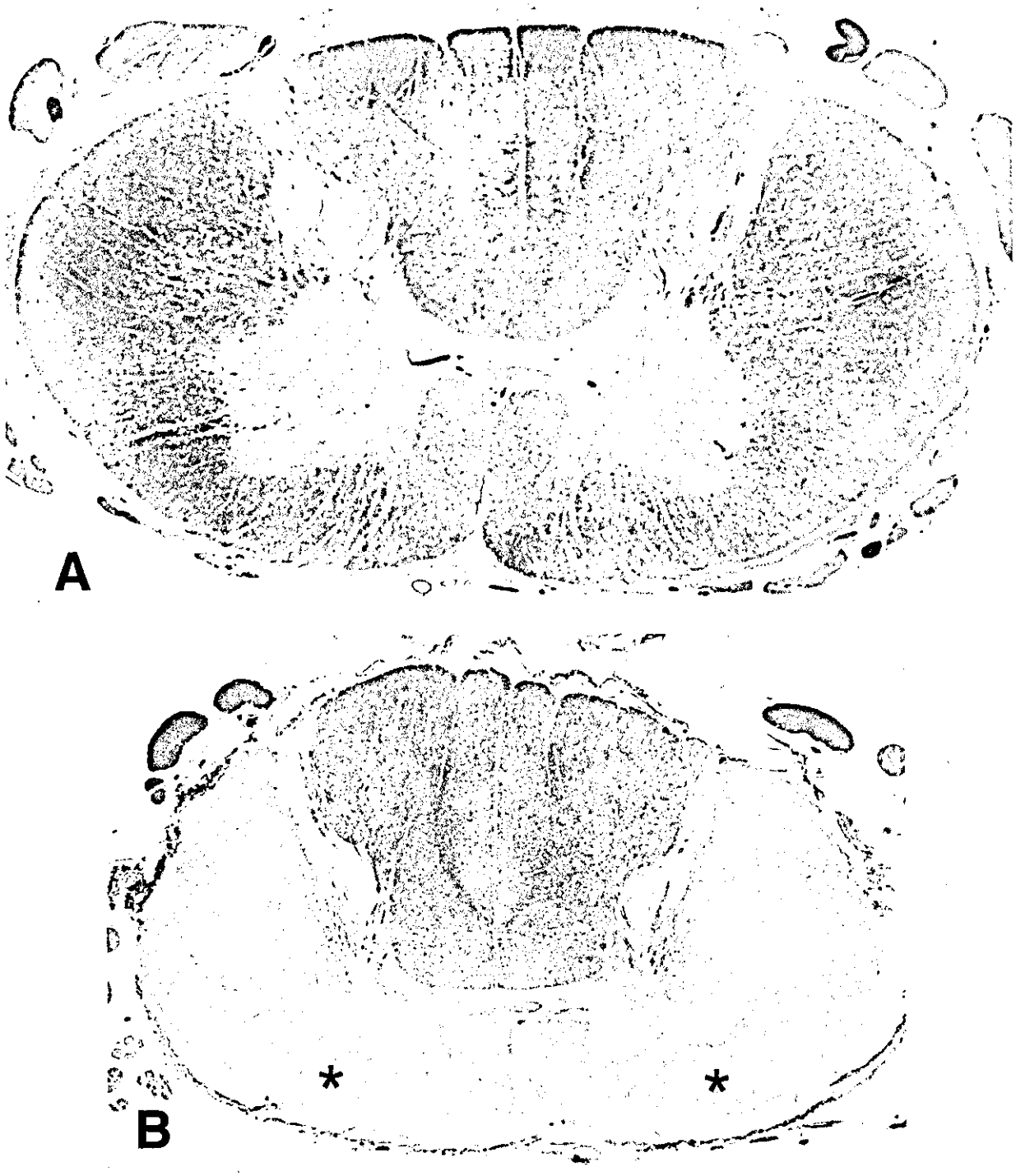



Fig. 1 Oyanagi et al.

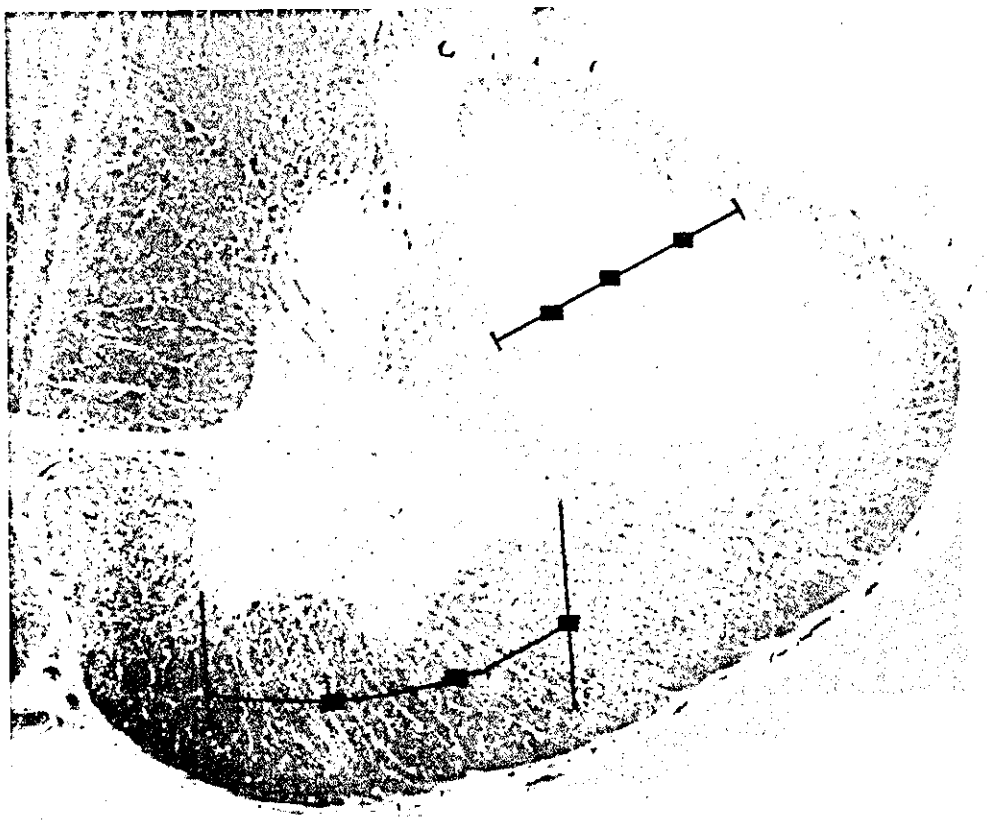


Fig. 2 Oyanagi et al.

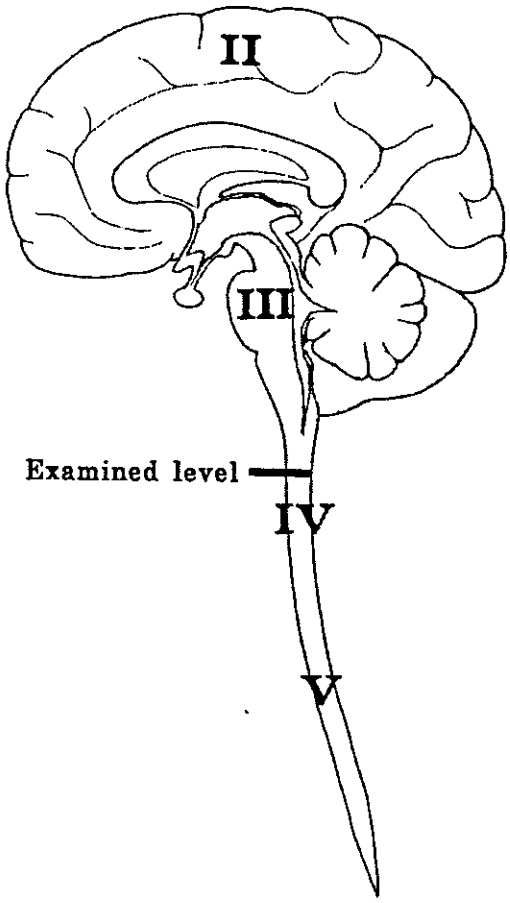
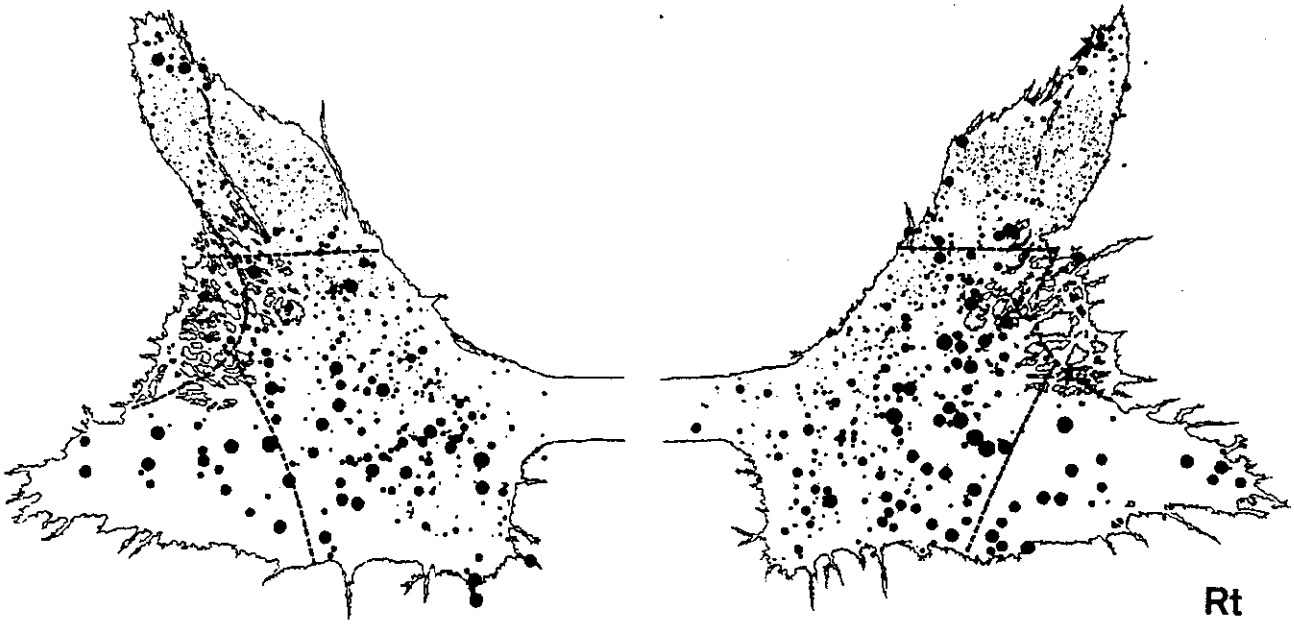



Fig. 3. Oyanagi et al.

Fig. 4. Oyanagi et al.

Fig. 5. Oyanagi et al.

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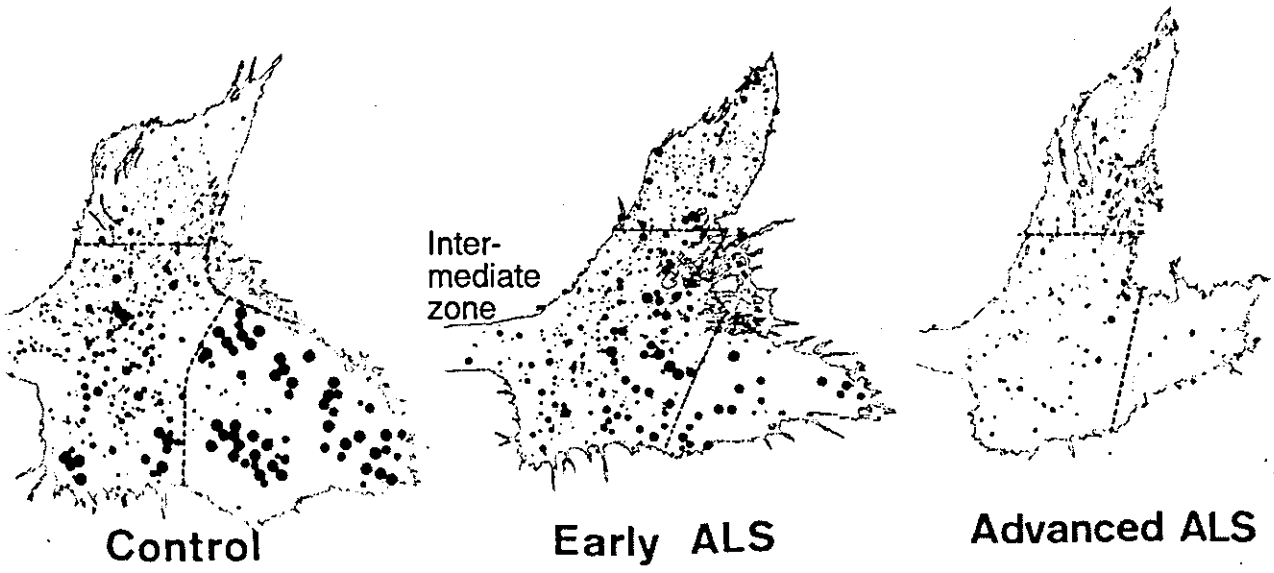


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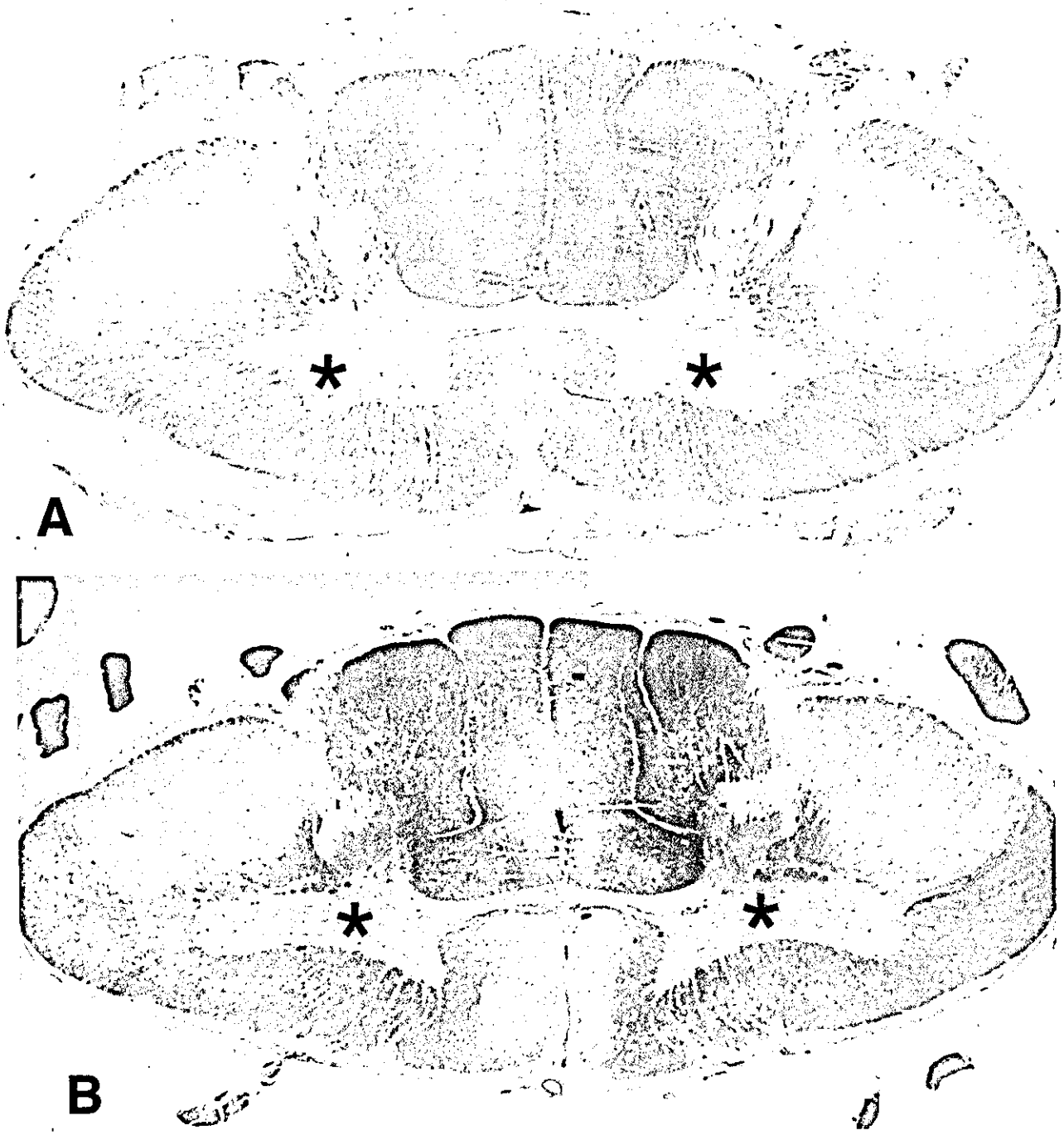
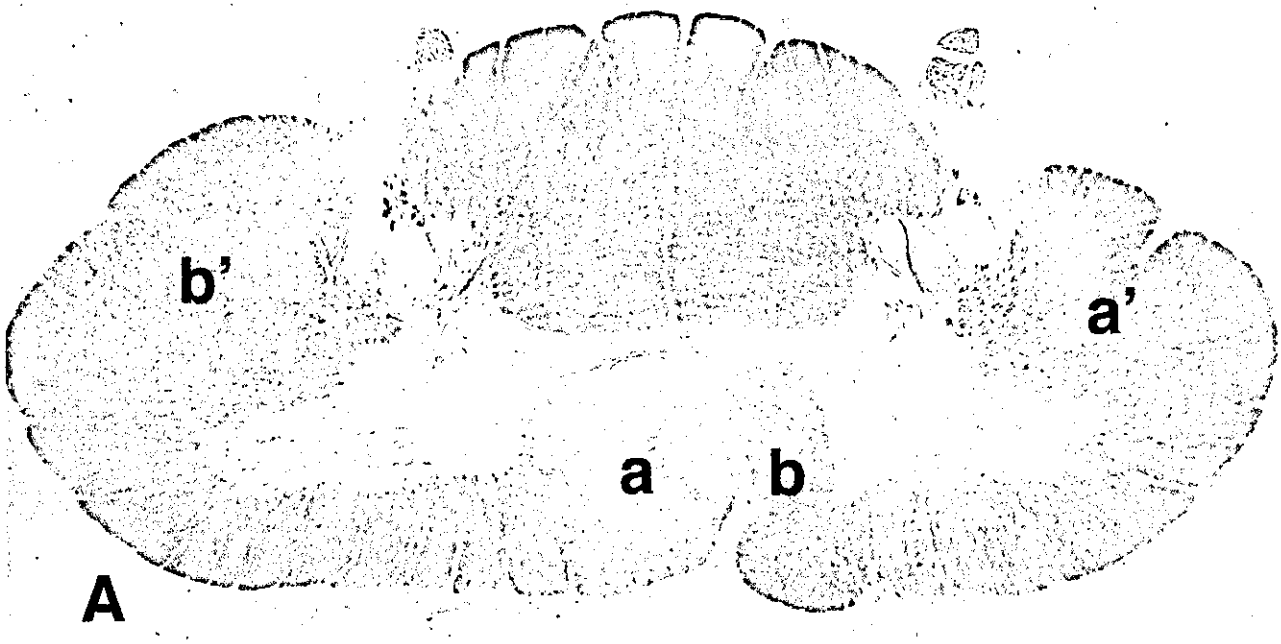



Fig. 8 Oyanagi et al.



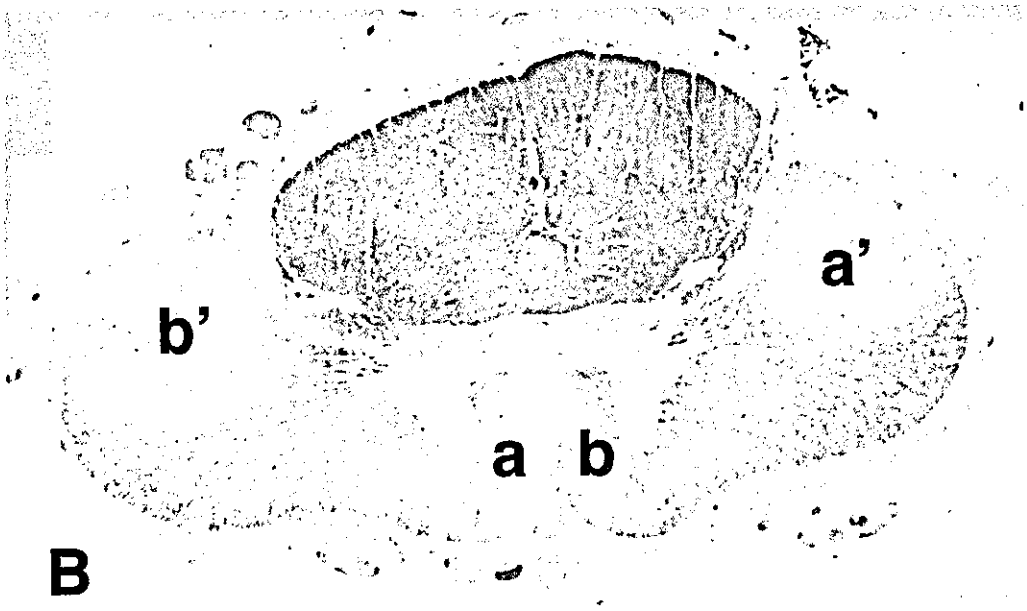




Fig. 9. Oyanagi et al.