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The location and characteristics of the thermal sudomotor pathways in the human brainstem: A reappraisal

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ABSTRACT

To elucidate location and characteristics of the central thermoregulatory sudomotor pathway in the human brainstem, thermoregulatory sweating (TS) in 91 patients with focal brainstem lesions was studied. TS was symmetric or minimally asymmetric in 40 subjects (Group S), and was apparently asymmetric in 51 patients (Group AS). In Group AS, the main abnormality was ipsilateral segmental hypohidrosis with a varying extent, involving predominantly the upper half of the body. Lesion locations, correlations between thermoregulatory sweat test results, and other autonomic and somatic functions were compared between the groups. The results suggested following: (1) The hypothalamospinal pathway related to TS may pass through the posterior hypothalamus and descend in the dorsolateral part of the brainstem, near the spinal trigeminal and spinothalamic tracts; (2) the pathway may descend together with those related to oculosympathetic and vasoconstrictor systems, but each of these may form distinct fiber groups; (3) the majority of the central TS fibers may reach ipsilateral sudomotor sympathetic neurons of the spinal cord, even though some fibers may cross at various levels; (4) in this descending pathway, somatotopic arrangements corresponding to each of the spinal sympathetic segments must be present; (5) There may be another fiber group passing through the central to dorsal paramedian portions of the brainstem, and lesions of these fibers also result in asymmetric TS, but seldom in oculosympathetic dysfunction. This second pathway probably exerts contralateral inhibitory influence on TS, but its origin, intracerebral course and exact physiological function require further clinical investigations.

1. Introduction

The main function of eccrine sweat glands of hairy skin is heat dissipation under hot environment and during exercise. The anterior hypothalamus and the preoptic area play critical roles in the neural control of thermoregulatory sweating (TS) and lesions of these structures may cause various forms of central thermoregulatory failure (Boulant, 2006; Benarroch, 2007). Though recent animal experiments facilitated understanding of the central mechanisms of thermoregulation, especially thermogenesis, the central mechanisms and pathways involved in heat dissipation remain unknown (Nagashima et al., 2000; Benarroch, 2007; Nakamura, 2011). This is mainly because TS is a uniquely developed function in humans. Therefore, physiological and clinical studies are mandatory to clarify the unresolved questions of human thermoregulatory mechanisms.

The TS-related hypothalamospinal pathways in the human brainstem were previously studied (Karplus, 1916; Guttmann and List, 1928; Kornyey, 1936; List and Peet, 1939; Foerster et al., 1939; Stead et al., 1942; Carmel, 1968; Schiffter and Pohl, 1972; Korpelainen et al., 1993). Carmel (1968) suggested that the sympathetic efferent pathway might descend in the area rostral and dorsal to the red nucleus, and ventral to the ventrolateral thalamic nuclei. For further caudal course, previous studies suggest that the main fiber group of TS-related hypothalamospinal pathways descends in dorsolateral tegmentum of the brainstem (Foerster et al., 1939; Freeman and Jaffe, 1941; Korpelainen et al., 1993), but an overall consensus has not been reached.

Foerster et al. (1939), while studying the neuronal regulation of sweating on the body, described that in patients with unilateral brainstem lesions, TS had diminished on the ipsilateral side of the lesions, but was not completely abolished. They postulated the presence of partially crossing fibers at the level of the brainstem and the spinal segments, and this was supported by other investigators (Stead et al., 1942; Carmel, 1968). On the other hand, List and Peet (1939) suggested that the TS-related fibers might decussate at two levels of the pons, whereas Schiffter and Pohl (1972) considered that they might descend ipsilaterally throughout the brainstem and the spinal cord. Thus, detailed features of the TS-related hypothalamospinal pathways in the human brainstem still remain obscure.

To further clarify the location and characteristics of central thermoregulatory sweating fibers, we investigated TS in 91 patients with

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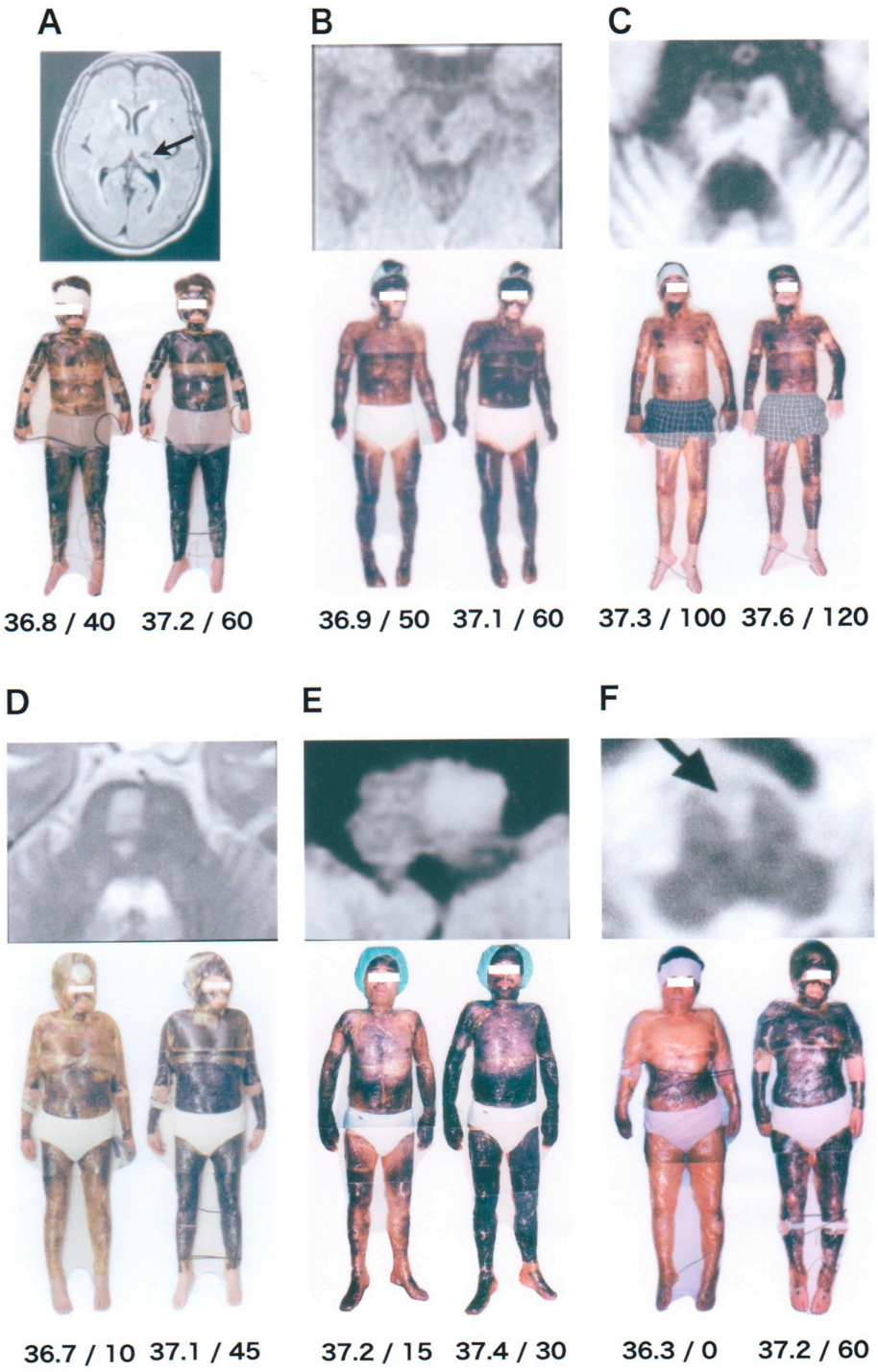

Fig. 1. Examples of patients with lesions resulting in qualitatively symmetric or minimally asymmetric thermal sweating (Group S). A: A 50-year-old woman with left thalamic hemorrhage. B: A 47-year-old man with a right-sided ventral paramedian infarction of the midbrain. C: A 50-year-old man with a right-sided ventral pontine infarction. D: A 74-year-old woman with a right-sided pontine infarction. E: A 57-year-old man with a left-sided infarction of the ventral medulla. F: A 74-year-old woman with a right medial medullary infarction.
In this and following figures, numerals on the bottom are core temperature and time in minute after the start of heating.

localized brainstem lesions, and analyzed correlations among the results of sweat tests, lesion sites, and other autonomic and somatic functions. The preliminary results of this study were published (Saito and Kogure, 1986; Saito, 2000; Saito, 2010).

2. Subjects and methods

2.1. Subjects

Subjects include 91 patients with localized brainstem lesions visualized on CT or MRI (55 men and 36 women; age: 14–88 years, 58 ± 15 years (mean ± SD)). TS was investigated at the Department of Neurology, Tohoku University Hospital, National Nishitaga Hospital and Sendai Eastern Neurosurgical Hospital after receiving the approval of the local ethics committee and informed consent for study participation by all patients or their family members. The nature of lesions was infarction in 64, hemorrhage in 20, tumors including hemangioma in five, and probable focal inflammation/demyelination in two patients. Causes of the brainstem lesions in 11 patients with age < 40 years were infarction because of vertebral artery dissection and embolism of cardiac origin (5) bleeding from hemangioma (3), possible inflammation/demyelination (2) and brain tumor (1). In one patient with motor neuron disease and previous lateral medullary infarction, the brainstem lesion was confirmed by an autopsy. Main lesions thus determined were at the level of thalamus and hypothalamus in 24, the midbrain in 9, pons in 17, and medulla in 41 patients. One patient had a massive

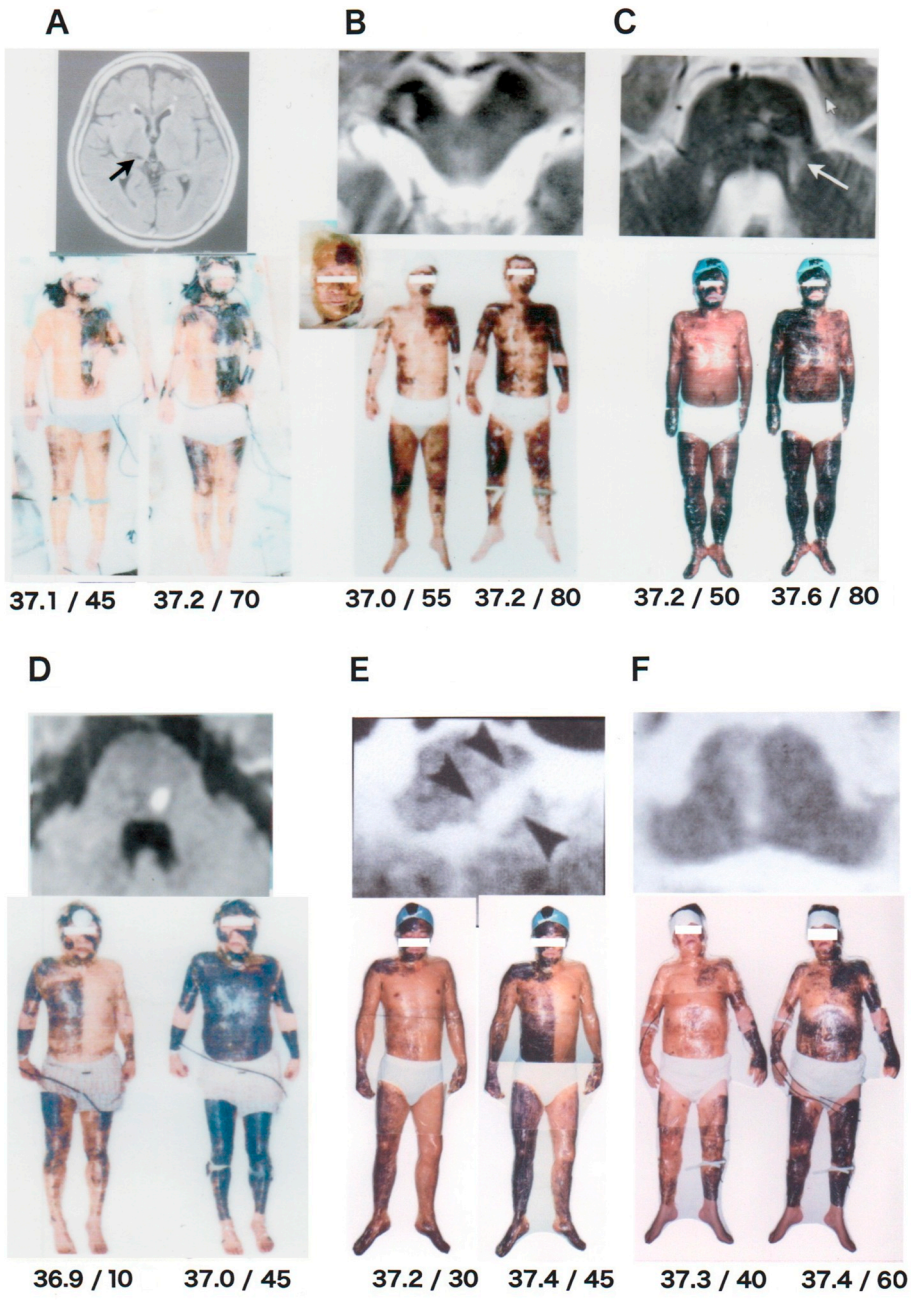

Fig. 2. Examples of subjects with lesions resulting in apparent laterality of thermal sweating (Group AS). A: A 60-year-old woman with right thalamic hemorrhage. B: A 74-year-old man with hemorrhage involving right subthalamus and midbrain presenting left-sided ballism. C: A 41-year-old man with left lateral and paramedian infarction of the pons. D: A 85-year-old man with a left-sided dorsal paramedian infarction of the pons. E: A 33-year-old man with a left lateral medullary infarction. F: A 68-year-old man with a right medial medullary infarction. Except for case B, all cases finally showed the discoloration on both sides.

hemorrhage mainly involving the left side of the midbrain and the upper pons. Brainstem lesions were associated with an infarction of the temporal or occipital lobes in four, and with ipsilateral cerebellar lesions in 15 patients. Twenty-three patients (13 men and 10 women) had diabetes mellitus, and one of these had an overt diabetic neuropathy. Other patients showed no signs or symptoms of neuropathy. Anticoagulants were used in about one-third of the patients, but no one used drugs with anticholinergic effects. The patients with vascular lesions were tested > 1 week after the onset (median value: 1.8 months) of symptoms.

2.2. Methods

The pupils were evaluated under semidarkness by an inspection and infrared photographs were taken in the case of 47 patients. Horner's eye sign was assumed, if the diameter of the pupil with preserved light reflex on the lesion side was < 0.5 mm less than that on the other side. The pupillary evaluation was not performed in three patients who had one-sided phthisis bulbi or repeated operations for cataract and glaucoma. Skin temperature was measured before heating on forearms or legs with surface thermistor thermometers (Core-temp-CTM-204, probe No: ME-PDS5, Terumo-Japan, Tokyo). Vasoconstrictor deficit was assumed if skin temperature on the lesion side was > 0.5 °C than on the contralateral side. The bladder function was assessed mainly by an interview.

The mode of TS was qualitatively evaluated with a modified Minor's colorimetric method (Saito et al., 1990). Under room temperature, test sheets were attached mainly on the anterior body surface of patients

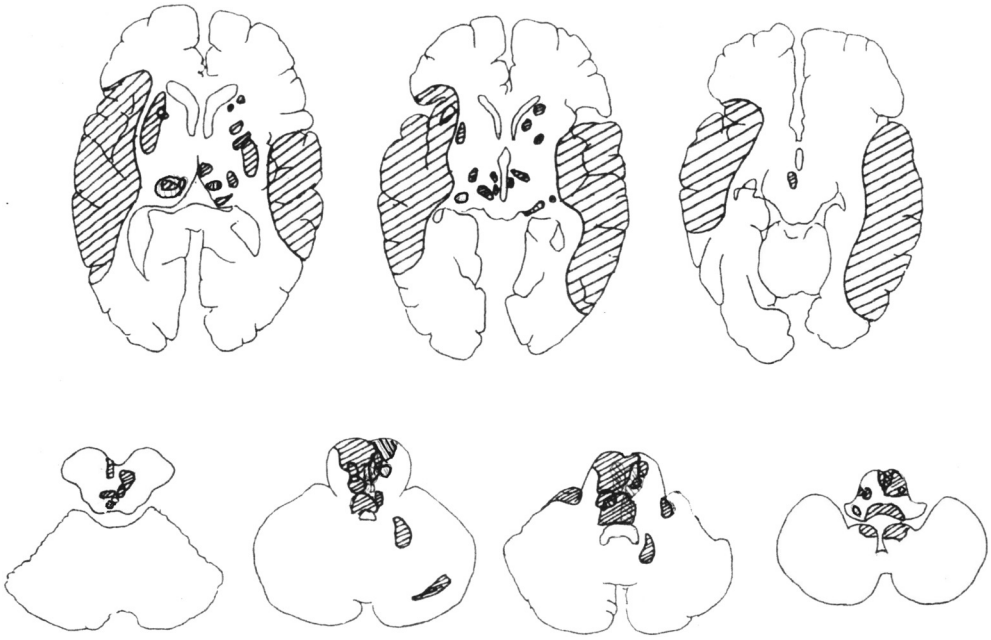

Fig. 3. A collective illustration of all confirmed lesions in Group S (N = 40).

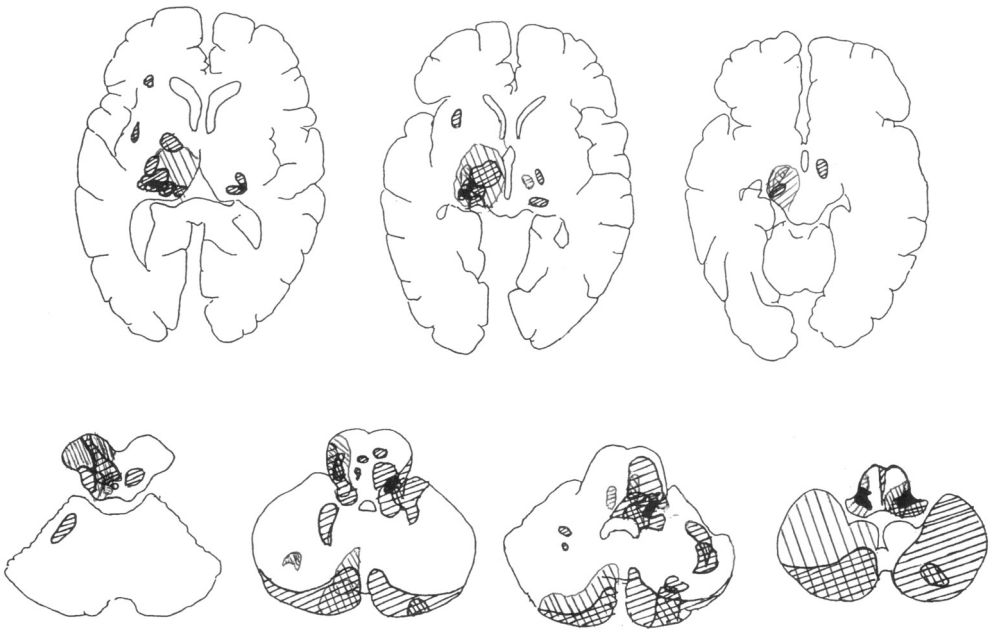

Fig. 4. Distribution of lesions in Group AS (N = 50). The predominantly left-sided massive hemorrhage in the midbrain and pons is not included.

wearing underwear. Then, patients were exposed to heat with electric blankets in the supine position until the deep body temperature increased by at least 1.0 °C. The approximate intracranial temperature was monitored on the forehead with a deep thermometer (Core-temp-CTM-204, probe No: PDK-161, Terumo-Japan, Tokyo) that can detect temperature at 15 mm-depth. The sweating patterns were successively sketched on the body scheme, and they were photographed on at least two different occasions during the sweat test. In 71 patients, sweat rates on both sides were measured at least on two of the following three areas of the body: the forehead, the volar surface of the forearm, and the lateral aspect of the leg by capacitance hygrometers (Hidrograph-AMU-2, Kyokuto-Denshi Company, Nagoya, and SKD4000, Skinos Company, Nagoya). Because the threshold and sweat rate varied largely depending on sex, age, and body sites, the ratio of sweat rate on lesion side to on the other side (I/C ratio) was also included for evaluation (Korpelainen et al., 1993). The results of qualitative sweat test were used to classify the subjects into the following two groups: subjects with symmetric or only minimally asymmetric TS (Group S), and those with apparently asymmetric TS (Group AS).

All brain lesions in each group were individually reproduced on the schema of the axial brain sections. The quantitative results from the two groups were compared with each other and with those obtained from the age-matched 50 subjects without autonomic deficits, serving as the control group (Group C). Statistical analysis was performed using ANOVA or two-tailed Student t-test, and values were considered significantly different at a confidence level of 95%.

Neurological deficits were classified into two categories: absent (−) and present (+). The correlation between the results of TS test and neurological impairments was assessed using contingency table analysis.

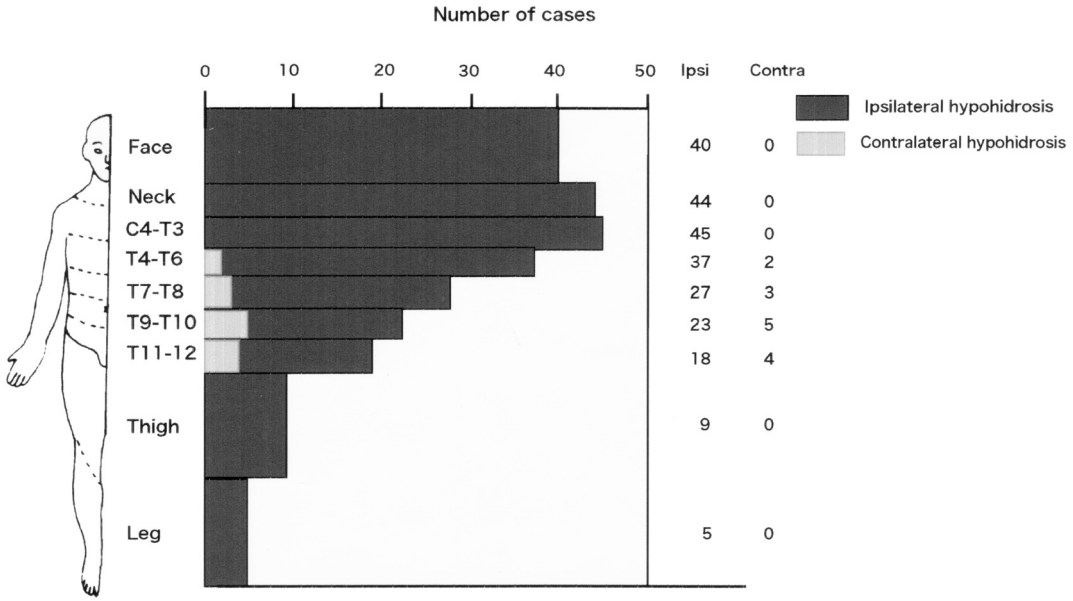

Fig. 5. Distribution of hypohidrotic areas in 51 patients with asymmetric sweating, indicating that the upper part of the body is mainly involved.

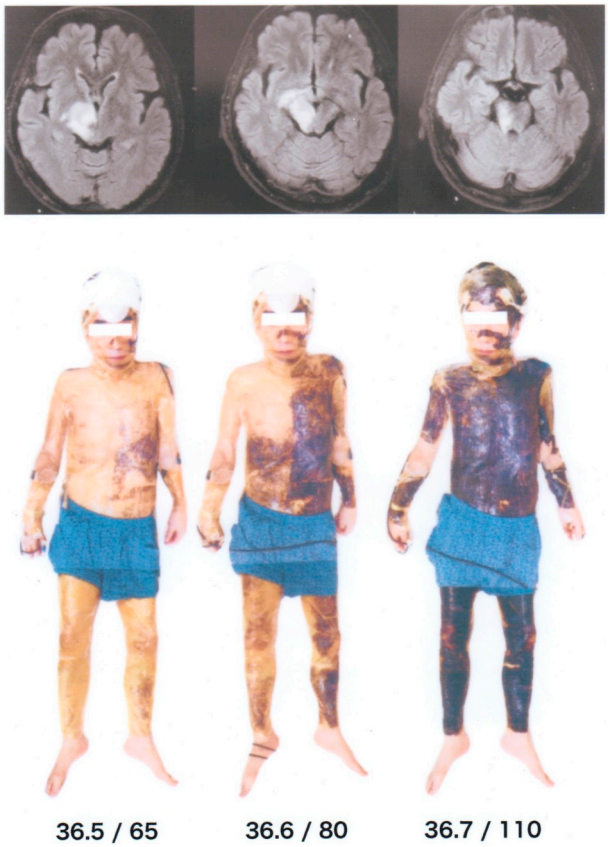

Fig. 6. A 67-year-old man with brain tumor extending from the thalamus to the pons. He had left-sided ballism and the ipsilateral hypohidrosis on the upper part of the body, but, finally showed almost whole body discoloration.

3. Results

3.1. Sudomotor laterality in qualitative evaluations

Twenty-one patients requested discontinuance of heating, before the body temperature increased 1.0 °C, because of "excessive hotness" or lumbago due to long-standing fixed posture. However, sweating patterns were recorded in all patients. Results of qualitative sweat test in 91 patients were classified into Group S (N = 40) and into Group AS (N = 51). Examples were shown in Figs. 1 and 2. Sweating before heating was observed in 16 patients: four in Group S and 11 in Group AS (p = 0.0690). In Group AS, the main abnormality was ipsilateral multi-segmental hypohidrosis with varying extent, predominantly involving the upper half of the body. No patient revealed anhidrotic area. All lesions found in both Groups were shown in Figs. 3 and 4. At the diencephalic level, distribution of lesions in Group S and Group AS could not be clearly delineated from each other, though lesions in Group AS appeared to be localized more on the ventral aspect, extending to the hypothalamus or subthalamus in some patients. All three subjects with contralateral ballism showed ipsilaterally decreased sweating. At more caudal levels, lesions in Group S showed a tendency to occupy the paramedian and ventral portions of the brainstem (Fig. 3), whereas those in Group AS were distributed mainly in the dorsolateral regions (Fig. 4). Four patients with lateral medullary infarction, however, were classified into Group S, and 7 out of 17 patients with lesions in paramedian portions of the brainstem were classified into Group AS (Figs. 2 D, F, and 4). The lesions in these seven patients involved primarily the central to dorsal paramedian parts. The latter patients had no signs of oculosympathetic paresis. Among three patients with medial medullary syndrome, one patient showed TS laterality, and his lesion extended to the most dorsal part of the medulla. (Fig. 2F), and lesions of remaining two patients did not involve the portion (Fig. 1F).

The hypohidrotic area in Group AS was seen predominantly on upper portions of the body (Fig. 5). Even a case of a massive tumor extending from the thalamus to the pons on the right side showed ipsilateral hypohidrosis on the upper part of the body (Fig. 6).

Among 28 patients in Group AS, 15 patients had lesions that were restricted to the more dorsal or more lateral portions of the medulla tended to show sweating laterality limited to the face, upper limb, and the upper chest (Fig. 7). In 13 patients with more extensive or more medially situated lesions, TS laterality appeared to involve not only upper parts of the body but also the middle to lower levels of the trunk or even the lower extremity (Figs. 2E, 8 and 9). In Group AS, seven patients showed, in addition to ipsilateral TS reduction, less marked (multi)-segmental hypohidrosis on the contralateral side below T_3 sensory dermatome (Fig. 2B, C and 5).

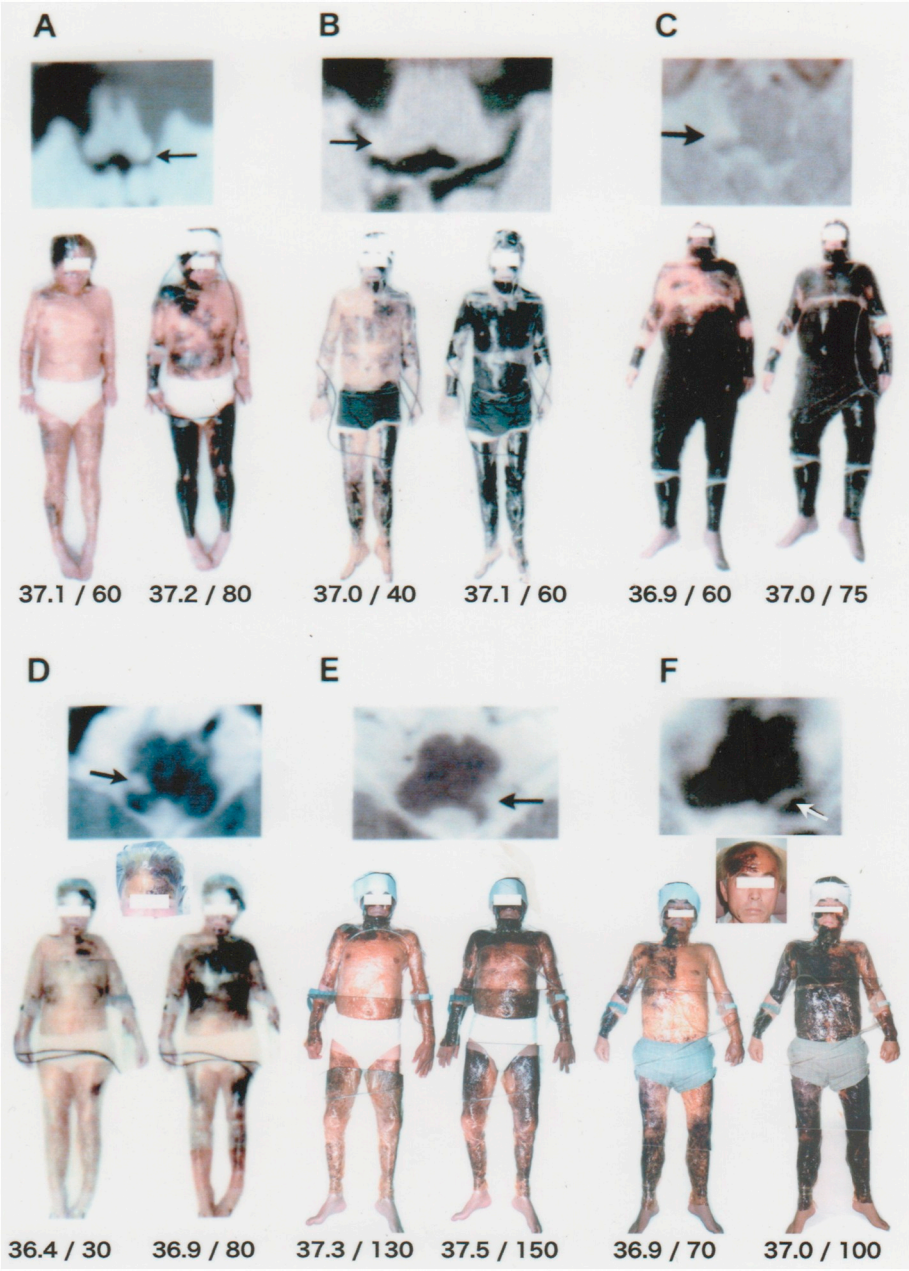

Fig. 7. Examples of thermal sweating patterns in patients with laterally localized medullary infarction. It is suggested that more laterally situated infarctions tend to impair sweating on the upper part of the body.

3.2. Relationship between TS and other autonomic and somatic functions

The relation between the results of qualitative sweat test and neurological deficits is shown in Table 1. An apparent TS laterality was significantly correlated with Horner's eye sign, asymmetric skin temperature, impairment of the spinal trigeminal tracts, paresis of the glossopharyngeal and vagal nerves, and with cerebellar ataxia. Dysuria, impairments of 6th, 7th, 12th cranial nerves, pyramidal signs, and impaired deep sensation showed no significant correlations with TS laterality. The presence of oculomotor nerve palsy or medial longitudinal fasciculus syndrome showed negative correlation with TS laterality.

There was no statistical difference in the number of diabetic patients in both groups (10 in Group S and 13 in Group AS, $p = 0.7930$). Eleven of them (6 in Group S and 5 in Group AS, $p = 0.5500$) showed, during early phase of sweating, irregular patchy sweating spots suggestive of postganglionic impairment. Thus, the main cause of TS laterality in Group AS must be central lesions.

3.3. Quantitative evaluation

Sweat rates (mg/cm^2/min: SRs) bilaterally of the three recording sites in Groups S and AS are shown in Fig. 10, along with the control group (Group C) sweat rates. There was no significant difference in laterality between Group C and Group S, whereas in Group AS, SR was significantly less on the lesion side than on the contralateral side. SRs of three recording sites in Group S did not differ from those in Group C. In Group AS, however, SRs in three recording sites on the lesion side were significantly less than those in Group C, but those on the contralateral side did not show significant differences. In Group AS, the mean value and standard deviation of SRs on the contralateral forehead appeared larger than those in Group C and Group S, though not statistically

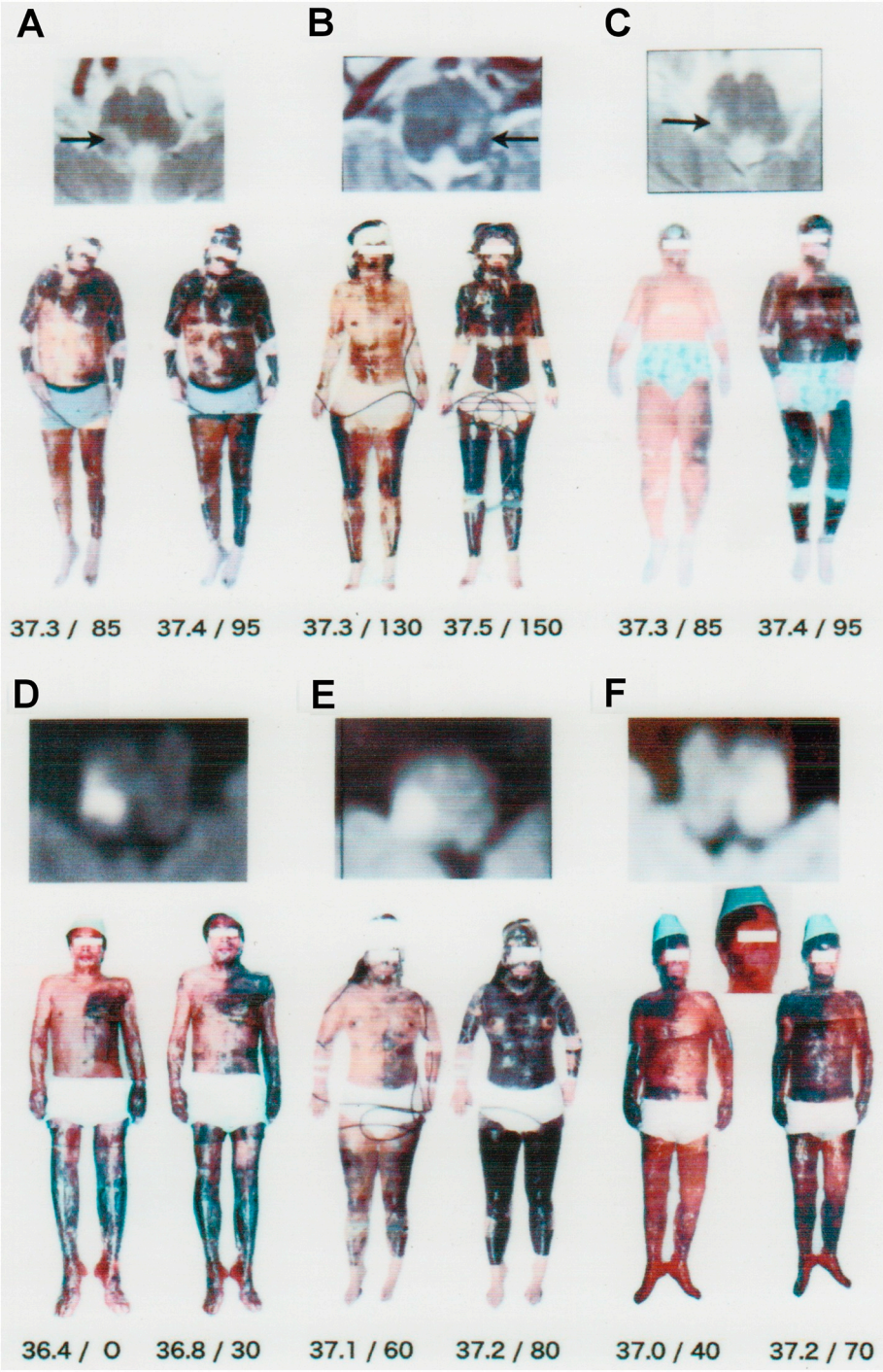

Fig. 8. Examples of thermal sweating patterns in patients with deeply situated or extensive lateral medullary infarctions. All cases finally showed the discoloration on both sides.

significant. This suggested that some patients in Group AS might have excessive sweating on the forehead opposite to the lesions. Comparison of sweat rate ratio bilaterally confirmed that SR laterality was more apparent on the face and forearm, and less marked on the leg (Fig. 11).

Threshold of sweating (°C) were 36.8 ± 0.3 on Group S ($N = 35$), and 36.9 ± 0.4 in Group AS ($N = 36$) ($p = 0.7229$). Number of sweat expulsions per 1 min were 8.1 ± 1.4 in Group S (N = 35) and 9.2 ± 5.8 in Group AS (N = 36) ($p = 0.2479$). Three patients in Group AS showed sweat expulsions of much higher frequency on the contralateral side than on the lesion side. The details of this finding will be reported elsewhere. Time lags in the start of sweating (minute) between contralateral and ipsilateral sides were 0.8 ± 1.5 in Group S (N = 35) and 14.9 ± 12.3 in Group AS (N = 36) ($p < 0.0001$). Differences in deep-body temperature (°C) at the start of sweating between on contralateral and ipsilateral sides were 0.007 ± 0.025 in Group S (N = 35) and 0.250 ± 0.425 in Group AS (N = 36; $p < 0.0012$).

4. Discussion

4.1. Location of thermal sweating pathways in the brainstem

In the present study, an apparent TS laterality was observed in 51

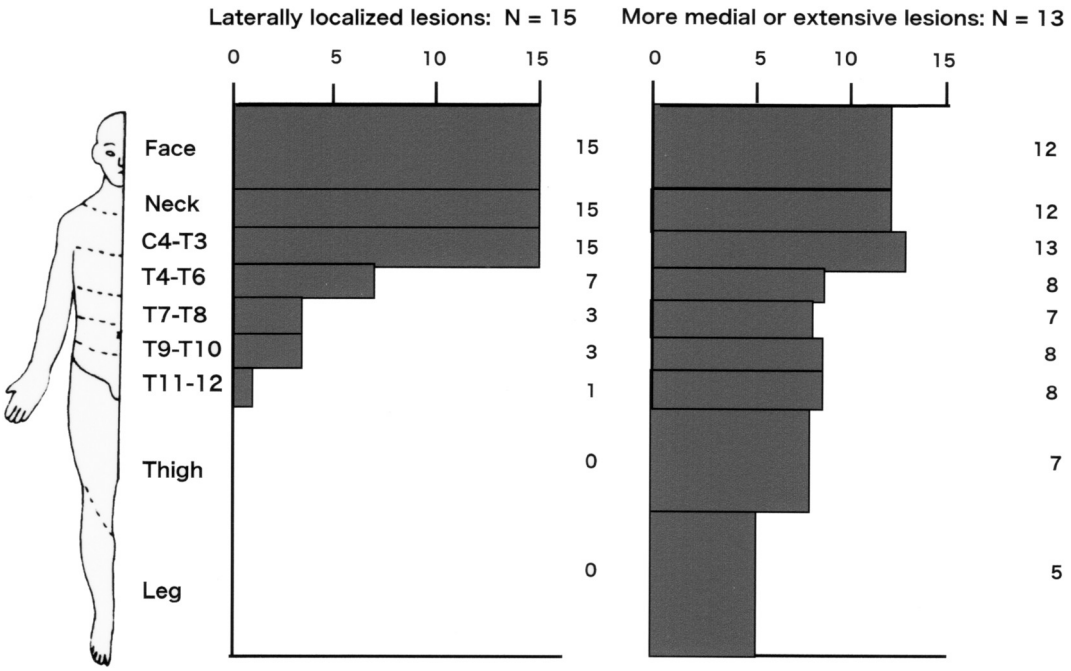

Fig. 9. Distribution of hypohidrotic areas in patients with laterally localized lesions and more medial or extensive lesions of the medulla showing that the extensive lesions interfere with not only upper but also lower parts of the body.

Table 1
Thermal sweating laterality and neurological deficits.

	Horner		Vasomotor		Dysuria		CN-III, MLF		CN-V-spinal		CN-VI		CN-VII	
	+	−	+	−	+	−	+	−	+	−	+	−	+	−
Group S	6	33	13	28	4	37	7	33	4	37	3	37	2	39
Group AS	37	12	29	21	3	46	2	47	17	32	1	48	1	49
P value	< 0.0001		0.0123		0.5215		0.0367		0.0053		0.2163		0.4442	

	CN-IX&X		CN-XII		Pyramidal		Q-thalamic		Sp-thalamic		Med-lem.		C-ataxia	
	+	−	+	−	+	−	+	−	+	−	+	−	+	−
Group S	3	38	1	40	24	17	19	22	29	12	16	25	8	33
Group AS	15	34	0	49	21	29	18	31	41	8	13	36	25	24
P value	0.0059		0.2716		0.1164		0.3563		0.1414		0.2065		0.0020	

C-ataxia: cerebellar ataxia; CN: cranial nerve; CN-V-spinal: spinal trigeminal tract; Lem-med: medial leminiscus; MLF: medial longitudinal fasciculus; Q-thalamic: quintothalamic tract; Sp-thalamic: spinothalamic tract; +: symptoms or sings of impairment are present; −: symptoms or sings of impairment are absent.

out of 91 patients with brainstem lesions (56%). The main abnormality was relative hypohidrosis on the ipsilateral side. The locations of lesions in the mid to lower brainstem causing TS laterality appeared to be concentrated in two foci: dorsolateral and dorsal paramedian regions.

Carmel (1968) studied sympathetic deficits in patients who had received a stereotaxic surgery for dyskinesia and parkinsonism, and concluded that the location of the descending hypothalamo-spinal sympathetic efferent pathways may be in the area rostral and dorsal to the red nucleus, and ventral to the ventrolateral thalamic nuclei. Results of the present study are roughly concordant with Carmel's observations. At more caudal levels, lesions in Group AS were distributed mainly in the dorsolateral tegmentum, whereas those in Group S occupied paramedian and ventral portions.

Clinicoanatomical studies on unilateral infarction of the midbrain and pontine tegmentum due to an occlusion of the superior cerebellar artery, ipsilateral Horner's syndrome and sweat diminution were described (Freeman and Jaffe, 1941; Luhan and Pollack, 1953). A case similar to the one in the present study also presented marked hypohidrosis of the upper part of the body (Fig. 2C). Freeman and Jaffe (1941) postulated that, if any concentration of the descending connections from the hypothalamus occurs at the pontine level, the probable location is in the tegmentum. Here List and Peet's (1939) description is perplexing. They reported results of sweat test on 18 patients with six pontine and 12 medullary lesions. Their two patients with unilateral lesion of the upper pons showed bilateral hypohidrosis except for face and neck. In other cases, sweating was decreased mainly on the lesion side. On the basis of these results, they postulated that the hypothalamospinal projection might decussate at two levels of the pons, and descends ipsilaterally, thereafter. Sato et al. (1989) reiterated this notion in their review. But if List and Peet's scheme is correct, there must be certain number of patients with pontine or more rostral lesions, who exhibit hypohidrosis limited to the contralateral side. However, such cases were not encountered in the present study or in earlier studies (Foerster et al., 1939; Stead et al., 1942). At the medullary level, Kornyey (1936) illustrated the descending autonomic pathways in the area ventral to the solitary nucleus and medial to the inferior cerebellar peduncle and the spinal trigeminal tract and nucleus. According to Foerster (1939) and Foerster et al. (1939), the connection between the

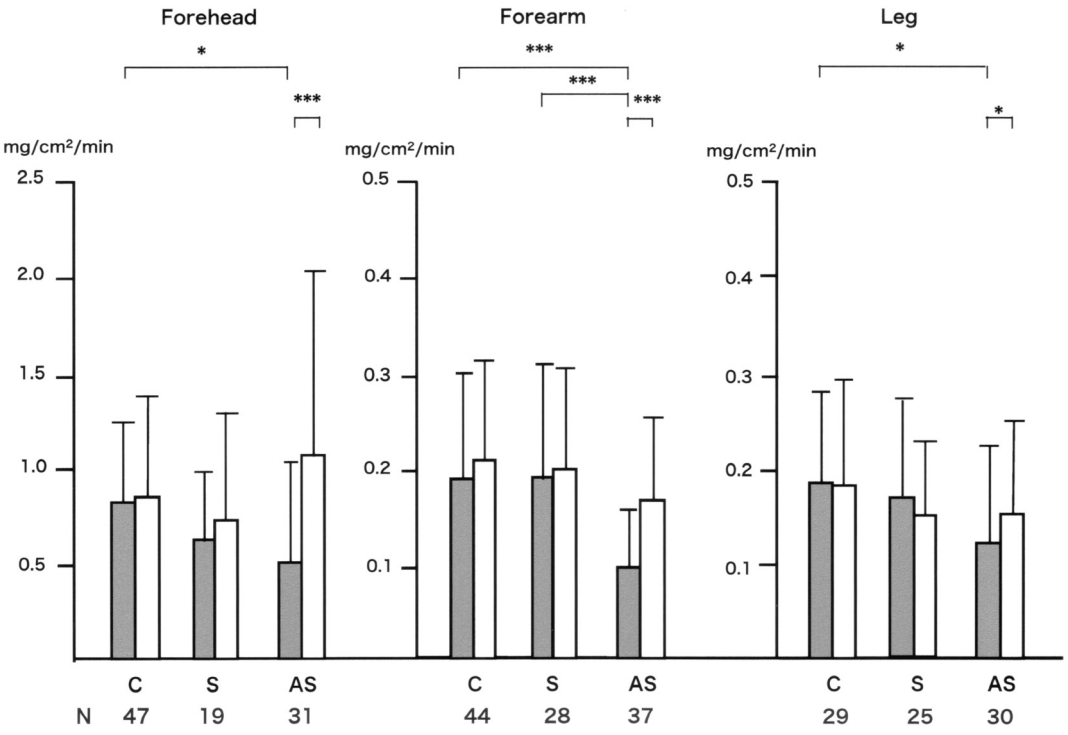

Fig. 10. Maximum sweat rates on three recording sites. In this and in Fig. 11: C = control subjects. S = patients with brainstem lesions and almost symmetric thermal sweating. AS = patients with brainstem lesions and asymmetric thermal sweating. N = number of subjects. Gray column = lesion side. White column = opposite side. Statistical significance: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

hypothalamus and the lateral horn of the spinal cord exists, and passes down through the tegmentum of the brainstem, and potions anterior to the lateral corticospinal tract of the spinal cord. Guttmann (1973) also described that, in the oblongata, most sweat fibers travel through an area occupied by the lateral reticulospinal tract. Although Harati (1993) described that the descending autonomic pathways are diffusely distributed in the spinal cord, our present results and previous reports indicate that the descending sympathetic pathways may pass through the restricted portions of the brainstem and the spinal cord (Foerster et al., 1939; Guttmann, 1973; Nathan and Smith, 1986; Nathan and Smith, 1987; Saito, 2009). In the present study, the correlation analysis between TS laterality and other sympathetic and somatic functions indicate that TS-related hypothalamospinal pathways may descend, together with pupillomotor and cutaneous vasomotor fibers, the dorsolateral part of the tegmentum in the vicinity of spinal trigeminal tract. Dissociation among these three sympathetic functions observed in certain number of patients in the present study, suggests that each of the pathways may form distinct fiber groups, as previously postulated by List and Peet (1939) and Stead et al. (1942).

In the present study, an apparent TS laterality was observed in seven out of 17 subjects with paramedian lesions of the brainstem. Oculosympathetic paresis, however, was seen in none of them. The results likely present two possibilities; (1) another TS-excitatory fibers may pass through the dorsal paramedian area, or (2) a putative TS-inhibitory pathway, possibly of cortical origin (Karplus, 1916; Guttmann, 1973; Labar et al., 1988), may pass through this portion. I suppose that the latter possibility might be more plausible, because, except some cases (Awada et al., 1991; Bassetti and Staikov, 1995; Rousseaux et al., 1996) in previously reported patients with contralateral hyperhidrosis due to brainstem lesions, lesions were located in the dorsal paramedian portion (Mon and Mizotani, 1992; Nakaso et al., 1995; Rey et al., 1996; Sato and Nitta, 2000; Pollecchia et al., 2003).

4.2. Crossing fibers in the brainstem

Animal experiments suggested that the hypothalamospinal projections are mainly ipsilateral, but some fibers cross at various levels (Loewy et al., 1973; Saper et al., 1976; Holstege, 1987). In the present study, a completely anhidrotic area was hardly seen, supporting Foerster's (1939) description. Furthermore, seven patients in Group AS showed, in addition to ipsilateral hypohidrosis, less extensive hypohidrotic area on the contralateral side. Though Schiffter and Pohl (1972) illustrated the TS pathway to be exclusively ipsilateral, the present investigations and literature (Foerster et al., 1939; Guttmann, 1973) suggest that the crossing fibers exist in the brainstem.

4.3. Somatotopic arrangement in the descending TS-sudomotor pathways

Korpelainen et al. (1993) reported results of quantitative sweat test on 18 patients with brainstem lesions (pons nine, medulla nine). Though the authors did not refer to lesion location in detail and sweating patterns in their cases, they concluded that in all recording sites, the sweating response to heat stimulus was lower on the lesion side than on the contralateral side. The present investigations confirmed their conclusions.

The qualitative and quantitative investigations of the present study indicated that TS deficits due to localized brainstem lesions rarely involve entire ipsilateral half of the body, but involve chiefly upper portions of the body with segmental distribution. These findings may indicate that, in the sudomotor hypothalamospinal projections, in addition to the existence of crossing fibers, there must be somatotopic arrangement corresponding to each of the thoracolumbar segments, as suggested in the spinal cord (List and Peet, 1939; Foerster et al., 1939; Guttmann, 1973). For the regional differences of hypohidrosis distribution, there might be two possibilities. First possibility is that the ipsilateral dominance of the sudomotor hypothalamospinal projections may be weak in the lower body and thus relatively abundant crossing

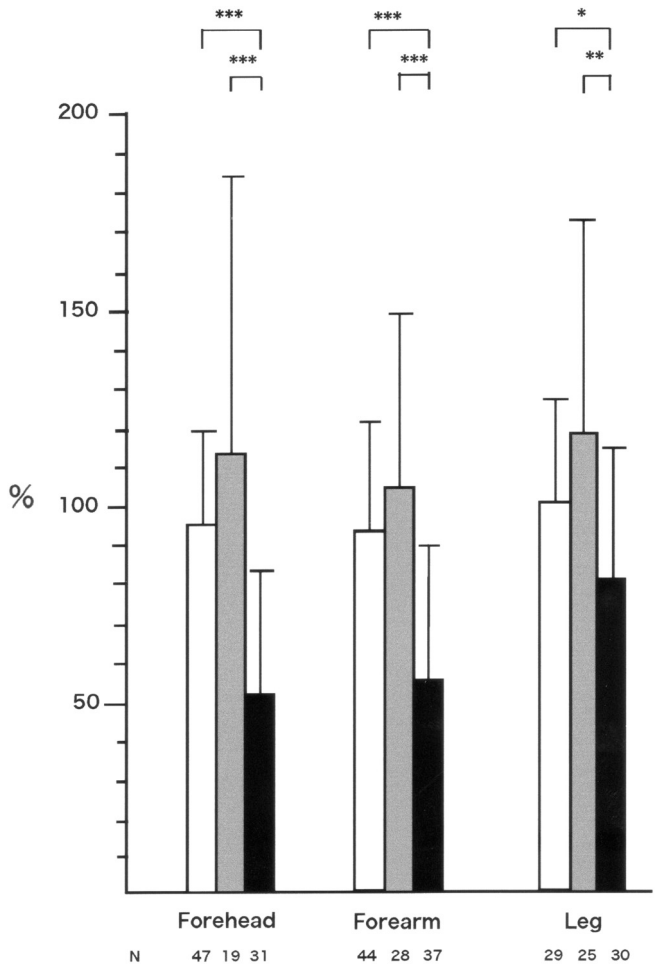

Fig. 11. Ratio of maximum sweat rates bilaterally (ipsilateral/contralateral × 100), showing the sweating laterality is less prominent on the leg. White column = Control Group. Gray column = Group S. Black column = Group AS, Statistical significance: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

fibers may contribute to TS of the lower body. Second possibility is that some of the lumbar preganglionic neurons may send communicating fibers to the lumbosacral sympathetic ganglions on the contralateral side (Cowley and Yeager, 1949; Webber, 1957).

5. Conclusion

It should be reemphasized that the sudomotor hypothalamospinal projections may not be diffusely distributed in the brainstem, but their main fibers must be concentrated in the dorsolateral tegmentum near the spinal trigeminal and the spinothalamic tracts. Confirmation of the possible TS-inhibitory pathway passing through the dorsal paramedian portions of the brainstem requires further clinical investigations.

Declarations of interest

Conflict of interest

None declared.

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