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Hemimegalencephaly with hemihypertrophy (Klippel-Trénaunay-Weber syndrome)

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Summary. A 17-year-old Japanese girl had right hemihypertrophy, vascular nevus of the right side of the body, right hemimegalencephaly, multiple haemangiomatosis, varicosis and chronic proliferative glomerulonephritis. The hypertrophied side of the cerebrum showed no malformations. Quantitative studies showed no significant differences between the two cerebral hemispheres in size, form, density or DNA content of nerve and glial cells. The hemimegalencephaly seemed to be due to an increase in the absolute number of nerve and glial cells in the ipsilateral cerebral hemisphere. Eight cases of hemihypertrophy with hemimegalencephaly have been reported to date, in all of them hemihypertrophy and hemimegalencephaly were on the same side. This condition seems to be due to unilateral overproduction of neuroblasts and glioblasts or hindrance of the normal loss of excess neurons, which may be induced by hemihypertrophy of the mesenchyme surrounding the CNS.

Key words: Hemihypertrophy – Hemimegalencephaly – Klippel-Trénaunay-Weber syndrome – Phacomatosis

Introduction

Meckel in 1822 and Wagner in 1839 reported the first autopsy cases of hemihypertrophy of the body and more than 100 cases have been reported since. With respect to dermal changes associated with hemihypertrophy, Klippel and Trénaunay in 1900 reported a case showing hemihypertrophy of bones and soft tissue, with dermal haemangioma and varicosis on the same side. In 1906, Weber reported other cases with vascular phacomatosis, varicosis on the side of hemihypertrophy and hypertrophy of one extremity, or hemihypertrophy. Thus this condition is now called the "Klippel-Trénaunay-Weber syndrome". Hemimegalencephaly was first reported by Sims in 1835. Later several other cases were reported, but descriptions of

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qualitative and quantitative changes of the CNS, and their relation to changes of other organs have sometimes been incomplete and conflicting.

Case history

A 17-year-old girl, born November 12, 1960; died December 21, 1977. Her birth weight was 3,840 g. Right hemihypertrophy, vascular nevus of the right of the face, trunk and extremities, and several haemangiomas in the skin were present from birth. Left hemiparesis and mental retardation were noted at 18 months. Seizures with grand mal fits developed from 12 years of age. At 15 years old, she was admitted to hospital with the nephrotic syndrome. She had vascular nevi and subcutaneous haemangiomas on the right of the face (Fig. 1a), tongue, conjunctiva, neck and extremities, and hemihypertrophy of the right of the face and trunk and right extremities (Fig. 1b). She was 160 cm in height and weighed 57 kg. Her IQ was 30, and so she could not write, but could take care of herself. The deep tendon reflexes were decreased but symmetrical. Muscle power and movement of the left extremities were reduced. Radiographs of the skull and bones of the upper and lower extremities showed hypertrophy on the right. Electroencephalography demonstrated diffuse slow waves of moderate to high voltage all over and scattered spike waves in the right anterior temporal lobe. Urinalysis showed proteinuria (2–6 g/day) and hematuria. She was treated with steroids and dieuretics. At 17 years old, she was readmitted to hospital suffering from a common cold. Seven days after admission, she died abruptly. Autopsy was performed 78-min after death.

Methods

1. Histopathological studies. Organs were removed and fixed in 10% formalin. Slices of all lobes of the brain were taken symmetrically from the two hemispheres, and embedded in paraffin. Sections were stained with haematoxylin and eosin, cresyl violet, phosphotungstic acid-haematoxylin, Holzer's stain for glia, Bodian's stain for neurofibrils and axons, and Klüver-Barrera's stain for myelin.

2. Quantitative observations on the brain. (1) The water content of one slice of a coronal section of each occipital lobe was measured by the incineration method. (2) The ratio of the areas of the cortex and white matter was measured with a Texture Analysing System (TAS, Leipzig) in coronal sections of the two frontal, temporal and occipital lobes, which were stained by Klüver-Barrera's method. (3) All nuclei in all layers of the cortex in a width of 260 μm from the surface at the gyri of F_1, rectal gyri, orbital gyri, and gyri of P_1 and O_3 were measured with a Colour Video Image Processor (VIP, Ikegami-Olympus). Measurements were made in the narrowest part of the each cortex which faced the sulcus, and more than 5 fields in each area were measured. (4) Transverse sections of the two longitudinal tracts of the basis pontis were taken symmetrically, refixed in 2% osmic acid, embedded in Epon 812, and sectioned at 1 μm thickness. Numbers of transverse myelinated fibers in 5 fields of 100 × 100 μm were counted in photographs at 1,000 enlargement. (5) Total numbers of myelinated fibers in the ventral and dorsal roots of the 8th cervical and first thoracic cords were counted with a TAS, after the transverse sections were treated as described in (4). (6) The content of intranuclear DNA was measured with a microphotometer (UVMPM-01, Carl Zeiss) in paraffin sections stained by the Feulgen reaction.

Results

1. Autopsy findings. Macroscopically, hemihypertrophy on the right side of the head, extremities and trunk, and diffuse pigmentation and vascular phacomatosis of the skin of the same side were noted. In addition, multiple subcutaneous haemangiomas the size of a thumb-tip were seen on the right side of the face, right arm, right shoulder, both sides of the abdominal wall, right thigh and right leg. The weights of bilaterally located organs were not abnormal, being as follows: kidneys (left 280, right 240 g), lungs (170, 200 g). The thyroid gland was

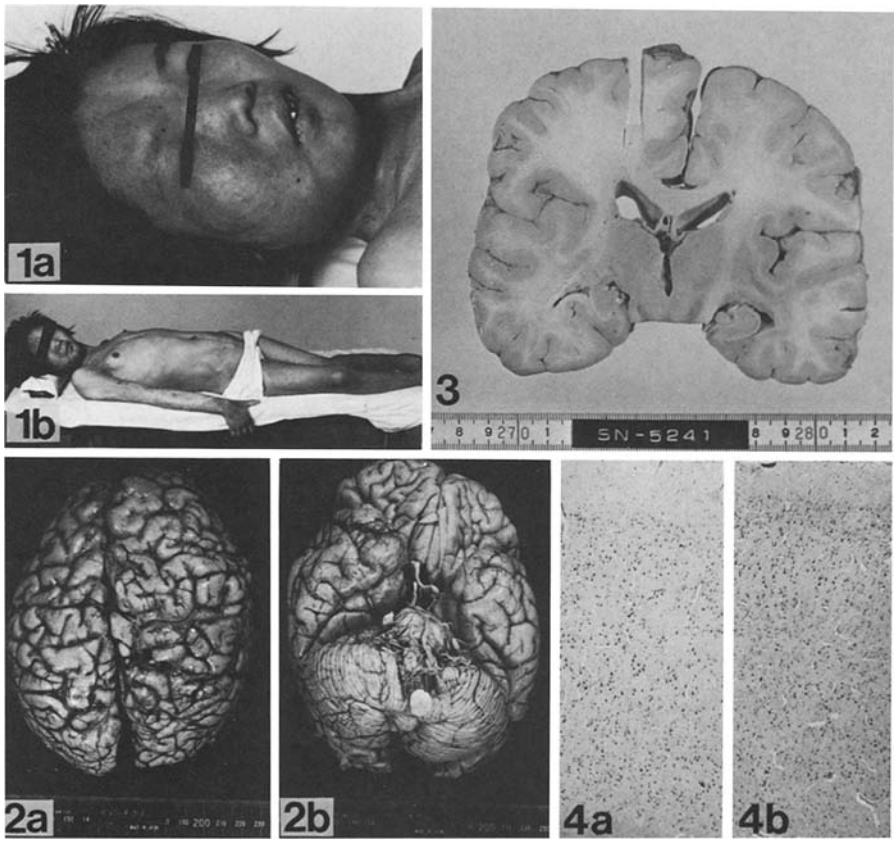

Fig. 1a, b. The right half of the face showing hemihypertrophy with vascular nevi and subcutaneous haemangiomatosis **a**. The right half of the trunk and extremities showing hemihypertrophy **b**

Fig. 2a, b. Appearance of the brain after fixation, showing hemimegalencephaly of the right half. Superior **a** and basal **b** aspects

Fig. 3. Hypertrophy of the right basal nuclei and thalamus in a cut-section

Fig. 4a, b. Sections of the two cerebral cortices showing normal cellular architecture. Left **a** and right **b** temporal lobes. Klüver-Barrera, × 32

symmetrical. The unfixed brain weighed 1,640 g. The right cerebral hemisphere appeared distinctly larger (right $17.2 \times 7.2 \times 12.0$, left $15.8 \times 6.3 \times 10.2$ cm) and weighed about 180 g more than the left (Fig. 2a, b). It was the same colour and consistency as the left hemisphere. The cerebral gyri and sulci were symmetrical and normal in configuration. The hemimegalencephaly involved the cerebellum and pons. In coronal sections, the right basal nuclei and thalamus appeared slightly hypertrophic (Fig. 3).

Histologically, the nerve cells on the hypertrophied side were well-developed and the laminar arrangement of the cortex was normal (Fig. 4a, b) except for a few focal areas of laminar loss of nerve cells in layers deeper than the fourth layer in the right parietal lobe. Astrocytes of Alzheimer type II were seen in the cerebral cortex. The white matter of the hypertrophied cerebral hemisphere, especially around the ventricle, showed rarefaction in

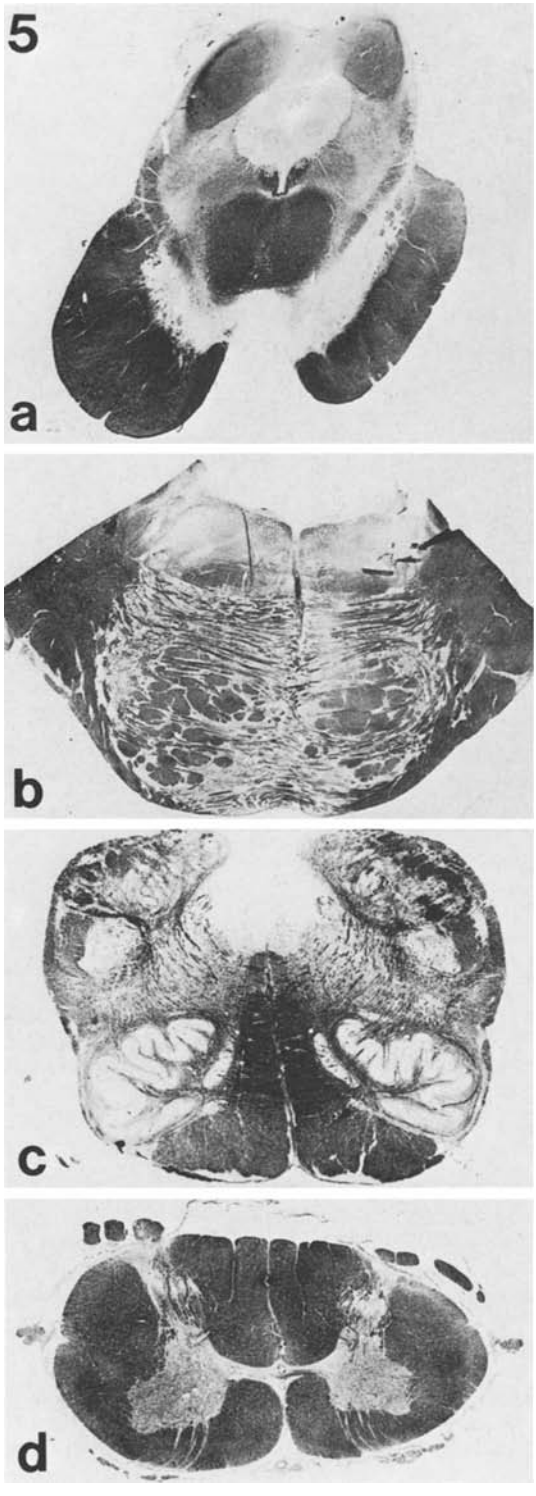

Fig. 5a–d. Sections showing hypertrophy of the right cerebral peduncle (left:right, 1:1.25) in the midbrain (**a**, ×2.8), right longitudinal tract (1:1.15) in the pons (**b**, ×2.7), and the right anterior and lateral funiculi (1:1.15) in the 6th cervical segment (**d**, ×6), but not the right pyramidal tract (1:1) in the medulla oblongata (**c**, ×6). Klüver-Barrera

Table 1. Quantitative analyses of the brain

A. Ratio of cortex to white matter

	This case		Control (3 cases)
	Left	Right	Mean value
Frontal lobe	2.88	2.06	1.38
Temporal lobe	2.65	1.85	1.44
Occipital lobe	2.02	1.60	1.56

B. Number of nuclear cells in the cerebral cortex

	Left	Right
F_1	766.3±56.0	771.6±42.3
G. rectus	436.2±85.3	428.8±28.5
G. orbitales	400.8±54.1	446.0±41.0
P_1	751.4±49.7	778.4±89.9
O_3	734.0±71.1	728.0±37.6

C. Number of myelinated fibers in anterior and posterior roots

		Left	Right
C-8	Anterior root	7,696	4,527
	Posterior root	11,744	3,166
Th-1	Anterior root	6,562	8,165
	Posterior root	5,809	13,658
C-8+Th-1	Anterior root	14,258	12,692
	Posterior root	17,553	16,824

myelin stain and slight astrocytosis. The cerebellum, midbrain, pons and medulla oblongata were apparently normal. The right cerebral peduncle, pons and pyramidal tract appeared hypertrophic compared with the left (Fig. 5a, b and c). In the cervical and thoracic cord, the white matter was also hypertrophic on the right compared with that on the left (Fig. 5d). The pyramidal tracts appeared to decussate normally in the medulla oblongata. The lumbar cord was symmetrical. To examine the hemihypertrophy of the right cortico-spinal tract, we measured the horizontal areas of the two tracts, in enlarged photographs using a planimeter. Results were shown in the legend of Fig. 5. Hemihypertrophy of the right cortico-spinal tract was confirmed in the crus cerebri, pons and cervical cord, but not in the medulla oblongata.

Findings in other organs: Multiple cavernous or capillary haemangiomatosis was recognized in the skin, mucosa of the tongue, lower part of the oesphagus and urinary bladder, and organs such as both kidneys, the liver, right adrenal gland and thymus, and in the pleura on both sides. Multiple telangiectasis were found in most lymph nodes, the uterine cervix, left adrenal gland, both ovaries, the spleen and liver. In the liver, cystic dilatation of sinusoids was prominent. A right pleural haemangioma had ruptured and caused haemothorax, which was the direct cause of death. Varicosis was found in the ileocaecal mesenterium and right parametrium. Microscopic examination of the kidneys showed chronic proliferative glomerulonephritis.

2. Quantitative analyses of the brain. (1) The water content of the left cerebral occipital lobe was 82.02% and that of the right was 82.72%, the difference between the two values being

negligible. (2) The ratio of the cortex to the white matter was much higher in both hemispheres than in normal controls (Table 1 a). Thus the relative volume of the cortex was abnormally large. The ratios in the two hemispheres were different for some unknown reason. (3) The cell numbers in various regions of the cerebral cortex (Table 1 b) were not significantly different ($P > 0.05$). (4) The densities of myelinated fibers in the longitudinal tracts of the pons on the two sides (left $127{,}020 \pm 21{,}325$, right $126{,}170 \pm 7{,}286/mm^2$) were not significantly different ($P > 0.05$). (5) The numbers of myelinated fibers in the ventral and dorsal roots of the 8th cervical and first thoracic segments of the spinal cord showed no consistent difference on the two sides (Table 1 c). (6) No difference was found in the intranuclear DNA-contents of nerve cells in the cerebral cortex on the two sides.

Discussion

Eight cases showing hemihypertrophy with hemimegalencephaly have been reported to date (Table 2). Five of them died early in life. It is noteworthy that in all these cases hemihypertrophy and hemimegalencephaly were on the same side. The dermal complications of nevus and haemangiomatosis were recognized only in our case, though one or other was found in some of the other cases. Anomalies besides hemimegalencephaly in the CNS, have been reported and include heterotopia (Gross 1955) and micropolygyria (Bignami et al. 1968), but cases with no associated malformations, as in our case, have also been reported (Hallervorden 1923; Rugel 1946). Cases of hemimegalencephaly without hemihypertrophy were more frequent than those with hemihypertrophy (Laurence 1964; Bignami et al. 1968; Townsend et al. 1975). In most of the former cases, malformations of the CNS such as heterotopia were recognized on the hypertrophied side, and the nuclei and nucleoli of the nerve cells on the hypertrophied side were 4–11 times larger than normal and contained larger amounts of DNA and RNA (Bignami et al. 1968; Manz et al. 1979). The cause of hemihypertrophy

Table 2. Reported cases of hemimegalencephaly with hemihypertrophy

	Sex	Age	Hemi-megal-ence-phaly: Side	Hemi-hypertrophy: Side, Total or partial	Dermal complications	
					Nevus	Haem-angioma
Demme (1891)	f	1 w	Left	Left, total	NS[a]	NS
Steffen (1894)	NS	11 w	Right	Right, partial	NS	NS
Gordinier (1918)	m	65 years	Left	Left, total	+	NS
Hallervorden (1923)	m	56 years	Left	Left, total	+	NS
Rugel (1946)	f	2 years	Right	Right, total	NS	+
Ward and Lerner (1947)	m	8 months	Right	Right, total	+	−
Gross and Uiberrak (1955)	f	9 years	Left	Left, partial	+	NS
Bignami et al. (1964)	m	1 month	Left	Left, partial	+	NS
The present case	f	17 years	Right	Right, total	+	+

[a] NS: Not stated

and hemimegalencephaly is still unknown, though various agents have been suggested as causative factors (Ward and Lerner 1947). Vascular lesions, such as vascular nevus, telangiectasis, varix, aneurysms and arterio-venous shunt were often associated with congenital total hemihypertrophy, and therefore, it is supposed that such vascular lesions caused hemihypertrophy through increase of the blood flow or through blood stagnation. However, since these vascular lesions were multifocal, and were not restricted to the hypertrophied side, they seem to be the result rather than the cause of the condition. There is some controversy about the chromosomal abnormalities in nerve cells and glial cells in this condition (Noé and Berman 1962; Benson et al. 1963; Ringrose et al. 1965). In our case there was no significant difference in the size, form or density of nerve and glial cells, or in the DNA-content of the two cerebral hemispheres. Moreover, the densities of myelinated fibers in the two longitudinal trancts in the pons were similar. Therefore, the macroscopic unilateral hypertrophy of the descending tracts, including the pyramidal tracts, in the pons was due to quantitative hypertrophy. In the spinal cord, the pyramidal tract on the right side was also hypertrophied, but the two posterior funiculi were not asymmetrical. This quantitative asymmetry between the two descending tracts in addition to the morphometric findings suggests that hemimegalencephaly in this case was due to increase in the absolute numbers of nerve and glial cells in the right cerebral hemisphere. Hypertrophy of the pyramidal tract of the spinal cord on the right side may be explained by incomplete decussation in the medulla oblongata.

The abnormalities in this case seemed to be due to unilateral overproduction of neuroblasts and glioblasts or hindrance of normal loss of excess neurons in the prosencephalon or telencephalon and diencephalon. These abnormalities could be induced by hemihypertrophy of the mesenchyme surrounding the CNS, since the mesenchyme and CNS both showed hypertrophy on the same side.

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