Pathogenesis of Chiari malformation: a morphometric study of the posterior cranial fossa

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To investigate overcrowding in the posterior cranial fossa as the pathogenesis of adult-type Chiari malformation, the authors studied the morphology of the brainstem and cerebellum within the posterior cranial fossa (neural structures consisting of the midbrain, pons, cerebellum, and medulla oblongata) as well as the base of the skull while taking into consideration their embryological development. Thirty patients with Chiari malformation and 50 normal control subjects were prospectively studied using neuroimaging. To estimate overcrowding, the authors used a “volume ratio” in which volume of the posterior fossa brain (consisting of the midbrain, pons, cerebellum, and medulla oblongata within the posterior cranial fossa) was placed in a ratio with the volume of the posterior fossa cranium encircled by bony and tentorial structures. Compared to the control group, in the Chiari group there was a significantly larger volume ratio, the two occipital enchondral parts (the exocciput and supraocciput) were significantly smaller, and the tentorium was pronouncedly steeper. There was no significant difference in the posterior fossa brain volume or in the axial lengths of the hindbrain (the brainstem and cerebellum). In six patients with basilar invagination the medulla oblongata was herniated, all three occipital enchondral parts (the basiocciput, exocciput, and supraocciput) were significantly smaller than in the control group, and the volume ratio was significantly larger than that in the Chiari group without basilar invagination.

These results suggest that in adult-type Chiari malformation an underdeveloped occipital bone, possibly due to underdevelopment of the occipital somite originating from the paraxial mesoderm, induces overcrowding in the posterior cranial fossa, which contains the normally developed hindbrain. Basilar invagination is associated with a more severe downward herniation of the hindbrain due to the more severely underdeveloped occipital enchondrium, which further exacerbates overcrowding of the posterior cranial fossa.

KEY WORDS • skull base • basilar invagination • Chiari malformation • occipital bone • posterior cranial fossa • syringomyelia

Chiari malformation is characterized by a downward herniation of the caudal part of the cerebellum and/or medulla oblongata into the spinal canal. This malformation is classified into at least two distinct types according to the degree of herniation: Type I displays herniation of the cerebellar tonsils and Type II exhibits herniation of the fourth ventricle and the medulla oblongata as well as the caudal part of the cerebellum. From a clinical point of view, Chiari malformation can also be divided into adult and pediatric types. The adult-type Chiari malformation falls mostly into Type I and usually presents after the second or third decade of life with symptoms and signs resulting from tightness of the posterior cranial fossa and/or from associated syringomyelia. This type is often accompanied by bone anomalies in the base of the skull such as basilar invagination, but is less frequently associated with brain abnormalities other than herniation of the cerebellar tonsils. The pediatric type mainly belongs to Chiari Type II and is characterized by myeloschisis at birth and brainstem dysfunction in the early periods after birth. Typical features include a small posterior cranial fossa and various neural abnormalities such as brainstem deformities and hydrocephalus.

Chiari malformation is considered to be a primary neurological disease involving the posterior cranial fossa and the hindbrain. Many investigators have tried to explain the pathogenesis of Chiari malformation from the standpoint of primary neural anomaly. However, clinical and experimental studies indicate that the chronic tonsillar herniation observed in Chiari malformation could result from overcrowding within a primary small and shallow posterior cranial fossa due to an underdeveloped occipital bone. Recent morphometric studies focusing on the bony part of the posterior cranial fossa in adult patients with Chiari malformation have lent support to this hypothesis.

In the present study, to estimate properly the overcrowding of the posterior cranial fossa in adult-type Chiari malformation without myelodysplasia, we quantitatively measured the volume of the whole posterior cranial fossa encompassed by both the bony and tentorial parts as well as the volume of the neural structures (the brainstem and cerebellum) within the posterior cranial fossa. The results obtained strongly suggest that overcrowding in the posterior cranial fossa due to an anomaly in the embryological development of the base of the skull is the pathogenesis of Chiari malformation.
**Clinical Material and Methods**

Patients with adult-type Chiari malformation (the Chiari group) who were selected for this prospective study were strictly chosen through surgical exploration of the major cistern in addition to neuroimaging. Of 58 patients with hindbrain herniation (without myelodyplasia) surgically treated at our hospitals, eight with basal meningitis or hydrocephalus were excluded. Another 20 patients who were diagnosed as having adult-type Chiari malformation before the era of magnetic resonance (MR) imaging were also excluded. The remaining 30 patients consecutively diagnosed as having adult-type Chiari malformation between June 1987 and June 1995 at Osaka City University Medical School and Osaka City General Hospital were investigated. Twenty-six of these patients displayed symptomatic syringomyelia and four presented with neurological signs caused by impairment of the cerebellum, medulla oblongata, or both due to a tight posterior cranial fossa. Of these 30 patients, 22 displayed no herniation of the medulla oblongata. The remaining eight showed mild herniation of the medulla oblongata below the foramen magnum in addition to tonsillar herniation; two had a downward herniation of the fourth ventricle with cervicomedullary kinking visible on the MR image, six had basilar invagination, one had assimilation of the atlas, and one had Klippel–Feil syndrome.25 All patients with basilar invagination manifested medullary herniation. As a control group we studied 50 normal individuals without central nervous system involvement between June 1987 and June 1995 at Osaka City University Medical School and Osaka City General Hospital. Table 1 provides a summary of the subjects of each radiological study.

**Quantitative Measurement by X-Ray Tomography**

An attempt was made to measure accurately the three occipital enchondral parts: the supraoccipt, exoccipt, and basioccipt. The axial length of the clivus (the basioccipt and basiphenoid) was measured from the top of the dorsum sellae to the basion (Fig. 1 upper). The length of the supraoccipt was defined as the distance between the internal occipital protuberance and the opisthion measured on midline films (Fig. 1 upper). The length of the exoccipt was measured from the bottom of the occipital condyle to the top of the jugular tubercle at the level of the hypoglossal canal in anteroposterior view films vertical to the orbitomeatal line (Fig.1 center).

Tomograms of the basicranium were obtained (Polytomome U tomographical system; Philips, Eindhoven, Holland), and measurements were recorded for all 30 patients and 50 control subjects.

**Volume Study by Computerized Tomography**

We defined the total volume of the posterior cranial fossa (PFCV: posterior fossa cranial volume) as the space encircled by the tentorium of the cerebellum, clivus, oc- cipital bone, and pyramidal bone. Axial images were obtained using computerized tomography (CT) (Somatom; Siemens, Erlangen, Germany) after intravenous administration of contrast medium.

The images were made with a reference line drawn between the basion and opisthion, corresponding to the horizontal plain of the foramen magnum, on the lateral scout view of the CT scan. The sigmoid sinus was arbitrarily included as part of the posterior cranial fossa but the jugular foramen was not. The petroclinoid ligament was regarded as the external margin and the tentorial hiatus as the most cephalic margin of the posterior cranial fossa. The slice width was 0.3 to 0.8 cm and the window level was set at 250/30 to 1000/30. The area calculated was multiplied by the slice width to obtain the volume. Computerized tomography scanning was used to study the PFCV in the 20 most recent patients and in 30 normal subjects.

**Morphometric and Volume Studies of the Contents Within the Posterior Cranial Fossa by MR Imaging**

The structures of the brain and base of the skull were investigated using MR imaging (Signa 1.5-tesla; General Electric, Milwaukee, WI) (Fig. 1 lower). The T₁-weighted images were obtained using a repetition time of 500 to 600 msec and an echo time of 15 to 40 msec; the T₂-weighted images were obtained using a repetition time of 3000 to 4000 msec and an echo time of 80 to 100 msec. Axial and sagittal images were obtained at 3- to 5-mm intervals.

The clivus was divided into two parts, basiphenoid and basioccipt, with the basiocciptal synchondrosis as the demarcation. Using midline sagittal MR imaging, we measured the length from the synchondrosis to the top of the dorsum sellae as constituting the basiphenoidal part of the clivus, and the length from the synchondrosis to the basion as the basiocciptal portion. To determine the axial length of the brainstem (pons and medulla oblongata), the distance between the ventral point of the midbrain–pons junction and the medullocervical junction was measured on both T₁ and T₂-weighted images.13 The medullocervical junction was defined as the level at which the pyramidal tract changed its route on the T₂-weighted image.13 The long axial length of the cerebellar hemisphere was measured on T₂-weighted sagittal images from the highest to the lowest point of the cerebellar hemisphere along a straight line drawn caudally and parallel to the bottom of the fourth ventricle. To estimate the steepness of the cere-
bellar tentorium, the angle of the cerebellar tentorium to Twining’s line was measured on sagittal images.

The volume of the brainstem and cerebellum within the posterior cranial fossa (PFBV; posterior fossa brain volume) was measured using MR imaging. The PFBV was defined as the volume of the neural structures contained within the posterior cranial fossa as measured on CT scans, including the parts of the brain that herniate into the spinal canal. The total PFBV thus consisted of the midbrain, pons, cerebellum, and medulla oblongata. This PFBV was measured on T1-weighted axial images, and the volume ratio of the PFBV to the PFCV was then calculated on the basis of results of CT and MR imaging by a volume study to estimate overcrowding of the posterior cranial fossa.

**Statistical Analysis**

The values of all parameters measured for the Chiari group and the control group were comparatively assessed using the Mann–Whitney test. The volume data, volume ratio, and angle of the tentorium were compared using the linear regression test.

**Results**

**Quantitative Measurement by X-Ray Tomography**

Although the mean length of the clivus in the Chiari group was not significantly shorter than that in the control group (49.7 mm in the Chiari group and 50.1 mm in the control group), it was significantly ($p < 0.01$) shorter (39.8 mm) in the six patients with basilar invagination of the eight patients displaying downward herniation of the medulla oblongata (Fig. 2 left).

A significant difference ($p < 0.001$) was found in the mean length of the exocciput from the bottom of the occipital condyle to the top of the jugular tubercle, which measured 16 mm (16 mm on the right side and 16.1 mm on the left side) in the Chiari group and 20.5 mm (20.9 mm on the right side and 20.2 mm on the left side) in the control group. It was significantly ($p < 0.001$) shorter irrespective of the side. It was also significantly ($p < 0.001$) shorter in patients with basilar invagination (16.8 mm on the right side and 16.7 mm on the left side) (Fig. 2 center).

A significant difference ($p < 0.001$) was also found in the mean length of the supraocciput between the internal occipital protuberance and the opisthion, which measured 38.9 mm in the Chiari group and 48.1 mm in the control group. It was also significantly ($p < 0.001$) shorter in patients with basilar invagination (38.9 mm) (Fig. 2 right).

**Volume Study by CT and MR Imaging**

There was no significant difference between the Chiari group and the control group in the mean PFCV as measured in the midbrain–pons Fig. 1 (continued) junction and the medulloccervical junction; $e =$ length of the hindbrain (cerebellar hemisphere); $f =$ angle of the cerebellar tentorium to Twining’s line. B = basion; D = top of the dorsum sellae; I.P. = internal occipital protuberance; op. = opisthion; S = sphenoccipital synchondrosis of the clivus; T = Twining’s line.
measured by CT scanning, which was 186 cm$^3$ in the Chiari group (188 cm$^3$ in patients without vs. 184 cm$^3$ in those with basilar invagination) and 193 cm$^3$ in the control group (Fig. 3 left). No significant difference was found in the PFBV, which was 156 cm$^3$ in the Chiari group (156 cm$^3$ in patients without vs. 157 cm$^3$ in those with basilar invagination) and 153 cm$^3$ in the control group (Fig. 3 center). Because the exact location of Twining’s line as the border of the bony and tentorial portions of this posterior cranial fossa could not be accurately observed on the

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**Fig. 2.** Graphs showing the lengths of the clivus, exocciput, and supraocciput. Left: The clivus. Patients with adult-type Chiari malformation displayed no significant difference in the length of the clivus compared to the control group, but the clivus of patients with basilar invagination was significantly (p < 0.01) shorter than that in the control group. Patients with medullary herniation also had a significantly (p < 0.01) shorter clivus than the control group. Asterisks = patients with downward herniation of the medulla oblongata below the foramen magnum in addition to tonsillar herniation. Center: The exocciput (the length between the occipital condyle and the jugular tubercle). The length in the Chiari group was significantly (p < 0.001) shorter than that in the control group, irrespective of basilar invagination or the side. Right: The supraocciput (the length between the internal occipital protuberance and the opisthion). The length in the Chiari group was significantly (p < 0.001) shorter than in the control group, irrespective of basilar invagination. Open circles = Chiari malformation with basilar invagination; closed circles = all cases of Chiari malformation.

**Fig. 3.** Graphs. Left: Posterior fossa cranial volume (PFCV) as measured by computerized tomography. Volume of the whole posterior cranial fossa. There was no significant difference in volume between the Chiari group and the control group. Center: The PFBV, consisting of the midbrain, pons, cerebellum, and medulla oblongata. No significant difference was found between the Chiari group and the control group with regard to the PFBV. Right: “Volume ratio” (the ratio of PFBV to PFCV). The volume ratio in the Chiari group without basilar invagination was significantly (p < 0.01) larger than that in the control group, and was significantly (p < 0.001) larger in the group with basilar invagination than in the Chiari group without invagination. Open circles = Chiari malformation with basilar invagination; closed circles = all cases of Chiari malformation.
axial MR images, the PFBV encompassed by each of the bony and tentorial parts could not be separately calculated. The overall results showed no significant difference in either the PFBV or PFCV between the Chiari and control groups.

Overcrowding of the Posterior Cranial Fossa

A significant difference (p < 0.001) was found, however, in the volume ratio of the PFBV to the PFCV (Fig. 3 right). The mean volume ratio was 0.833 in the Chiari group (0.813 in patients without vs. 0.863 in those with basilar invagination) and 0.790 in the control group. The volume ratio in the Chiari group without basilar invagination was significantly (p < 0.01) larger than in the control group, and the volume ratio in the group with basilar invagination was even significantly (p < 0.01) larger than the ratio in the Chiari group without invagination.

Morphometric Study Using MR Imaging

Compared to the control group, regardless of basilar invagination there was a significant difference (p < 0.001) in the mean angle of the cerebellar tentorium against Twining’s line, which was 44.6° in the Chiari group (44° in patients without vs. 44.9° in those with basilar invagination) and 36.2° in the control group. This indicated that the cerebellar tentorium was significantly steeper in the Chiari group than in the control group.

The relationship between the volume ratio and the steepness of the tentorium was significant (y = 121x – 58.3, p < 0.01) in all the individuals studied (Fig. 5). No significant relationship was found, however, between the volume of the herniated brain below the foramen magnum (range 1.2–3.8 cm³, mean 2.2 cm³, standard deviation 0.8 cm³) and the PFCV or between the volume of the herniated brain below the foramen magnum and the volume ratio.

The sphenooccipital synchondrosis was clearly visible in 14 of 20 patients with adult-type Chiari malformation and in 25 of 44 normal control subjects who underwent MR imaging, although it was not demonstrated by x-ray tomography (Table 1). Of the individuals with a clearly visualized sphenoooccipital synchondrosis, the top of the dorsum sellae, which was defined as the top of the clivus, was clearly demonstrated in the MR images of 10 patients in the Chiari group and 10 in the control group. Although there was no significant difference in the length of the basipsphenoidal or basioccipital part of the clivus between the Chiari and control groups, patients with basilar invagination had a significantly (p < 0.01) shorter basiocciput than the control group. The mean length of the basipsphenoidal part in the Chiari group was 18.5 mm versus 20.6 mm in the control group; the mean length of the basioccipital portion in the Chiari group was 24.4 mm versus 28.1 mm in the control group and was even shorter in patients with basilar invagination at 20.8 mm (Fig. 6).

Comparing the Chiari group to the control group, no significant difference was found in the length of the brainstem from the midbrain–pons junction to the medullocervical junction (50.2 mm in the Chiari group and 49 mm in the control group) or in the long axial length of the cerebellar hemisphere (49.1 mm in the Chiari group and 47.7 mm in the control group) (Fig. 7), and no significant difference in these lengths was found between the patients with and without basilar invagination. In the 20 patients with adult-type Chiari malformation studied by MR imaging, eight displayed downward herniation of the medulla oblongata below the foramen magnum. Of these eight patients, six had accompanying basilar invagination and the remaining two displayed a very short clivus (46 mm and 47.3 mm) (Fig. 2 left).

Discussion

Overcrowding of the Posterior Cranial Fossa

To estimate overcrowding in the posterior cranial fossa...
Pathogenesis of Chiari malformation

Patients with adult-type Chiari malformation were strictly selected through surgical exploration of the major cistern in addition to neuroimaging because various pathological conditions, such as hydrocephalus, arachnoiditis at the major cistern, spinal shunt for hydrocephalus, and others, which could induce secondary tonsillar herniation, might have misled the results of the morphometric study.20

Associated Occipital Hypoplasia

The present study showed that patients with adult-type Chiari malformation had various degrees of occipital hypoplasia and structured abnormalities of the tentorium, but displayed no significant abnormalities of the neural structures (that is, the hindbrain) in the posterior cranial fossa. In the Chiari group (with and without basilar invagination), two embryogenic parts of the occipital bone (the exocciput and supraocciput) were significantly shorter than in the control group (Fig. 2 center and right), although no significant difference was revealed in the long axial lengths of the hindbrain (the pons, medulla oblongata, and cerebellum) (Fig. 7). The present study also showed that the cerebellar tentorium in the Chiari group was significantly steeper than in the control group, even though no significant difference in the total PFCV was found (Fig. 4).

When the more prominent structural abnormalities in the occipital enchondrium are considered in conjunction with the less significant structural abnormalities in the hindbrain in the posterior cranial fossa, the overcrowding observed in adult-type Chiari malformation can be regarded as the primary cause of downward herniation of the normally developing caudal hindbrain.8 Overcrowding in the posterior cranial fossa may induce a consistent upward shifting of its contents, leading to a significantly steeper tentorium as well as a downward shifting of the hindbrain. The volume of the herniated brain below the foramen magnum displayed no relationship to the volume of the posterior cranial fossa and the volume ratio of the PFBV to the PFCV. The volume of the herniated brain below the foramen magnum was quite small (< 2%) compared to the volume of the tentorial parts of the posterior cranial fossa, and thus was only minimally related to overcrowding. The volume ratio and the angle of the tentorium showed a significant correlation (Fig. 5), indicating that the volume of the tentorial parts of the posterior cranial fossa may relieve overcrowding of the posterior cranial fossa. The upward shifting of the cerebellar tentorium may explain why the PFCV was not significantly smaller in the Chiari group. It can be inferred that overcrowding of the posterior cranial fossa induces remodeling of neural structures as the cerebellar tentorium shifts upward and the cerebellar tonsils herniate to accommodate the growing brain, rather than remodeling the cranium.

When we looked into the incidence of basilar invagination and downward herniation of the medulla oblongata in patients with adult-type Chiari malformation, we found that eight patients with medullary herniation in addition to tonsillar herniation, six had basilar invagination and the remaining two had a very short clivus (Fig. 2 left). Of the six patients with basilar invagination, four in whom the sphenooccipital synchondrosis was identified on MR

of patients with adult-type Chiari malformation, we used the volume ratio of the PFBV to the PFCV. This ratio in the Chiari group, associated basilar invagination notwithstanding, turned out to be significantly larger than in the control group (Fig. 3 right). This result was obtained even though there was no significant difference in the PFCVs, encompassed by both the bony and tentorial structures (Fig. 3 left) or in the PFBVs, consisting of the midbrain, pons, cerebellum, and medulla oblongata (Fig. 3 center). In a previous report we looked at the distance from the basilar artery to the posterior aspect of the clivus at the midportion of the clivus on vertebral angiograms in adult-type Chiari malformation; we found significant encroachment of the basilar artery with respect to the clivus as an indirect sign of overcrowding in the posterior cranial fossa.20 The present study clearly showed overcrowding of the posterior cranial fossa in adult-type Chiari malformation by direct measurement of the volume of the posterior cranial fossa and the volume of the neural structures contained within it.

Three recent morphometric studies have suggested a significantly smaller volume in the lower half, or bony portions, of the posterior cranial fossa in adult patients with Chiari malformation.23,25,28 However, the authors failed to consider the upper half, or tentorial part, of the posterior fossa and ignored the size of the neural structures contained in the posterior cranial fossa.23,25,28 To estimate overcrowding properly, we decided that it was necessary to use the volume ratio of the PFBV to the PFCV (Fig. 3).

Patients with adult-type Chiari malformation were all cases of Chiari malformation. Circles = Chiari malformation with basilar invagination; closed circles = all cases of Chiari malformation.
imaging had a significantly short basiocciput (Fig. 6). On the other hand, the eight patients with medullary herniation showed no significant difference in their hindbrain structures from the normal control subjects. Looking at the upper part of the clivus composed of the sphenoidal bone, no significant difference was found among the patient group, the patient group with basilar invagination, and the control group. Thus, the downward herniation of the medulla oblongata observed in adult-type Chiari malformation with basilar invagination can be explained by shortening of the basiocciput rather than by a primary neural abnormality associated with Chiari malformation, in addition to overcrowding in the posterior cranial fossa due to occipital hypoplasia.24

Embryological Aspects of the Base of the Skull in Adult-Type Chiari Malformation

The present study took into consideration the embryological development of the human occipital enchondrium, and each part of the base of the skull in patients with adult-type Chiari malformation was compared to that of normal controls using available neuroradiological techniques. Although the results obtained were for only a limited number of individuals in the patient and control groups, it was found that two parts of the occipital enchondrium (the exocciput and supraocciput) were underdeveloped in patients with adult-type Chiari malformation, and that all three parts of the occipital enchondrium (the exocciput, supraocciput, and basiocciput) were underdeveloped in patients with basilar invagination (Figs. 2 and 6). No significant difference was found in the length of the basisphenoid of the sphenoidal bone between the Chiari group and the control group. O’Rahilly and colleagues20 have proved that the basioccipital and exoccipital portions of the occipital bone up to the top of the jugular tubercle are derived from the occipital somites in the human fetus. The results of the present morphometric study strongly imply normal development of the hindbrain and underdevelopment of the occipital somites in patients with adult-type Chiari malformation.

Marin-Padilla and Marin-Padilla16,17 suggested a hypothesis of cephalic axial skeletal neural dysraphic disorder to explain the brain abnormalities associated with pediatric-type Chiari malformation and postulated that paraxial mesodermal insufficiency contributed to a cephalic axial skeletal neural dysraphic disorders as anencephaly, a dysraphic anomaly, or even Chiari malformation. According to this hypothesis, paraxial mesodermal insufficiency or primary lesion of the somitic structures may induce various neural abnormalities in pediatric-type Chiari malformation. Thus, when paraxial mesodermal insufficiency is regarded as the pathogenesis of Chiari malformation, adult-type Chiari malformation can be considered a mild form and the pediatric type a severe form.

Surgical Treatment of Syringomyelia Associated With Adult-Type Chiari Malformation

The syringomyelia quite often associated with adult-type Chiari malformation is now treatable by different types of surgical intervention, such as drainage of cere-
brospinal fluid (CSF) or decompression of the foramen magnum with or without plugging the central canal. Recent flow studies of CSF by MR imaging have shown that blockage of CSF flow at the foramen magnum between the intracranial and intraspinal subarachnoid space is the most important factor exacerbating syringomyelia associated with adult-type Chiari malformation. Overcrowding in the posterior cranial fossa, in addition to downward herniation of the caudal portion of the hindbrain, can induce such a CSF blockage at the foramen magnum. We believe that the most suitable treatment for syringomyelia associated with adult-type Chiari malformation is not to drain the fluid in the syrinx, but to improve CSF flow around the foramen magnum by expansion of the abnormally small space surrounded by the underdeveloped occipital bone.11,12,27

Conclusions

Our results lead us to the conclusion that adult-type Chiari malformation is most likely produced primarily by underdevelopment of the occipital encephondrium, possibly due to underdevelopment of the occipital somite originating from the paraxial mesoderm. Overcrowding in the posterior cranial fossa due to a normal-sized hindbrain in the underdeveloped occipital encephondrium secondarily induces a downward herniation of the brain as well as an upward shift of the cerebellar tentorium. Associated basilar invagination due to a more severely underdeveloped occipital encephondrium further exacerbates overcrowding of the posterior cranial fossa.

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