Clinical Article

Stereological and Morphometric Analysis of MRI Chiari Malformation Type-1

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Objective : In this study, we aimed to investigate the underlying ethiological factors in chiari malformation (CM) type-I (CMI) via performing volumetric and morphometric length-angle measurements.

Methods : A total of 66 individuals [33 patients (20–65 years) with CMI and 33 control subjects] were included in this study. In sagittal MR images, tonsillar herniation length and concurrent anomalies were evaluated. Supratentorial, infratentorial, and total intracranial volumes were measured using Cavalieri method. Various cranial distances and angles were used to evaluate the platybasia and posterior cranial fossa (PCF) development.

Results : Tonsillar herniation length was measured 9.09±3.39 mm below foramen magnum in CM group. Tonsillar herniation/concurrent syringomyelia, concavity/defect of clivus, herniation of bulbus and fourth ventricle, basilar invagination and craniovertebral junction abnormality rates were 30.3, 27, 18, 2, 3, and 3 percent, respectively. Absence of cisterna magna was encountered in 87.9% of the patients. Total, IT and ST volumes and distance between Chamberlain line and tip of dens axis, Klaus index, clivus length, distance between internal occipital protuberance and opisthion were significantly decreased in patient group. Also in patient group, it was found that Welcher basal angle/Boogard angle increased and tentorial slope angle decreased.

Conclusion : Mean cranial volume and length-angle measurement values significantly decreased and there was a congenital abnormality association in nearly 81.5 percent of the CM cases. As a result, it was concluded that CM ethiology can be attributed to multifactorial causes. Moreover, congenital defects can also give rise to this condition.

Key Words : Cavalieri method · Morphometry · Chiari malformation · MRI.

INTRODUCTION

Chiari malformation (CM) is originated from embryonic development abnormality of the hindbrain region and characterized by the pathological caudal displacement of the cerebellar tonsils below the foramen magnum. It is generally congenital but, rarely it can be of acquired origin. It has been estimated that the CM incidence is about 1 in every 1000 births. CM is generally related to occipital bone dysplasia and it is frequently associated with various conditions such as platybasia, basillar invagination and clivus concavity in addition to decrement in posterior cranial fossa (PCF) size[17,43]. In current clinical practice, CM cases are more commonly diagnosed with the recent improvements achieved in magnetic resonance imaging (MRI) field[12,17,28]. Most of the patients (60−80%) have occipital headache or upper cervical pain[26]. Some may have symptoms consistent with brainstem or cranial nerve dysfunction[41].

Although numerous hypotheses have been postulated for CM type-I (CMI) etiopathogenesis so far, underlying mechanism is still unclear. Beside this, developmental disorder of the PCF in early embryogenetic phase or a possible developmental abnormality of the paraxial mesoderm, which in turn may lead to a scratch and compression in hindbrain region, are possible factors implied in pathogenesis of CM[7,24,31,44]. Compaction abnormal-

ity of the PFC along with clinical manifestations is a frequent finding in type-I CM cases[1,2,18,26,31,32,43,44]. Whereas in type-II CM[6] in which normal PCF structure and accompanying cerebellar tonsillar herniation are present, tethered cord syndrome is associated with increased intracranial pressure and intraspinal hypotension[28]. In CM, it is considered that abnormal growth of PCF bones leads to herniation in neuronal tissue[18,21,22,26,31,46-48]. The flow dynamics of cerebrospinal fluid (CFS) can be deteriorated in CMI[25,27] and syringomyelia can occur mainly in cervical region in approximately 20−72 percent of the cases related to CSF disorder. Craniovertebral junction abnormalities such as basilar invagination, platybasia, small posterior fossa, concavity of the clivus, occipitalization of the atlas and spina bifida in upper cervical region can be encountered at nearly 20−30 percent rate[3,9,11,13-17,19,20,23,30,33,37,42].

The volume and volume fraction approach of stereological methods provides information about volumetric relations of the components of structures on the basis of Cavalieri's principle[38]. The Cavalieri method which is also called as the method of indivisibles, was developed by Bonaventura Cavalieri to calculate volumes[34]. In this method, volume estimation of an object can be calculated via using parallelized slices of consequent MRI or CT images taken through the related object[36,39].

We have evaluated the volume relation of cerebellum, brain stem, cerebrum and total brain volume (TBV) using the volume and volume fraction approach of modern stereological methods. The main aim was to reveal whether volumetric differences or congenital abnormalities play more important role in ethiology of CM via making a comparison between the current findings and retrospective control group. Beside this, cranial distance and angle measurements were performed to evaluate the diameter of foramen magnum, PCF volume and platybasia condition. We assumed that component size of intracranial neural structures should have proportional relations among them.

MATERIALS AND METHODS

A total of 66 individuals (33 patients with CMI and 33 healthy controls) were included in this study. Before the initiation of the evaluation, necessary study approval was taken from the Local Ethical Committee of Afyon Kocatepe University Faculty of Medicine. MRI images were retrospectively obtained from Neurosurgery, Neurology, Radiology Departments of Afyon Kocatepe University and Afyonkarahisar State Hospital. Images were established from the individuals via using a 1.5-T MRI unit (30 mT/m) (Intera, Philips Medical Systems, Best, The Netherlands) with standard head coil. Sagittal images with 4 mm of slice thickness were obtained according to the standard cranial MRI protocol. In CMI group, symptomatic or asymptomatic participants have had no intracranial space occupying lesion. The control group consisted of healthy individuals who meet the following criteria : having no intracranial bulk mass, having no congenital or systemic disease.
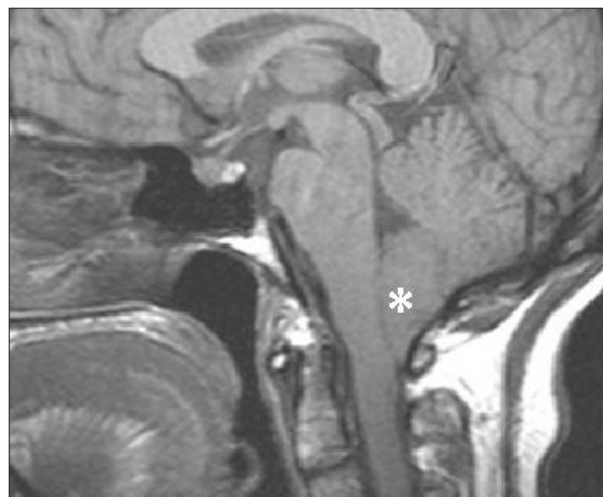
Fig. 1. A MR imaging of Chiari malformation type-I. *Tonsillar herniation.

Complete physical examination and neurological evaluation were applied to whole participants. In CMI group, 27 patients (82%) were symptomatic and 6 were not (18%). The most frequent symptoms were suboccipital headache, tinnitus, sleep apnea and extremity pain. In neurological examination, various findings including limb dysesthesia, ataxia, nystagmus and reflexive weakness were observed.

MRI method is the best diagnostic tool for detecting Chiari malformation. MRI provides detailed anatomical information regarding the structures located at the cranial basement. Patients who have intracranial space occupying lesions including bulbar and 4th ventricular herniations were excluded from the study.

Tonsillar herniation and associated abnormalities : In sagittal MR images given in Fig. 1, tonsillar herniation length and concurrent abnormal conditions were evaluated. The mean length of tonsillar herniation extending inferiorly through foramen magnum was measured in millimeters in patients with CMI. Moreover, the extent of herniation was graded as follows : between 5 and 9 mm (slight), between 10 and 14 mm (moderate) and above 14 mm (severe)[16,48].

The accompanying abnormalities including syringomyelia in upper cervical region, clivus concavity/defect, herniation in fourth ventricle and bulbus, basilar invagination and other craniovertebral junction anomalies were evaluated.

Supratentorial (ST), infratentorial (IT), and total intracranial volumes were measured via using the Cavalieri method, which is being utilized with gradually increasing popularity in clinical studies especially in last years. This method allows construction of 3D structure models from 2D CT and MRI images taken in a parallel multislice imaging manner. Structural volumetrics can also be calculated in an impartial and effective way by using Cavalieri method[34,36].

Cranial distance parameters such as McRae line[4,18], Chamberlain line and dens axis distance[18], Klaus index (KI and clivus length)[18], Twining line and angles, Platibasia angles : Welcher basal angle, Wackenheim clivus angle, Basal angle, Boogard an-
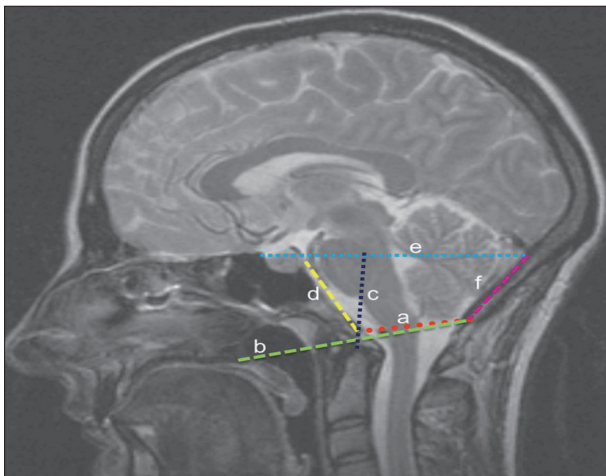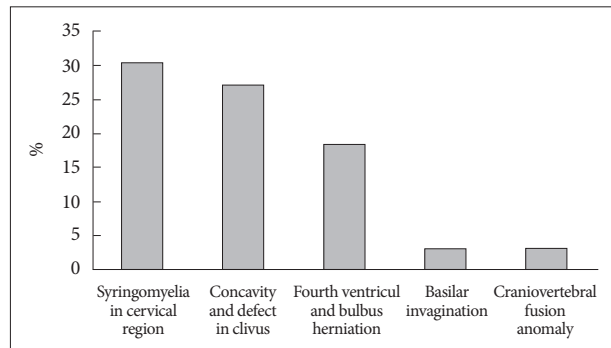
Fig. 2. A MR imaging of McRae line (a), Chamberlain line (b), Klaus index (c), clivus length (d), Twining line (e), and length of supraocciput line (f).
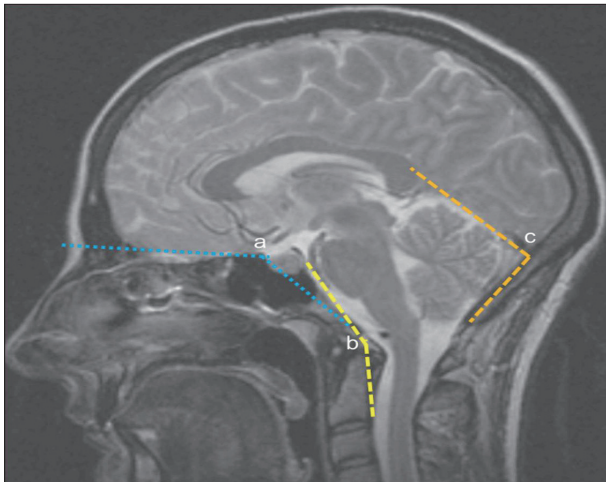
Fig. 3. A MR imaging of Welcher basal angle (a), Wackenheim klivus angle (b) and Slope of Tentorium Cerebelli (c).
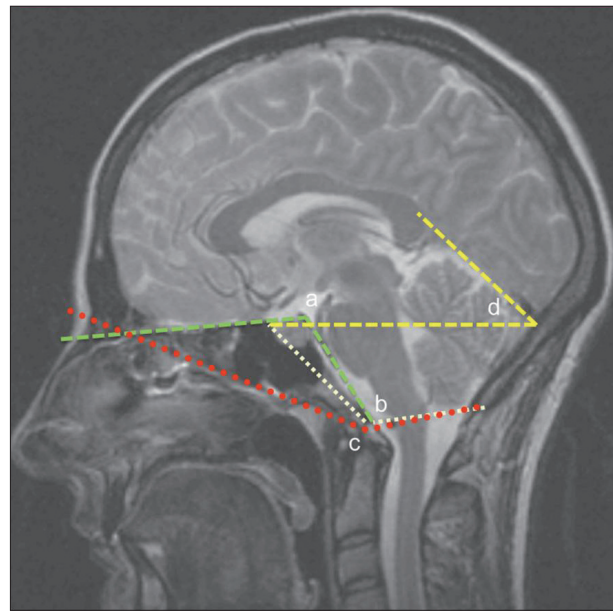
Fig. 4. A MR imaging of Basal angle (a), Boogard angle (b), Nasion-basion-opisthion (N-B-O) angle (c), and Tentorium Cerebelli-Twining Line angle (d).

Fig. 5. The midsagittal MRI for the cranial fossa and cerebellum with a grid overlaid for the calculation of volumes using the Cavalieri method.

gle, Nasion-basion-opisthion (N-B-O) angle and Tentorial angles : Tentorium Cerebelli-Twining Line angle[18], Slope of Tentorium Cerebelli were used in platybasia evaluation and PCF development were measured (Fig. 2, 3, 4). Results obtained from control and CMI groups were statistically analyzed. Comparisons and relations were assessed between groups.

Stereological estimation of the SI, IT, and total intracranial volumes : ST, IT, and total intracranial volume measurements were performed via using cranial MRI images of each patient on the picture archiving and communication system (PACS) (Enlil, Eskisehir, Turkey). In Cavalieri method, a square grid system with d=0.5 cm were placed randomly on each cross section ST, IT, and total intracranial MR images. Points hitting the surface area of ST, IT, and total intracranial structures were counted for each section (Fig. 5). Counting procedure was repeated three times for each cross-sectional image and average values were recorded. Points corresponding to the boundaries of ST, IT, and total intracranial structures areas were included in count-

ing. Other points placed outside of the boundaries were not included to the counting process even if they were very close. The coefficient of error (CE) is an extensively used standard statistical value in stereological literature, which is defined as the SD divided by the mean. Point counts and other data were entered for each ST, IT, and total intracranial volume and the following formula was used :

$$V = t \times \{[SU) \times d]/SL\}2 \times \Sigma P$$

where t is the sectioning interval for number of consecutive sections, "SU" is the scale unit of the printed film, d is the distance between the test points of the grid, "SL" is the length of the scale on the MRI images and "ΣP" is the total number of points hitting the section cut surface areas of ST, IT, and total intracranial structures[5,29].

Statistical analysis

Data were given as mean±SD. Statistical analysis was per-

formed by using independent samples Student t-test, Kolmogorov-Smirnovt, Mann-Whitney U-test, Pearson correlation and chi-square tests (SPSS software version 16.0, SPSS Inc., Chicago, IL, USA).

RESULTS

In control group, there were 8 males and 25 females and the mean age was 39.88±11.30 years (range, 20–56 years). Also in CM group, there were 8 males and 25 females with 41.91±10.86 years of mean age (range, 20–65 years). There was no difference between two groups in terms of age and gender (p>0.05).

Distance and angle measurements : Distance measurements used for evaluation of platybasia including the distance between Chamberlain line and tip of dens axis, Klaus index, clivus length, distance between internal occipital protuberance and opisthion were significantly decreased in the patient group. Welcher basal angle and Boogard angle were found to be increased, tentorial slope was found to be decreased. TC-TH angle from Tentorial angles, bevel of TC, another tentorial angle, the distance between the Chamberlain line and dens axis apex were shown in Table 1, 2.

Intracranial volume measurements : In control and CMI groups; Total, IT, and ST intracranial volumes values were shown in Table 3. These parameters prominently decreased in CMI group.

Tonsillar herniation and concurrent congenital anomalies : The mean length of tonsiller herniation was 9.09±3.39 mm (5–18 mm range) in CM group. The herniation grading status was slight in 22 (66.7%, 5–9 mm), moderate in eight (24.2%, 10–14 mm) and heavy in three (9.1%, greater than 14 mm) patients. Tonsillar herniation and concurrent syringomyelia, concavity and defect of clivus, herniation of bulbus and fourth ventricle, basilar invagination and craniovertebral junction anomaly rates were found to be 30.3%, 27%, 18.2%, 3%, and 3%, respectively (Fig. 6). Absence of cisterna magna was encountered in 87.9% of CMI cases. According to decades, tonsillar herniation degrees were shown in Table 4. Demonstrative examples were shown in Fig. 1. There was no meaningful correlation between the herniation grade-age and herniation grade-syringomyelia.

DISCUSSION

CMI is caused by paraxial mesodermal defect of the embryon-

Table 1. The result of angle measurements of control and cases with CMI

Angles	Control	CMI	p
Welcher basal angle	130.8±4.116	133.4±566.8	0.034
Wackenheim kilvus angle	164.2±6.591	160.8±7.535	>0.05
Basal angle	114.5±5.130	116.5±4.698	>0.05
Boogard angle	136.9±4.961	141.2±9.351	0.025
Nasion-basion-opisthion angle	165.5±5.568	167.5±5.896	>0.05
TC-TH angle	137.6±5.562	139.1±5.241	>0.05
TC bebel	94.73±6.166	90.39±5.244	0.031

CMI : chiari malformation type-I

Table 2. The result of distance measurements of control and cases with CMI

Distances (mm)	Control	CMI	p
McRae line	36.21±2.607	36.82±1.911	>0.05
The distance between chamberlain and dens axis	5.151±2.279	3.030±4.538	>0.05
Klaus index	40.58±3.326	38.00±4.287	0.026
Klivus length	39.82±2.952	37.48±3.134	0.001
POI-opsthion length	39.67±2.901	36.67±3.739	0.001

CMI : chiari malformation type-I

Table 3. The distribution of total, infratentorial and supratentorial intracranial volume of cases with CMI

	Control	CMI	p
IT volume (mL)	184.3±22.91	167.4±23.79	0.009
ST volume (mL)	1176±90.01	1104±125.8	0.007
Total volume (mL)	1358±101.9	1272±145.6	0.015

CMI : chiari malformation type-I

Table 4. The result of herniation degree according to decades

	3rd decade	4th decade	5th decade	6th decade	7th decade
Herniation degree (mm)	8.6	8.5	8.1	11.7	9
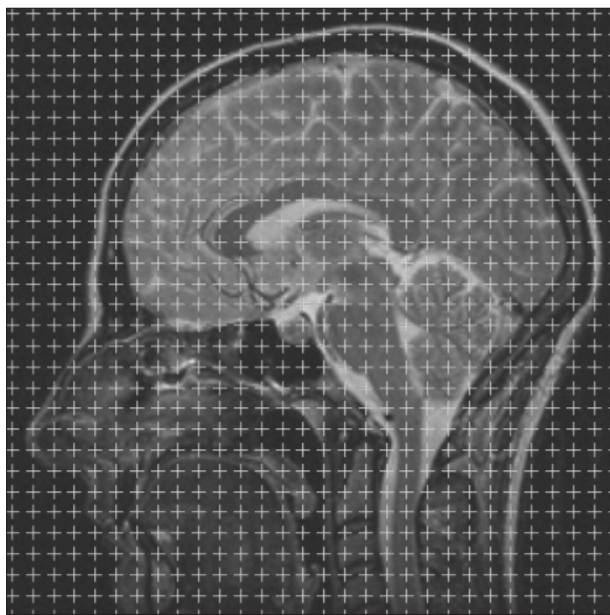
Fig. 6. The distribution of abnormalities associated with cerebellar tonsil herniation in cases with CMI.

ic cranial region or premature stenosis of the sphenooccipital synchondrosis[8]. CMI generally presents as a sporadic disease with mild female dominance or equal rate of male and female. The mean age range of the cases who have admitted to clinics is between 25 and 40 years[13,17,35,37]. In our study, the mean age of patients with CMI was 41.91±10.86 years and the female/male ratio was 3.12. The mean age of cases was partly similar to literature findings but the ratio of female vs. male was higher.

CMI is characterized by herniation of cerebellar tonsils through the foramen magnum into the spinal canal as 5 mm or more[10,28,46]. This parameter is generally used for clinical diagnosis. In the present study, the herniation was found as 9.09±3.29 mm in the patients. The herniation degrees were mild in 66.7%, middle in 24.2%, and strike in 9.1% of cases. A tonsillar herniation up to 3 mm is accepted as within the physiological limits in most of the articles[40]. Karagoz[17] found the tonsillar herniation amount as 11.7±7.8 mm in her study, too. Our findings showed similarity with the results in literature.

The circulation of CSF may disrupt in CMI[13,25]. Therefore, syringomyelia especially in cervical region is shown in 20−72% of cases. In addition, craniovertebral junction abnormalities (basilar invagination, platybasia, small posterior fossa, concavity in clivus, occipitalization of atlas, spina bifida in upper cervical region) are shown in 20−30% of cases[9,11,15,19]. Karagoz[17] has reported the syringomyelia and craniovertebral abnormalities as 69.5% and 50%, respectively. In our study, we have found that there were also some conditions associated with CMI including syringomyelia in upper cervical region (30.3%), clivus defect and concavity (27%), herniation in fourth ventricle and bulbus (18.2%), basilar invagination (3%) and craniovertebral junction abnormalities (3%). The cause of lower syringomyelia percentage in our study than the literature can result from imaging

only medulla and upper spinal cord and not evaluating lower spinal cord in MRI. The clival concavity and defect have been included in craniovertebral fusion abnormalities class in the literature. However, we have evaluated this defect as a diverse entity. If this parameter were included, craniovertebral junction abnormalities would have been compatible with the literature at approximately 30% rate.

It has been a relationship would occur between syringomyelia and herniation degree in CMI[11,19]. Stovner et al.[45] have investigated the tonsillar herniation and found that syringomyelia degree was lower in patients with mild herniation under 5−9 mm and advanced herniation upper 14 mm; whereas they found it was higher in middle degree herniation between 10−14 mm[11]. In our study, tonsillar herniation rates were 50%, 40%, and 10% in 5−9 mm, 10−14 mm, and over 14 mm, respectively and there was no significant difference between herniation amount and syringomyelia in terms of this parameter. Our results were in contradiction with previous results. We think that the degree of tonsillar herniation does not necessarily reflect the degree of illness. Therefore, it would be more favorable to take into consideration the clinical condition of the patients and associated neuro-radiological findings, rather than the presence and degree of tonsillar herniation in decision-making of a surgical intervention. This approach is also in accordance with the literature[4].

The absence of "cisterna magna" may be a more important finding than tonsillar herniation degree for diagnosis of CMI. Karagoz[18] has stated that none of their cases with CMI had cisterna magna, however they have found that cisterna magna was not present in only one case in the control group. Karagoz[17] have also mentioned that the absence of cisterna magna may be the most important permanent finding in CMI. Milhorat et al.[26] have declared that the absence of cisterna magna is a very important factor in morphometric measurement in addition to tonsillar herniation. We have found that the cisterna magna was absent in 29 cases (87.9%), too. Our results are compatible with the literature[1,2,18,26,31,32,43,44]. Small PCF is a frequent finding in CMI[1,2,18,26,31,32,43,44]. Morphometric analysis of PCF is important for the neuroradiological evaluation of CMs. Abnormally small PCF is frequently observed along with the supporting clinical evidence in classic CMI cases. It is supposed that there is a herniation in neuronal tissue as a result of abnormal growth of the bones surrounding PCF in CM[18,21,22,26,31,46,47]. Nishikawa et al.[31] have reported that there was a growth retardation in supra- and exo-occiput along with basiocciput in CMI. Whereas, Milhorat et al.[25] have founded that there were short basi- and supra-occiput in CMI. Trigylidas et al.[47] found smaller posterior fossa volume (PFV) in pediatric CMI patients and suggest that posterior fossa volumetric measurements might be used as a predictor of symptom development in CMI. In addition to smallness of PCF in literature, the decreasing of ST and total intracranial volume was thought that developmental failure will affect not only PCF but also the entire cranium. Badie et al.[2] says that CMI patients with a smaller PFV become symptomatic sooner in life. We performed mea-

surement of ST and IT volumes. We thought that our findings were related to volume measurement of Milhorat et al.[28] and area measurement of Karagoz's study[17].

The McRae line (FM), gives a clue about area and wideness of FM, was found as 36.21±2.6 mm and 36.82±1.91 mm for control and CMI groups respectively in our study. Statistical difference was not observed for comparison of length. Milhorat et al.[28] measured McRae line within the normal limits but they found the transverse diameter and area to be smaller than the control. Karagoz[17] did not observe a difference between McRae line in CMI and control groups. The area of foramen magnum is concordant with a given intracranial volume (ICV) in pediatric CMI patients and both the ICV and FM area do not differ significantly from the normal pediatric population[9]. Besides Noudel et al.[32] implicates that later growth impairment occur in the basichondrocranium in CMI. Our findings were compatible with the previous studies. However the McRae line doesn't always give correct knowledge about narrowness of FM as shown in the study of Milhorat et al.[28]. Therefore we thought that the measurement of FM area or sagittal and transvers axis length will give more certain results. The distance between the Chamberlain line and dens axis apex were measured. While there was a difference between two groups, it did not reach to the statistical significance level. Additionally dens axis apex was under Chamberlain line in control group. However dens axis apex was on Chamberlain line 6 of the patients (18%) in CMI group.

We thought that the high SD (heterogenic distribution) in the CMI group is the possible cause for the comparison to be insignificant. The distance of clivus and Klause height (or index, KI) parameters together gives information about basiocciput development. Dagtekin et al.[8] suggests that abnormality of the occipital bone might be the cause of CMI.

Karagoz[17] found that the h value and KI can be used to show the flat of PCF as lower and interpreted as growing to front side of compensator of PCF in cases with CMI. In accordance with this study, KI was found to be significantly lower in CMI group in current study.

Milhorat et al.[28] found clivus length as shorter in cases with CMI. In accordance with this study, The clivus length was found to be significantly lower in CMI group in our study.

The POI-O line is a parameter showing the distance of supraocciput[17,28,31]. In our study, the distance of POI-O was found to be significantly lower in CMI group. Those findings were compatible with studies of Milhorat et al.[28] and Karagoz[17].

The measurement of head basis angles shows the predisposition to platybasia[5,17]. In our study, Welcher basal angles were found to be significantly higher in CMI group. The changes of Wackenheim clivus and the basal angles were not significant. Karagoz[17] found higher basal angles showed platybasia in CMI. We thought that the smaller number of cases in our study might be the result of this insignificance.

We found Boogard angle to be significantly higher in CMI group. Karagoz[17] found higher Boogard angle showing platyba-

sia in CMI. Our findings were compatible with their study. Additionally, the change of N.B.O. angle was not significant in-group comparisons. Karagoz[17] found higher N.B.O. angle showing platybasia in CMI cases. The changes of TC-TH angle from Tentorial angles were not significant in-group comparisons. Karagoz[17] and Nishikawa et al.[31] found this angle more extended in CMI cases.

The bevel of TC was significantly lower in CMI group. Karagoz[17] has reported larger TC bevel, but this was not statistically significant. Milhorat et al.[26] have observed larger TC bevel in CMI. Nishikawa et al.[31] have suggested that the TC was pushed toward front and steepened to compensate the volume of PCF in CM. In this way, the neural tissue may herniate, such as spinal channel moving toward upper site. In addition to these findings mentioned above, we have observed an increment in TC bevel in our study, which in turn may suggest that the compensation mechanism doesn't always occur. In other words, the alteration of TC bevel does not necessarily occur in CMI and the alteration of PCF bone structure may happen for compensation as mentioned above. Hence, using TC-TH angle can give valuable results to evaluation of CM[17].

CONCLUSION

Considerable decrease was observed in total, IT, and ST intracranial volumes in CMI in the present study. Especially, the IT intracranial volume decrease was prominent. Thus, in tonsillar herniation cases with normal IT volume, other possible underlying causes should be taken into consideration. Beside absence of cisterna magna, syringomyelia and craniovertebral junction abnormalities frequently accompany with the tonsillar herniation. We think that manifestation of CMI is likely depends on multiple factors and special attention should be paid to the accompanying congenital abnormalities in CMI. Further morphometric studies with larger series of patients are required to get more insight into the complex underlying mechanism in CMI.

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