

# Growth Curves for Intracranial Volume and Two-dimensional Parameters for Japanese Children without Cranial Abnormality: Toward Treatment of Craniosynostosis

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## Abstract

In the management of patients with craniosynostosis, it is important to understand growth curve of the normal cranium. Although three-dimensional (3D) computed tomography (CT) images taken in thin slices are easily available nowadays, data on the growth curves of intracranial volume (ICV), cranial length, cranial width, and cranial height in the normal cranium are mainly based on older studies using radiography, and there are insufficient reports using CT images especially taken in thin slices. The purpose of this study was to establish growth curves in the normal cranium of Japanese children using thin-slice images. Cranial images of 106 subjects (57 males, 49 females; aged 0–83 months) without significant cranial abnormalities were retrospectively analyzed. Using thin-slice CT images, the ICV and two-dimensional parameters such as cranial length, cranial width, and cranial height were measured by iPlan, followed by generating growth curves and calculating cephalic index (CI). ICV calculated from thin-slice CT images was compared with that obtained by substituting two-dimensional parameters into Mackinnon formula. The ICV growth curves for males and females were similar in shape. As with the ICV, the two-dimensional parameters increased most rapidly in the first year after birth. There was no significant difference in CI between the sexes or among any age groups. ICV calculated from thin-slice 3D CT images was 60% of that obtained from Mackinnon formula. These data will enable us to compare these specific measurements in craniosynostosis patients directly with those of normal children, which will hopefully help in managing these patients.

Keywords: normal cranial morphology of Japanese children, intracranial volume, cranial length, cranial breadth, cranial height

## Introduction

Craniosynostosis involves the premature fusion of one or more cranial sutures, which alters the

morphology of the cranial vault. This rare condition, which affects 1 in every 2100 to 2500 births, is classified as syndromic in up to 24% of cases. Growth of the craniosynostotic skull is insufficient in the direction perpendicular to the affected sutures and compensatorily excessive at the nonaffected sutures.<sup>1)</sup> Intracranial hypertension occurs in both syndromic craniosynostosis and nonsyndromic craniosynostosis.<sup>2,3)</sup>

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The goals of surgical treatment for craniosynostosis are to prevent or treat elevated intracranial pressure and to obtain better cranial morphology.<sup>1,4)</sup> As for cranial morphology, one of the current problems is that there is insufficient common understanding of what constitutes improvement in cranial morphology after cranioplasty. This is probably due to several reasons. The first reason is the lack of an evaluation method that can adequately assess complex cranial morphology. In explaining the improvement in morphology after cranioplasty, we depend heavily on subjective evaluation such as appearance, since there is no well-established objective evaluation method except for the cephalic index (CI). CI has been used in a number of publications for evaluation of therapeutic efficacy in the treatment of craniosynostosis patients.<sup>2,5,6)</sup> In cases with complex morphological abnormalities, however, the CI is not a sufficient measurement of cranial morphology, as it incorporates measurements from only one horizontal plane.<sup>4,7)</sup> The second reason is that not all cranioplasties aim to improve morphology sufficiently. Unlike nonsyndromic craniosynostosis cases, syndromic cases often require multiple surgeries. In these cases, instead of aiming for sufficient morphological improvement in the first surgery, the strategy may be to prioritize cranial vault expansion to reduce intracranial pressure and aim for morphological improvement as a result of multiple surgeries. The third reason is that short-term morphological improvement obtained in a single treatment does not necessarily mean long-term improvement, because there is a possibility of long-term relapse after cranial vault expansion. To obtain better cranial morphology, we have been treating craniosynostosis patients by modifying the cranial morphology to be as normal as possible based on the mid-sagittal vector analysis (MSVA) of the normal morphology of Japanese children,<sup>4,8)</sup> but there is room for debate as to whether this is the best treatment for the long-term course. These factors complicate the evaluation of cranial morphology. Nevertheless, it would be beneficial to understand the standard cranial growth curves of intracranial volume (ICV) and two-dimensional parameters in the management of patients with craniosynostosis.

Although three-dimensional (3D) computed tomography (CT) images taken in thin slices are now easily available, the data on the growth curves of ICV and two-dimensional parameters such as cranial length, cranial width, and cranial height in the normal cranium are mainly based on older studies. These old studies are based on X-ray radiography data, which seem to have some limitations in reliability when compared with those based on CT images taken in thin slices. On the contrary, there

are still insufficient reports using CT images especially taken in thin slices.

The purpose of this study was to establish standard growth curves for the ICV and several two-dimensional cranial shape parameters based on CT images taken in thin slices previously collected from Japanese children with normal cranial morphology.<sup>4)</sup>

## Materials and Methods

### Patients

With approval from the Okayama University Hospital ethics review committee (research no. 1905-035), CT images were collected from the medical records of children (age range: 0–83 months) who had been scanned at Okayama University Hospital between January 2012 and December 2016. These CT images were retrospectively reviewed, and candidates without significant cranial abnormalities on imaging were included in this study.

### Exclusion criteria

The exclusion criteria were as follows: history of low birth weight (<2500 g), low or high stature growth rate (<-2 standard deviations [SDs] or >+2 SDs from the Japanese standard growth curve), severe epilepsy (requiring long-term medication), craniosynostosis, intracranial tumor or mass lesion, intracranial arachnoid cyst, hydrocephalus, underlying diseases that can cause low growth (e.g., cardiovascular malformations and endocrine disorders), chromosomal abnormalities, and fractures in the measurement area. Patients with benign epilepsy permitting normal intellectual development and patients with disorders that were predicted to have no effect on cranial morphology at the time of the scan (e.g., acute encephalopathy scanned shortly after disease onset) were included in the study.<sup>4)</sup>

### Measurement of ICV and two-dimensional parameters

Regions of interest in each image were determined so as to optimize bone versus soft tissue density. Concretely, the window level was set to 1200 Hounsfield unit (HU) and the window width was set to 300 HU with minor modification of the previously reported method.<sup>1)</sup> Slice thickness was required to be 2 mm or less to enable accurate ICV measurement and generate a best-fit logarithmic curve, although previous studies analyzed ICV using images with 4–5 mm slice thickness.<sup>9,10)</sup> As a result, images with slice thickness larger than 2 mm were excluded in this study. ICV was calculated from the 3D CT images using iPlan (BrainLab, Tokyo, Japan), a neuronavigation program. Semi-automated image

segmentation was also performed using this software. The intracranial space was defined as the region spanning the vertex cranially to the foramen magnum caudally, shown in Figure Supplement 1 (All Supplementary Files are available Online), as previously reported.<sup>1,10–13)</sup> The border lines of the fontanelles, foramen magnum, orbits, and skull sutures were drawn manually. After segmentation was finished, ICV was automatically calculated by iPlan.

Following the procedure outlined by Kim et al., we measured the dimensions of the cranial vault on CT images.<sup>14)</sup> Cranial length was defined as the distance between the most anterior and posterior points of the outer surface of the skull. Cranial breadth was defined as the distance between the leftmost and rightmost points on the outer surface of the skull. Regarding cranial height, cranial height (ba-br) was defined as the distance between the basion and the bregma. In addition, cranial height (eam-v) was defined as the distance between the midpoint of the external auditory meateus and the vertex, and the cranial height (po-br) was defined as the distance between the deepest point of the posterior fossa and the bregma.

### CI, Cranial Vault Asymmetry Index (CVAI) and comparison of ICV

The CI was calculated according to the following previously reported equation: (cranial breadth (b))/ (cranial length (a))  $\times$  100, as shown in Figure Supplement 2.<sup>15)</sup>

According to the previous report, we measured CVAI to measure the extent of deformational plagiocephaly; CVAI of less than 5% was defined as normal, 5% or more and less than 7% as mild, 7% or more and less than 10% as moderate, 10 or more and less than 14% as severe, and 14% or more as very severe.<sup>16)</sup>

In addition to cranial width and cranial length, previous literature has also reported the measurement of cranial height (eam-v) and cranial height (po-br) to calculate ICV in a simplified manner according to the following Mackinnon formula:<sup>9,17,18)</sup>

$$0.51 \times [0.5\{\text{cranial height (po-br)} \times \text{cranial length} \times \text{cranial width}\} + \{\text{cranial height (eam-v)} \times \text{cranial length} \times \text{cranial width}\}]$$

We compared the ICV obtained by substituting these two-dimensional parameters measured in our study into Mackinnon formula with those calculated from 3D CT images by iPlan.

### Statistical analysis

The measurements of each parameter (ICV, cranial length, cranial breadth, and cranial height) were plotted according to age and sex, and best-fit logarithmic curves were plotted. The study group was divided into four age categories: 0–11 months, 12–23 months, 24–35 months, and 36–83 months. Data in each group were compared between two groups with the Mann–Whitney U-test and were compared among four groups with the Kruskal–Wallis test using SPSS software (version 20; SPSS, Inc., Chicago, IL, USA). The statistical difference between groups was assessed at the level of  $p < 0.05$ .

## Results

### Patients

Of the 2057 CT images initially collected, 1799 were excluded according to the criteria described earlier. Of the remaining 258 images, a further 152 were excluded because of inadequate slice thickness (larger than 2 mm). Finally, 106 subjects (57 males, 49 females; median age: 23.5 months; age range:

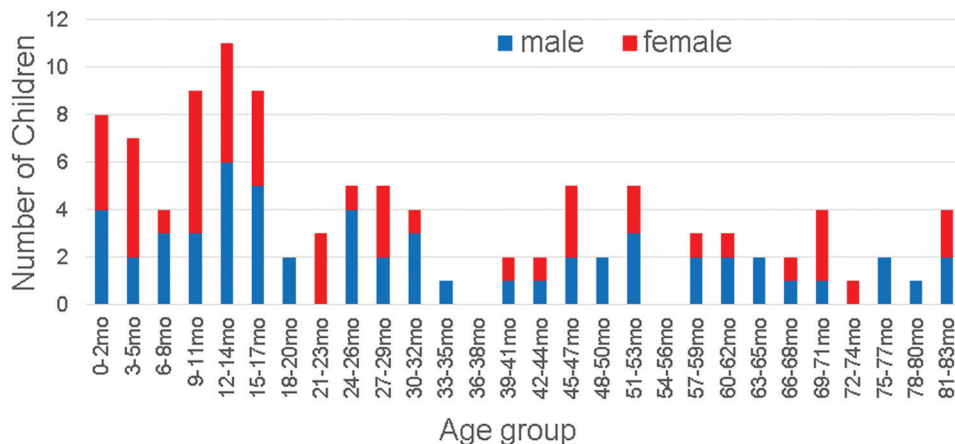
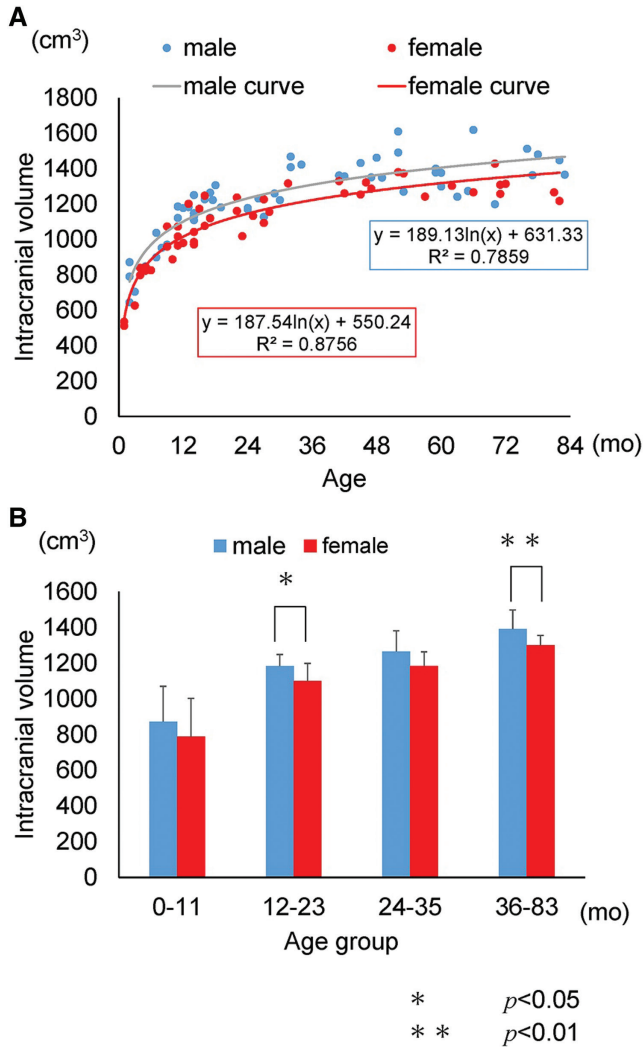


Fig. 1 Patient age and sex distribution in this study.



**Fig. 2** Growth curve for ICV and statistical analysis of ICV. (A) Growth in the ICV is most rapid from birth to 12 months of age. (B) In some age categories, ICV was significantly higher in males than in females. ICV: intracranial volume.

0–83 months) were analyzed for the ICV and the two-dimensional parameters in this study. Figure 1 shows patient age and sex distribution.

### Growth curve of ICV

Before generating a best-fit logarithmic curve, the ICV of 12 patients was measured twice in order to evaluate the reproducibility; the error of the two measurements of ICV was  $0.19 \pm 0.17$  (mean  $\pm$  standard error [SE])%. The scatter plots of ICV measurements against age (in months), shown in Fig. 2, were used to generate a best-fit logarithmic curve for males, namely,  $y = 189.13 \ln(x) + 631.33$  ( $R^2 = 0.7859$ ), and another for females, namely,  $y = 187.54 \ln(x) + 550.24$  ( $R^2 = 0.8756$ ). As these

curves reveal, growth in the ICV is most rapid from birth to 12 months of age, after which the rate of growth declines slightly. Average ICV was compared between the sexes in each of the four age categories. In children aged 12–23 months and 36–83 months, ICV was significantly higher in males than in females ( $p < 0.05$  for 12–23 months,  $p < 0.01$  for 36–83 months).

### Growth curves of two-dimensional parameters

Scatter plots and best-fit logarithmic curves were similarly generated for cranial length, cranial breadth, and cranial height.

For cranial length, Fig. 3(A) shows the best-fit curves for males, namely,  $y = 11.278 \ln(x) + 119.21$  ( $R^2 = 0.7313$ ), and females, namely,  $y = 10.161 \ln(x) + 120.28$  ( $R^2 = 0.7884$ ). Like ICV, cranial length increases most rapidly during the first 12 months of age, with a slightly lower growth rate later in childhood. Unlike ICV, there was no significant difference in cranial length between the sexes in any age category.

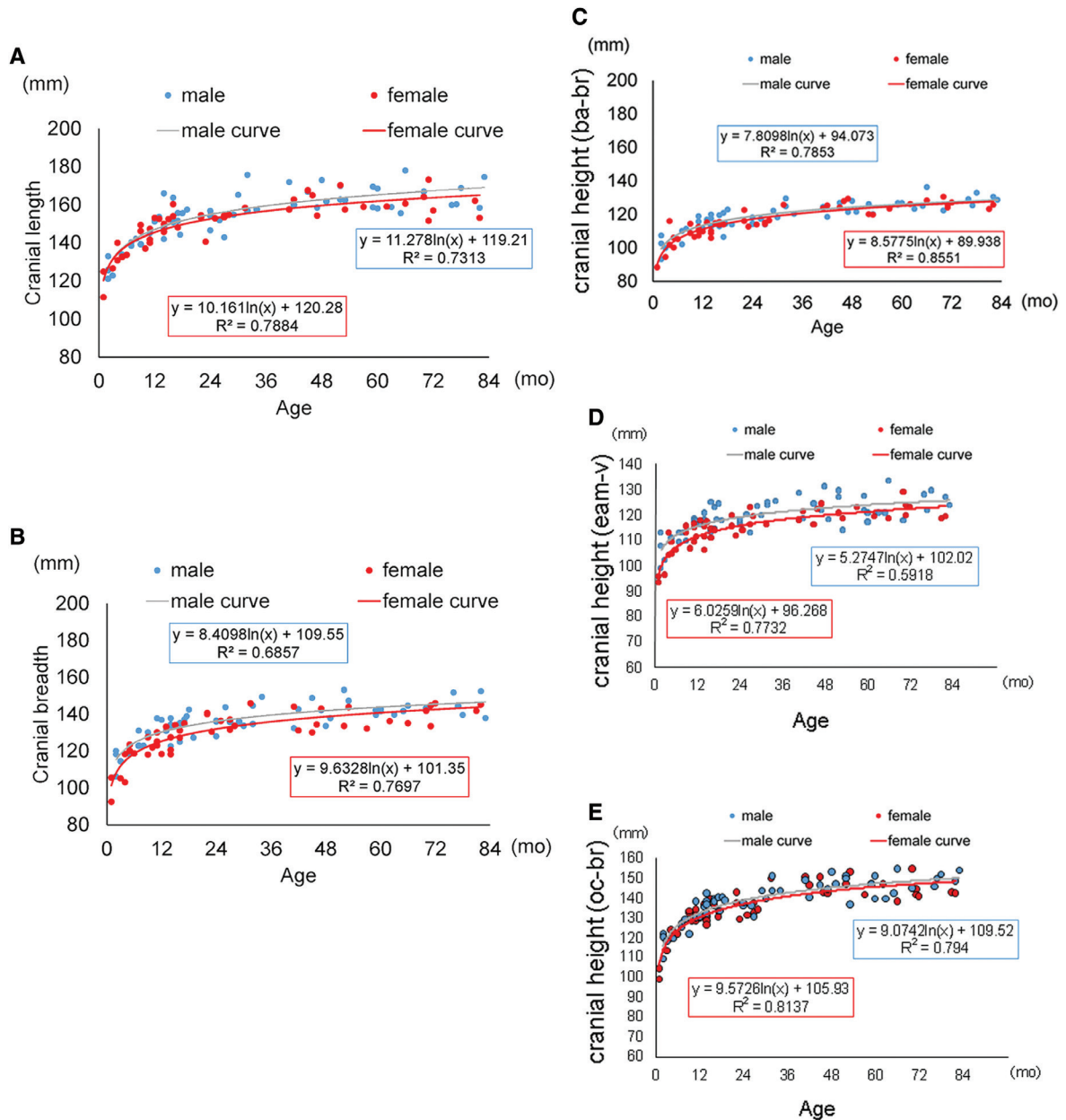
For cranial breadth, Fig. 3(B) shows the best-fit curves for males, namely,  $y = 8.409 \ln(x) + 109.55$  ( $R^2 = 0.6857$ ), and females, namely,  $y = 9.633 \ln(x) + 101.35$  ( $R^2 = 0.7697$ ). Like cranial length and ICV, cranial breadth increases most rapidly from birth to 12 months of age, with a slightly lower growth rate later in childhood. As in cranial length, there was no significant difference in cranial breadth between the sexes in any age category.

For cranial height (ba-br), Fig. 3(C) shows the best-fit curves for males, namely,  $y = 7.8098 \ln(x) + 94.073$  ( $R^2 = 0.7835$ ), and females, namely,  $y = 8.5775 \ln(x) + 89.938$  ( $R^2 = 0.8551$ ). Like the other metrics, cranial height (ba-br) increases most rapidly from birth to 12 months of age, with a slightly lower growth rate later in childhood. As in cranial length and cranial breadth, there was no significant difference in cranial height (ba-br) between the sexes in any age category.

For cranial height (eam-v), Fig. 3(D) shows the best-fit curves for males, namely,  $y = 5.2747 \ln(x) + 102.02$  ( $R^2 = 0.5918$ ), and females, namely,  $y = 6.0259 \ln(x) + 96.268$  ( $R^2 = 0.7732$ ). Like the other metrics, cranial height (eam-v) increases most rapidly from birth to 12 months of age, with a slightly lower growth rate later in childhood. In children 12–23 months, the cranial height (eam-v) was significantly larger in males than in females.

For cranial height (po-br), Fig. 3(E) shows the best-fit curves for males, namely,  $y = 9.0742 \ln(x) + 109.52$  ( $R^2 = 0.794$ ), and females, namely,  $y = 9.5726 \ln(x) + 105.93$  ( $R^2 = 0.8137$ ). Like the other metrics, cranial height (po-br) increases most rapidly from





**Fig. 3** Growth curves for two-dimensional parameters such as cranial length (A), cranial breadth (B), cranial height (ba-br) (C), cranial height (eam-v) (D), and cranial height (po-br) (E). The two-dimensional parameters increased most rapidly in the first year after birth as with the ICV. ICV: intracranial volume.

birth to 12 months of age, with a slightly lower growth rate later in childhood. As in cranial length and cranial breadth, there was no significant difference in cranial height (po-br) between the sexes in any age category.

### Cephalic index

The average CI was 88.1 among males and 86.3 among females, as shown in Table 1. There were no significant differences between the sexes or among any of the age groups.

### Cranial Vault Asymmetry Index

Although CVAI of moderate severity or more is considered an indication for helmet therapy,<sup>19)</sup> CVAI of all ages and sexes in this study was classified as “normal” or “mild,” which is milder than moderate, as shown in the supplemental table.

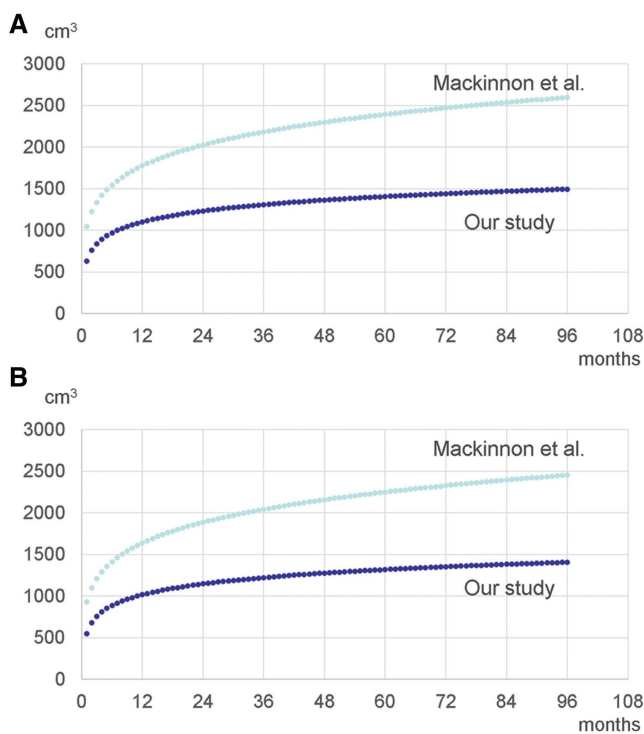
### Comparison of ICV

We compared the ICV obtained by Mackinnon formula with that calculated from 3D CT images by iPlan. As shown in Fig. 4 (A: male, B: female),

**Table 1** CI in Japanese children without cranial abnormality

Age (mo)	No. (female)	CI		
		All (SD)	Male (SD)	Female (SD)
0–11	28 (16)	87.8 (5.9)	90.2 (4.5)	86.1 (6.2)
12–23	25 (12)	86.9 (5.7)	87.7 (6.2)	86.0 (5.0)
24–35	15 (5)	88.5 (5.4)	88.5 (6.4)	88.4 (2.3)
36–83	38 (16)	86.8 (5.7)	87.2 (5.3)	86.3 (6.1)
Total	106 (49)	87.3 (5.7)	88.1 (5.7)	86.3 (5.6)

CI: cephalic index, SD: standard deviation.



**Fig. 4** Growth curves for ICV in male (A) and in female (B). Regardless of gender, the ICV calculated by iPlan was approximately 60% of the ICV calculated by Mackinnon formula in all months evaluated in this study. ICV: intracranial volume.

considerable differences were observed. The ICV calculated by iPlan was approximately 60% (mean  $\pm$  SE:  $59.6 \pm 0.2$ ,  $59.4 \pm 0.2$ , male, female, respectively) of the ICV calculated by Mackinnon formula in all months evaluated in this study.

## Discussion

In this study, using thin-slice CT images, we generated growth curves for ICV, and two-dimensional

parameters such as cranial length, cranial breadth, and cranial height for Japanese children with normal cranial morphology and assessed CI. We also compared the ICV obtained by substituting these two-dimensional parameters measured in our study into Mackinnon formula with those calculated from 3D CT images by iPlan. We found that the ICV calculated by iPlan was approximately 60% of the ICV calculated by Mackinnon formula. To the best of our knowledge, this is the first report to analyze the detailed skull growth processes for both ICV and two-dimensional parameters in normal Japanese children.

## ICV, two-dimensional parameters, and CI data

The ICV growth curves calculated herein showed almost the same shape as those previously reported.<sup>9,12,13</sup> Growth is most rapid from birth to 12 months of age; after 12 months of age, growth continues but gradually slows. It should be noted that the subjects in this study were exclusively Japanese children, as our data yielded ICV growth curves that were slightly larger in both sexes than those in previous reports on other races.<sup>9–12</sup> Moreover, the shapes of our growth curves for cranial length, breadth, and height were similar to those for ICV. These curves enable us to understand the relationship between age and size for each parameter. Recently, 3D growth pattern of the cranium of healthy Japanese infants was reported.<sup>20</sup> They divided the period up to 17 months of age into six age groups and analyzed which parts of the cranium grew during the two adjacent age groups. They reported that up to 5 months of age, the entire area of cranium, except for the occipital region, undergoes rapid growth. They also reported that the occipital region increases in size from 9 to 17 months of age. Although it is difficult to identify which part of the cranium grows in our analysis for two-dimensional parameters, the very rapid increase in both cranial length and cranial breadth during the first 6 months of life is similar to that reported by them. Previous reports showed that there is racial differences in CI.<sup>15</sup> Our CI data also differed from international data in that our subjects did not show a significant difference in CI between the sexes and were more brachycephalic.<sup>21,22</sup> Our CI results were comparable to those reported previously.<sup>15,20,23</sup>

## Clinical importance of this study: Possible application to craniosynostosis treatment

The goal of surgery for craniosynostosis is to reduce intracranial pressure and improve morphology.<sup>1,4</sup> In the treatment of severe syndromic craniosynostosis, we first perform posterior cranial vault distraction (PCVD) when the patient is around 3 months

old in order to reduce the increased intracranial pressure. Next, we perform a multi-directional cranial distraction osteogenesis (MCDO) procedure after the patient is aged 1 year.<sup>8)</sup> PCVD is useful in that it can efficiently increase ICV, and it is often performed with the plan of maximum extension to the limit of PCVD, which may exceed 25 mm, regardless of the normal value of the anterior–posterior diameter at each age, in order to reduce intracranial pressure.<sup>24,25)</sup> In the current situation, where intracranial pressure measurement cannot be performed noninvasively, it is reasonable to set the minimum required amount of distraction length to reach the normal values of the anterior–posterior diameter and ICV at each age, and to perform PCVD beyond the minimum required amount in order to control intracranial pressure.

For morphological improvement, we perform the MCDO procedure and postoperative distraction using the MSVA for the normal morphology of Japanese children as a reference, considering that the improvement in skull morphology in craniostylosis treatment involves being closer to the normal morphology of the skull.<sup>4,8,26)</sup> This is why MSVA is an essential tool in the analysis of cranial morphology for us. MSVA has some disadvantages, however. For example, MSVA cannot be analyzed immediately in an outpatient clinic like the CI can. Further, MSVA is based on the sagittal plane, which does not consider cranial width. Although it is not possible to evaluate cranial morphology in the sagittal plane as finely as MSVA, measuring cranial length, cranial breadth, and three types of cranial height of craniostylosis patients does not take long time; that is why measuring these parameters in craniostylosis patients followed by comparing these parameters with normal growth curve would be helpful for preoperative surgical planning and determination of the amount of postoperative distraction.

In the management of patients with craniostylosis, measuring these two-dimensional parameters and comparing them with normal growth curves is expected to reveal specific differences in the growth patterns of normal and craniostylosis skulls.

### Limitations

This study has two limitations. First, the subjects included patients with various clinical conditions. As none of these conditions were predicted to have an effect on cranial morphology, we included these subjects in our study just as Senoo et al. did.<sup>4)</sup> The collection of head CT data from completely healthy children would involve unnecessary radiation

exposure and expenditures. Against this background, we designed a retrospective study on children who had already undergone CT scans for other medical reasons. Next, in order to measure the ICV more accurately, we decided to analyze only the CT data taken with a thickness of 2 mm or less. Although our sample size was comparable to those of similar previous studies,<sup>12,13,15)</sup> only 106 subjects were finally analyzed.

In the present study, it was confirmed that both cranial morphology and ICV showed a large exponential growth change under 2 years old (especially under 1 year old). Although the number of cases was limited in this study, further data collection in this age group will enable us to obtain more accurate growth curves for ICV and two-dimensional parameters. In addition to cranial morphology and ICV, data on the size of the fontanelle, which may affect the timing of cranioplasty for craniostylosis patients, would be useful in determining the timing of surgery. Moreover, it would be useful to collect data on the growth rate of the mandible and facial bones when dealing with syndromic craniostylosis patients.

Recently, 3D scanners have been widely used to measure cranial and facial morphology, and it is expected that 3D scanners will be more commonly used than CT for data collection in healthy subjects. On the other hand, the volume of the brain and ventricles cannot be studied with the 3D scanner. It is not easy to collect data on healthy children because of the disadvantages of CT, such as radiation exposure, and MR, such as the need for sedation. In addition to cranial morphology and ICV, the data on standard brain growth changes would be beneficial for the management of craniostylosis.

These issues will be discussed in a future multi-center, prospective study, if such a study can be conducted.

### Conclusion

We retrospectively analyzed the normal growth patterns of ICV and cranial length, breadth, and height and produced normal growth curves. In ICV and each of the two-dimensional parameters, the most rapid growth occurred from birth to 12 months of age. Our normal growth curves for ICV and these two-dimensional parameters based on thin-slice CT images can be used as more reliable references in the management of craniostylosis patients.

### Conflicts of Interest Disclosure

All authors have no conflicts of interest.

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