学 位 論 文 の 要 旨

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論 文 内 容 の 要 旨

INTRODUCTION

The cranial base plays important roles not only supporting but also interacting with the brain during development, and many congenital anomalies of the brain correspond to cranial base anomalies. Therefore, a detailed analysis of cranial base development is not only fundamentally but also clinically significant because of its complex ossification pattern and its close relationship to brain development. We previously reported a wide variation in the timing of appearance of cartilage centers in the cranial base as well as in the development of orofacial structures in human embryos and fetuses. However, variations and growth patterns of the ossifying fetal cranial base have not been fully documented. Development of the human cranial base has been studied using dissection, computed tomography (CT), and magnetic resonance imaging (MRI), each of which has advantages and disadvantages. In the present study, we examined development of the normal human fetal cranial base using the bone staining method, which allows for direct observation of the ossification centers and precise three-dimensional measurements.

MATERIALS AND METHODS

We observed alizarin red S-stained sphenoids and basiocciputs of 22 normal formalin-fixed human fetuses that belonged to the Kyoto collection of human embryos with crown-rump lengths (CRL) of 115–175 mm (15–20 weeks of gestation). They were divided into four groups according to their CRL stages (i.e., approximately 120, 130, 140, and 170 mm). We defined a total of 20 landmarks to capture the morphology of the fetal cranial base and measured sphenoids and basiocciputs using a fine caliper. We observed and measured the areas of ossification in the sphenoid as well as in the basioccipit of all the specimens. To further examine the relationship between the cranial base and the brain, different sets of 22 fetuses of CRL 105–186 mm from the Kyoto collection were dissected, the length and width of the cerebrum and pons were measured with calipers, and the pituitary was weighed. Student's t-test was used to assess the differences in the ratios of the lengths or widths of the part of the skull base to the length or width of the cranial base between two groups which have different ossification patterns of the basisphenoid. We used discriminant analysis to determine whether these two groups could be distinguished by these ratios during the fetal period.

RESULTS AND DISCUSSION

Because of the bone staining characteristics, we could clearly locate the ossification centers and observe bone growth texture, which inferred the direction of bone growth. Recent studies have evaluated drug-induced changes in the rabbit fetal skeleton by micro-CT and alizarin-red bone staining, and in a few cases, skeletal malformations, variations, and incomplete ossification were detected by bone staining, but not by micro-CT. Moreover, MRI is basically only useful for soft tissue, and pitfalls of using MRI to interpret changes in hard tissues have been repeatedly documented. To accurately evaluate the size and shape of small ossifying bones, the bone staining method has an advantage over these other methods, and is suitable to precisely observe developing bones, describe variations, and establish the standard.

We observed cases in which development of orbitosphenoidal ossification did not appear in chronological order between the CRL130 and CRL140 stages, suggesting complex individual differences in the orbitosphenoid ossification pattern. We observed two different basiphenoid ossification patterns, i.e. single and double ossification centers at CRL120, CRL130, and CRL140 stages. There were significant differences in distance between the most medial points on the orbitosphenoids and distance between the most lateral points on the basisphenoids, as well as their ratios to distance between the most superior-lateral points on the temporal squamas, between the single and double ossification center groups, whereas no significant differences were observed for other measurements. The mechanism to produce these different sphenoid bone ossification patterns and its relationship to pituitary development as well as that with the holoprosencephaly spectrum requires further analysis.

The cerebrum developed relatively slowly from the CRL110 to CRL140 stages and increased relatively rapidly after the CRL140 stage. The cranial base developed relatively rapidly from the CRL120 to CRL140 stages, whereas it grew relatively slowly after the CRL140 stage, suggesting relatively earlier development of the cranial base than that of the cerebrum. The previous β-catenin transgenic study showed that the larger brain size (i.e. encephalized brain) was accompanied by reduced cranial ossification in the neonate age group, and the authors speculated that this difference in ossification levels could indicate the ontogeny of the brain (an extremely metabolically costly structure) at the expense of other structure of the skull. The relatively earlier development of the cranial base than that of the cerebrum and the decreased growth of the cranial base after the cerebrum started to grow rapidly in the present study may be consistent with this notion. The present data showed the large correlation coefficients to CRL of the basioccipital length and width and those of the pons length and width, suggesting that basioccipital ossification and development of the pons have a close positive relationship with CRL. Scatterplots showed that pituitary gland and basisphenoid development corresponded linearly to the CRL, and that a relatively wide variation was observed in the weight of the pituitary from the CRL120 to CRL140 stages.

The present observations confirmed the reported ossification sequence of the cranial base bones, and suggest that the growth pattern and relative growth rate change depending on developmental stage, therefore, a detailed analysis is necessary to accurately evaluate the growth pattern of the cranial parts.

CONCLUSION

Our observations and measurements based on the bone staining method clearly showed early progressive ossification of the human fetal cranial base. The appearance and extent of ossification did not appear to always correspond with increases in body size. Different orbitosphenoid ossification patterns at the CRL130 and CRL140 stages and two different developmental patterns of the basisphenoid ossification center (single or double) were observed from the CRL120 to CRL140 stages. Significant differences in some midline diameters were found between the single- and double-basisphenoid ossification groups. These findings suggest that ossification of the orbitosphenoid and basisphenoid develop differently based on gestational age and as a normal developmental variation rather than as anomalies. Close relationships were observed between the ossification centers of corresponding parts of the cranial base and development of the cerebrum and pons.