Sex-related differences in the developmental morphology of the atlas: A computed tomography study

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Abstract

**Study Design.** A retrospective study.

**Objective.** To elucidate sex-related differences in the age at synchondroses closure, the normative size of the atlas, and the ossification patterns of the atlas in Japanese children.

**Summary of Background Data.** The atlas develops from three ossification centers during childhood. The anterior and posterior synchondroses, which are separate ossification centers, mimic fracture lines on computed tomography (CT). Sex-related differences of age dependent morphological changes of the atlas in a large sample size have not been reported.

**Methods.** This study analyzed data of 688 subjects (449 boys) between 0 to 18 years old who underwent CT examination of the head and/or neck between January 2010 and July 2016. The age at synchondroses closure, anteroposterior outer, inner, and spinal canal widths of the atlas, and variations of the ossification centers were examined.

**Results.** Anterior synchondroses closed by 10 years in boys and by 7 years in girls. Significant earlier closure of anterior synchondroses was observed in girls than in boys (p<0.05 at 4 and 5 years old). Posterior synchondrosis closed by 6 years in boys and by 5 years in girls. The outer, inner, and spinal canal widths increased up to 10 to 15 years in both sexes, although all three parameters in girls peaked three years earlier than those in boys. All parameters in boys were significantly larger than those in girls, except in the 10-12-year-old age category. Two or more ossification centers in the anterior arch were observed in 18.3% subjects, and 6% had midline ossification centers in the posterior arch of the atlas.
Conclusion. Distinct sex-related differences in the age at anterior synchondroses closure and the size of the atlas were observed in Japanese children. Knowledge of morphological features of the atlas could help distinguish fractures from synchondroses.

Key words: Atlas, cervical spine, childhood, computed tomography, first vertebra, sex-related difference, ossification center, spinal canal, synchondrosis closure, Japanese

Level of Evidence: 3
Introduction

The first cervical vertebra or the atlas adopts some unique morphological features during its development.\textsuperscript{1-3} The atlas typically develops from three ossification centers, one anterior and two lateral. These are separated by two anterior neurocentral synchondroses and posterior midline synchondrosis (Fig. 1). The greater part of the atlas has a cartilaginous structure at birth, followed by ossifications of the cartilaginous arch, and then closure of synchondroses, finally developing into the osseous ring vertebra. Moreover, there are several variations of ossification centers of the atlas during its development.\textsuperscript{2,4-8}

Currently, cervical spine injuries in children are routinely assessed by computed tomography (CT), especially in an emergency setting. The upper cervical spine is the most susceptible site of cervical injury in children aged 8 or younger.\textsuperscript{9,10} Synchondroses are likely to be misdiagnosed as fractures, because of their similar appearances on CT images.\textsuperscript{11-14} Thus, adequate knowledge of the timing of synchondroses closure as well as the ossification patterns of the atlas during childhood is the key to successfully differentiating fractures from normal synchondroses.

Several studies have explored the age at synchondroses closure and variations of ossification patterns involving cadavers, plain radiographs, or CT images in Americans and Europeans.\textsuperscript{2,6-8,15} However, no studies have focused on sex-related differences in the timing of synchondroses closure of the atlas. Moreover, few studies have examined the effects of sex-related differences with respect to the growing size of the atlas.\textsuperscript{16} The primary purpose of this study was to elucidate sex-related differences in the age at synchondroses closure and age-dependent bony and spinal canal growth of the atlas in Japanese children. The secondary aim was to examine frequency variations of ossification centers of the atlas during childhood.
Materials and Methods

Data of 1,563 subjects 18 years old or younger with head and/or neck CT images captured between January 2010 and July 2016 at Enshu Hospital in Hamamatsu, Japan were initially examined. Among those, data on subjects with skeletal dysplasia, history of neck injury, prior operations of the atlas, and subjects without readable CT images of the atlas were excluded. Finally, data of 688 subjects were available for morphological evaluation of the atlas. There were 449 boys and 239 girls between the ages of four days after birth to 18 years. The number of subjects in each age category is shown in Fig. 2. When bony bridges between the anterior arch and lateral ossification centers on both sides were confirmed on axial CT images, the anterior arch was regarded as synchondrosis closure. When a bony bridge between the posterior sides of the lateral ossification centers was confirmed, the posterior arch was regarded as synchondrosis closure. The outer and inner anteroposterior diameters of bony atlas and anteroposterior diameters of the spinal canal at the atlas level were measured on axial CT images (Fig. 1).

Examination was performed on CT scanners (Revolution CT, GE Healthcare, Little Chalfont, UK; and Aquilion 64, Toshiba Medical, Otawara, Japan), with <5 mm slice width. Because reconstructed CT images were not available, confirmation for synchondroses closure, measurements of bony and spinal canal widths, and ossification patterns were examined on axial planes only. Evaluations for synchondroses closure and measurements of the anteroposterior widths of the atlas and spinal canal were conducted by two authors (MA and TF) in a blinded manner. If judgment was different between the two authors, a discussion was held until a final agreement was reached. To determine the intraobserver reproducibility of the width measurements of the atlas or spinal canal, two measurements in 20 randomly selected subjects were performed during a 2-week interval. To determine the interobserver reproducibility, single measurements of 20 randomly selected subjects were
performed by two authors (MA and TF), independently. This retrospective study was approved by the institutional review board of Enshu Hospital.

Statistical analysis

Data were analyzed with SPSS software (PASW Statistics, version 18, IBM, Armonk, NY, USA). Closure rate of the anterior and posterior synchondroses in each age category was indicated as the percentage of the total number in each age category. Intra- and interobserver reproducibility were analyzed by interclass correlation coefficients. Inner and outer diameters of the atlas and the anteroposterior spinal canal diameters were indicated by mean. Sex-related differences in the timing of synchondroses closure for each 1-year age category were examined using the chi-square test. Because the number of subjects with width measurements of the atlas were limited, the subjects were divided into six age categories comprising 3-year intervals: 0-3, 4-6, 7-9, 10-12, 13-15, and 16-18 years old. Sex-related differences for inner, outer, and spinal canal diameters of the atlas in each 3-year age category were examined by Mann-Whitney U tests. Comparison of numerical data among the 3-year age categories was examined by analysis of variance, followed by Tukey's HSD post-hoc test. P values <0.05 were considered significant.

Results

 Evaluations for synchondroses closure were completed for all 688 subjects. Results indicated that the anterior synchondroses closed during 4-10 years in boys and 3-7 years of age in girls (Fig. 3-
A). The posterior midline synchondrosis closed during 2-6 years in boys and 2-5 years of age in girls (Fig. 3-B). Significant differences in anterior synchondrosis closure rates between boys and girls were observed at the age of 4 (p<0.05) and 5 years (p<0.05), respectively.

The reproducibility of measurements had an intra- and interobserver correlation coefficient of 0.962 and 0.951, respectively. Because the entire atlas could not be detected on one axial CT image in several subjects, 558 (81.1%) were evaluated for measurement of inner anteroposterior diameters, 272 (39.5%) for outer diameters, and 565 (82.1%) for spinal canal diameters. For boys, both outer and inner diameters of the atlas in each of the 3-year age categories up to 10-12 years old were significantly different from those in the upper age categories; however, there was no difference between those in the 13-15 and 16-18-year-old age categories (Fig. 4). For girls, both outer and inner diameters in each of the 3-year age categories up to 7-9 years were significantly different from those in the upper age categories; however, there were no differences among 10-12, 13-15, and 16-18 years old categories (Fig. 4). As for age-related changes in spinal canal diameters of the atlas, a significant increase was observed up to the 10-12 years old category for boys and 7-9 years old category for girls, and there were no differences among categories thereafter in both boys and girls (Fig. 5). All outer, inner, and spinal canal diameters of the atlas in all 3-year age categories in boys were significantly larger than those in girls, except for outer and spinal canal diameters in the 10-12 years old category (Table 1).

Ossification patterns were evaluated in all 688 subjects. Anterior synchondroses were closed completely in 453 out of 688 subjects. The anterior ossification center was not visible in 11 subjects aged 4 days-20 months. In the remaining 224 subjects, the following ossification patterns were observed: a single ossification center in 183 subjects (81.7%), two ossification centers in 40 (17.9%), and three or more ossification centers in one (0.4%, Fig. 6-A, B) subject. In 556 subjects, posterior synchondrosis was closed or completely ossified. Among the remaining 132 subjects, eight (6.0%) had
midline ossification centers (Fig. 6-C). The paramedial cleft was not observed in any subject. One 14-year-old girl had a posterior arch defect.

Discussion

To differentiate fractures of the atlas from synchondroses, it is essential to acquire knowledge of the timing of synchondroses closure in boys and girls, and the normal variants of ossification centers of the atlas during its development. In addition, normative data of the size of the atlas and spinal canal space in boys and girls, respectively, could assist in the diagnosis of congenital craniocervical disorders or spinal tumors.\textsuperscript{17,18}

There are five studies on the morphological features of the atlas evaluated by CT images in the literature.\textsuperscript{3,6-8,15} All studies were conducted in either American or European subjects. No research targeting Asians has been reported. The timing of the synchondroses closure during childhood varies and remains controversial. In these studies, the age at anterior synchondroses closure was reported as 7-12 years, while the age at posterior synchondrosis closure was 2.8-5 years.\textsuperscript{3,7,8} As per the current study, anterior synchondroses were closed completely by 10 years of age in boys and 7 years of age in girls, and posterior synchondrosis by 6 years of age in boys and 5 years of age in girls. The timing of closure for anterior synchondroses is similar to that in Americans and Europeans; however, it may be later for posterior synchondrosis. Later closure for posterior synchondrosis in Asian children than in European or American children could partly be explained by racial differences in skeletal maturity. Delayed skeletal age in Asian children in comparison to American children, judged by Greulich-Pyle standards using hand radiographies, was reported by Roche et al.\textsuperscript{19}
No studies regarding sex-related differences in the timing of synchondroses closure of the atlas have been performed. In our study, sex-related differences in closure age could be detected only for anterior synchondroses. No sex-related differences in the age at posterior synchondrosis closure might be explained by narrower distribution of the closing time of posterior synchondrosis than that of anterior synchondroses. The occurrence of a closure of the neurocentral cartilage in the thoracic spine 1 year earlier in boys than in girls was also reported by Yamazaki et al. Estrogen has biphasic effects on bone growth; low doses accelerate the growth spurt in early puberty, while high doses lead to epiphyseal fusion. Significantly higher levels of serum estradiol in girls than in boys during childhood might result in earlier closure of synchondroses in girls.

Sex-related differences in the size of the atlas were also observed in this study. The outer, inner, and spinal canal diameters increased during 10-15 years of age in both sexes, although an earlier peak was observed in girls than in boys. The occurrence of peak diameters in our study was 3-6 years later than those reported by Rao et al., who investigated 54 American children. It is unclear whether the discrepancy between our findings and those of Rao et al. is due to racial differences, or different sample sizes. In this study, all three diameters in boys were larger than those in girls. Larger sizes of the lumbar and cervical vertebral bodies, the canal area of the cervical spine, and the foramen magnum in boys than in girls, have also been previously reported. Higher levels of androgen and growth hormone-insulin-like growth factor-I axis in boys than in girls may play a key role in sex-related differences between the duration and the size of radial bone growth. However, details remain unclear. Normative data for growth size of the atlas could help to distinguish congenital cervical anomalies or spinal tumors.

There are only two reports on normal variants of ossification patterns evaluated by CT images. Regarding the anterior ossification variants, excluding those synchondroses already closed or those that were not visible yet, a single ossification center was observed in 73%, and two or more
ossification centers were observed in 27% of American children. In Swiss children, a single ossification center was observed in 66%, and two or more ossification centers were observed in 34% of subjects. In our study, a higher number of subjects (81.7%) demonstrated single ossification centers than those in previous papers. Regarding the posterior arch, more than 90% subjects in previous studies and in our study had no ossification center, and less than 10% had variants including posterior midline ossifications or paramedian cleft. Variants of morphology of ossification centers in anterior arches were less in Japanese than in American or European subjects. The prevalence of racially homogeneous populations in Japan might explain this difference. However, a direct comparison among different races with respect to the variants of ossification centers is warranted.

We acknowledge several limitations in this study. First, as mentioned earlier, the measurements of the diameters of the atlas and spinal canal space were available only in limited numbers. This could have resulted in possible subject selection bias. Nevertheless, we believe the use of more than 273 subjects for analyzing morphometric measurements strengthens the reliability of our findings. Second, aspects of subjects’ physical status, including body weight, height, and skeletal maturation index value, were not considered in this study. Including data of physical status could have added more detailed information for the morphometric analysis for the growth of the atlas. Third, our results may not apply to children world-wide because our subjects were limited to Japanese. As mentioned earlier, racial differences in skeletal maturation should be taken into consideration when applying our results to the general population. Information for skeletal age judged by Greulich-Pyle standards would help to indirectly compare our results with those of American or European children. Fourth, we used a cross-sectional, retrospective design, so we could not examine the actual time-dependent morphological changes of the ossification centers.
Conclusion

There were distinct sex-related differences in the age at anterior synchondroses closure and the outer, inner, and spinal canal widths of the atlas in Japanese children. Variants for anterior ossification centers were more frequent than those for posterior ossification centers. Knowledge of the timing of synchondroses closure, normative data of the size of the atlas, and variants of ossification centers could differentiate fractures from synchondroses and help to distinguish congenital anomalies of the upper cervical spine in childhood.
References


20. Yamazaki A, Mason DE, Caro PA. Age of closure of the neurocentral cartilage in the thoracic


Figure legends

Fig. 1

An axial CT image demonstrating two lateral ossification centers and an anterior ossification center of the atlas in a 1-year-old boy and the measured parameters. The thick white arrows indicate neurocentralsynchondroses and the thin white arrow indicates posterior synchondrosis. Distance A-E indicates outer anteroposterior diameters, distance B-D indicates inner anteroposterior diameters, and distance C-D indicates spinal canal anteroposterior diameters.
Fig. 2

Distributions of the numbers of subjects available in each age category.
Fig. 3

(A) Closure rates of anterior neurocentral synchondroses. The boxes indicate the percentage of subjects out of the total group in each age category. (B) Closure rates of posterior synchondrosis. The boxes indicate the percentage of subjects out of the total group in each age category.
Fig. 4

Mean outer and inner anteroposterior diameters in each three-year age category in boys and girls.
Fig. 5

Mean anteroposterior spinal canal diameters in each three-year age category in boys and girls.
Fig. 6

Axial CT images demonstrating variations of ossification centers in anterior and posterior arches. (A) A 2-year-old girl with two anterior ossification centers. (B) A 2-year-old girl with four anterior ossification centers. (C) A 1-year-old boy with one posterior ossification center.
Table 1. Comparison of bony and spinal canal widths between the sexes.

**Outer anteroposterior diameters**

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**Inner anteroposterior diameters**

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Anteroposterior spinal canal diameters

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