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ORIGINAL ARTICLE

MDCT evaluation of sternal development

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Abstract

Background and purpose Sternal ossification starts in utero, and continues throughout puberty in various patterns. In this study, our objective was to evaluate the correlation of ossification with age and to determine whether age can be predicted.

Materials and methods Individuals younger than 30 years old without congenital anomalies, chronic disease, and history of long-term chemotherapy who had chest CT imaging with a slice thickness < 3 mm were retrospectively reviewed. Data of ossification centers, horizontal and vertical fusion were collected. Spearman correlation test and ROC analysis were performed to correlate age with fusion. Kruskal–Wallis test was used to perform gender wise comparisons. Sensitivity, specificity, positive predictive value and negative predictive value of cut-off points, estimated according to ROC analysis, were calculated.

Results Segmented ossification centers were more common in males, with significant difference in third and fourth mesosternal ossification centers ($p < 0.05$). Females had more vertical fusion at each level ($p < 0.05$). Spearman correlation test showed significant correlation between age and horizontal and vertical fusion for both genders. ROC analysis was performed and cut-off values were estimated. Sensitivity was very high (84.6–100%) but specificity was low (43.3–79.9%) for horizontal fusion. Sensitivity of vertical fusion (64.8–100%) was similar but specificity was higher (74.7–100%).

Conclusions Horizontal and vertical fusions of sternal ossification centers correlate with age significantly. Vertical fusion might be a better indicator of age with higher sensitivity and specificity, while horizontal fusion has lower accuracy. Large-scale studies should be conducted to confirm our results.

Keywords MDCT · Sternal development · Age

Introduction

Sternum is a flat bone which has three parts: manubrium, body and xyphoid. It is derived from a pair of mesenchymal bars, lying on each side at the midline anterior thoracic wall. Mesenchymal bars can be identified at sixth week in utero [5]. These bars unite, chondrify and then ossify, respectively, and form the sternum. After chondrification, sternum ossifies, usually from six ossification centers (OCs): one forms the manubrium, one forms the xyphoid, and the others form mesosternum (Fig. 1). These OCs may consist of one or more segments. If more than one segment is present, these segments fuse during growth, so ossification patterns cannot be identified in adulthood [2]. Irregular fusion of these segments may lead to formation of sternal foramina or fissure. Also OCs unite with each other vertically, which usually starts in puberty, and develops caudocranially, excluding the xyphoid [11].

It is shown that there is a correlation between age and area of ossification center [16]. Our objective was to investigate the relationship of fusion, age and sex and determine whether age can be estimated from the developing sternum.

Materials and methods

Patient selection

The study was approved by the Institutional Ethics Board and adhered to the tenets of the Declaration of Helsinki. Informed consent was not obtained as the study was retrospective and images were anonymized. Patients younger

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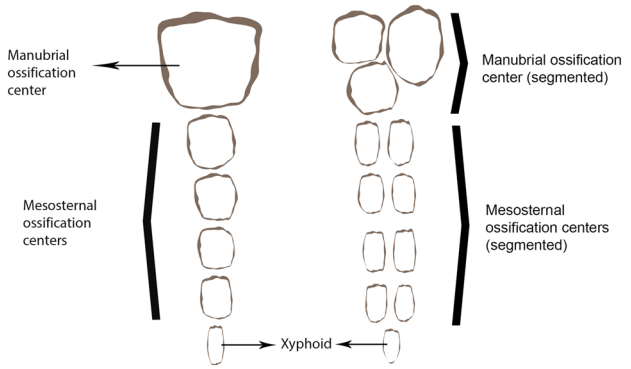

Fig. 1 Sternum illustration. Sternum develops form six ossification centers (OC), one forms manubrium, four centers form the mesosternum and the last forms the xyphoid. These centers may consist of several segments, which unite eventually

than 30 years old who had chest CT imaging between June 2012 and December 2013 were reviewed. If a subject had repeat scans, initial scan was evaluated. To design a normal population, medical records of each patient were studied in detail, and patients with congenital anomalies, chronic diseases such as chronic kidney disease, metabolic and genetic problems or endocrinologic abnormalities, history of long term chemotherapy (more than 6 months) and sternal masses were excluded, as there are reports suggesting a relation between congenital heart diseases and sternal ossification abnormalities [1, 10, 18, 19], and reports indicating that chemotherapy may cause growth retardation or impairment of bony structure [3, 6, 9, 13].

Assessment and evaluation of images

CT images (with or without contrast medium) were obtained with 2-sliced (Emotion Duo, Siemens), 16-sliced (SOMATOM Sensation 16, Siemens AG; Light Speed, GE Healthcare) or 64-sliced (SOMATOM Definition, Siemens AG) CTs, with a slice thickness of ≤ 3 mm. Coronal and sagittal maximum intensity projections (MIP), curved planar reconstruction (CPR) and multiplanar reconstructions (MPR) were made and data including the features of OCs and their relationship with each other were collected.

Fusion is defined by calcification between segments and OCs. It is evaluated both vertically and horizontally. Horizontal fusion corresponds to the fusion between segments of the same ossification center, whereas vertical fusion corresponds to the union of different OCs (Fig. 2). OCs are numbered according to the costochondral junctions. Second costochondral junction lies between manubrium and the first mesosternal (Ms) OC, third one separates the first and second Ms OCs, fourth one separates the second and third Ms OCs, and fifth one separates the third and fourth Ms OCs. If sixth and seventh costochondral junctions are attached to the lateral border of the sternum, it confirms that the fourth Ms OC is present. However, if they unite with the inferior border, the fourth Ms OC is accepted to be absent.

Development and fusion of xyphoid process is not evaluated as it is known to be formed during puberty and fusion occurs during adulthood [17].

Statistical analysis

Statistical analysis was performed using the SPSS software version 24. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) to determine whether they are normally distributed. Kruskal–Wallis test was done to compare the distribution of both genders. Spearman correlation test was performed for evaluating the relationship of age with horizontal and vertical fusion. ROC analysis was performed for each level of horizontal and vertical fusion and cut-off values are calculated. Sensitivity, specificity, positive and negative predictive values are calculated using the cut-off values.

Results

Five hundred and sixty-one people with chest CT images were collected; two hundred and sixty-six people (one hundred and fifty-seven males and a hundred and nine females) conforming the aforementioned criteria were included in the study. Kruskal–Wallis test revealed no significant difference of age distribution between genders.

Presence of ossification centers

The manubrial, first and second Ms OCs were present in all individuals. Three individuals did not have third Ms OC; a 5-year-old female, a 10-year-old and an 11-year-old male. Fourth Ms OC was not found in 82 people (30.8%); 40 males (25.5%) and 42 females (38.5%). Fourth Ms OC was more common in males ($p < 0.05$).

Horizontal fusion

Manubrial OCs usually developed from one segment. Thirteen males (8.3%) and five females (4.6%) had more than one segment; composed of two ($n = 11$), three ($n = 6$) or four ($n = 1$) segments. Segmented form was not encountered in males older than 9 and females older than 3 years old. Segmented first mesosternal OC was rare. Two males and one female had segments, consisting of two pieces. Males were 2 and 13 years old, while the female was 6 years old. Twenty-three males (14.6%) and nine females (8.3%) had segmented second Ms OC; thirty-one

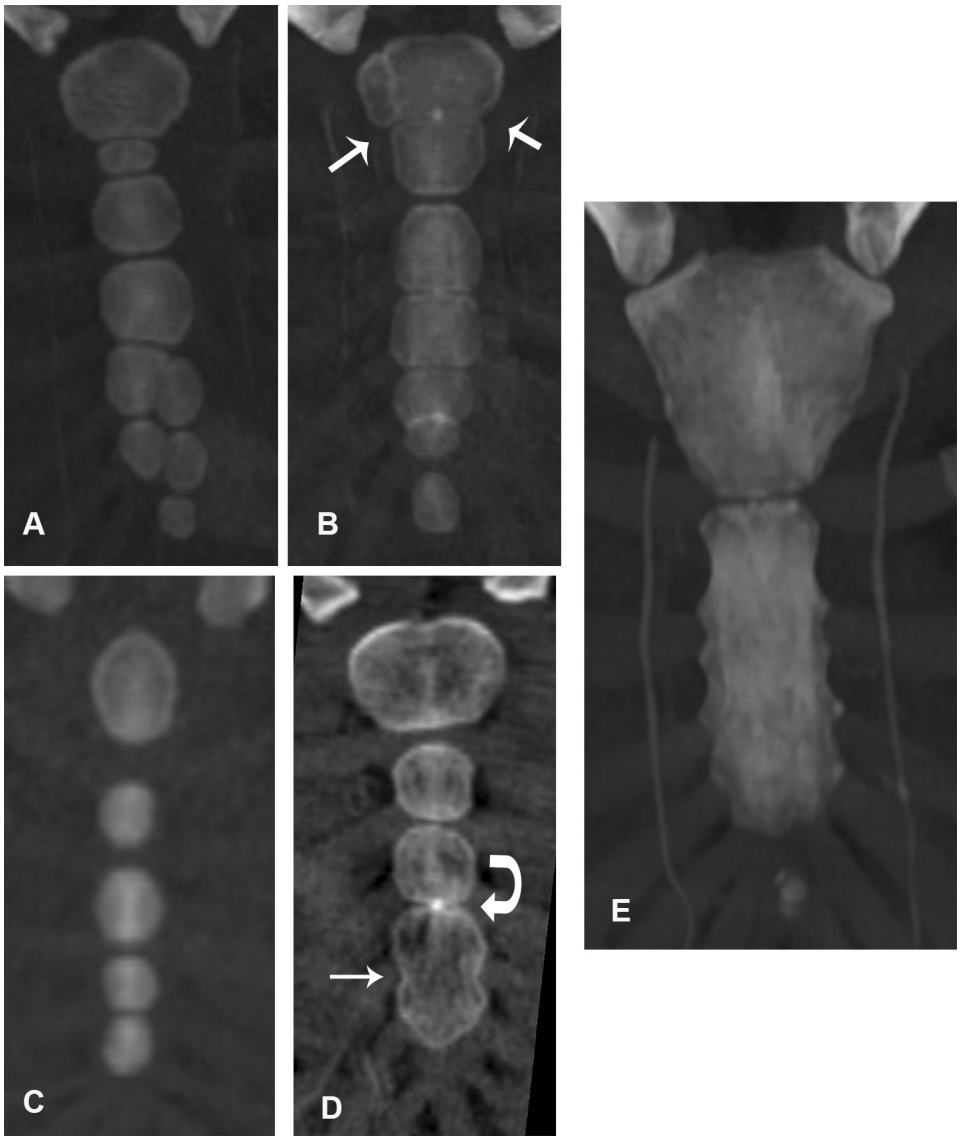

Fig. 2 In **a** an infant's sternum is shown, with six ossification centers, manubrial ossification center is composed of two segments, first and second mesosternal OCs and the last OC are nonsegmented, third and fourth mesosternal OCs are composed of two segments. **b** Demonstrates horizontal fusion in a 3-year-old sternum that shows merging of the segments of manubrial OC (arrows). **c** Displays an infant sternum which develops from five nonsegmented ossification centers. **d** Displays vertical fusion in another 3-year-old sternum, which reveals that the third and fourth mesosternal ossification centers are united (arrow), the second and the third ossification centers has begun to fuse. **e** Represents the adult form of the sternum

individuals had two segments and one female had three segments. More than one segment was not detected in males older than 13 years and females older than 10 years. Forty six males (29.7%) had segmented third Ms OC; one of them consisted of four segments, three males had three segments, and the others were composed of two segments. Fifteen females had segmented third MS OC, which were composed of two segments. Segmented third Ms OC was not detected in males older than 13, and females older than 10 years. Twenty-three males (19.5%) had segmented fourth Ms OC; one consisted of three, and the others consisted of two segments. Three females had segmented fourth Ms OC, composed of two segments. Segmented forms were not detected in males older than 19 and females older than 7 years old. Segmented OCs were more common in males than females at each level (Table 1). Chi-square test revealed that the frequency of segmented third and the fourth Ms OCs differed significantly between two genders ($p < 0.05$). Sensitivity, specificity, positive predictive and negative predictive values based on cut-off values obtained from ROC analysis are summarized in Table 2.

Table 1 Ratio of segmented OC

	Male	Female	
Manubrium	8.3	4.6	
First Ms OC	1.2	0.9	
Second Ms OC	14.6	8.3	
Third Ms OC[a]	29.7	13.9	$p < 0.05$
Fourth Ms OC[a]	19.5	4.5	$p < 0.05$

Ratio of segmented OCs in percentiles

Ms OC mesosternal ossification center

[a]Absent OCs were not included in the calculation

Table 2 Spearman correlation and ROC analysis of horizontal fusion

	r	ROC analysis					
		AUC	Cut-off value (age)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Males							
Manubrium	0.322[a]	0.837	3	79.9	84.6	98.3	27.5
Second MS OC	0.327[a]	0.767	13	43.3	100	100	23.2
Third MS OC	0.465[a]	0.794	13	53.2	100	100	47.4
Fourth MS OC	0.338[a]	0.746	13	57.9	95.7	98.2	35.5
Females							
Manubrium	0.287[a]	0.895	5	73.1	100	100	15.1
Second MS OC	0.317[a]	0.832	10	59	100	100	18
Third MS OC	0.460[a]	0.884	8	69.9	100	100	34.9
Fourth MS OC	0.265[a]	0.870	7	71.9	100	100	14.3

Sensitivity, specificity, positive predictive and negative predictive values were calculated depending on ROC analysis

r Spearman's rho, *AUC* area under curve

[a]Correlation is significant at the 0.01 level (two-tailed)

Table 3 Ratio of vertical fusion among genders given in percentiles

	Male	Female	
Manubrio-mesosternal fusion	7.6	19.3	$p < 0.05$
Fusion of first–second Ms OCs	47.8	69.7	$p < 0.001$
Fusion of second–third Ms OCs[a]	60	79.8	$p < 0.001$
Fusion of third–fourth Ms OCs[a]	81.3	92.5	$p < 0.001$

Ms OC mesosternal ossification center

[a]Absent OCs were not included in the calculation

Segmented first Ms OC was so rare that it was not included in these calculations.

Vertical fusion

Fusion of manubrial and first Ms OC, which is actually the ossification of manubriosternal junction, was not encountered in males younger than 10 years of age, whereas three females (6%) younger than 10-year-olds had fusion. Overall, twelve males (7.6%) and twenty-one females (19.3%) showed fusion. Seventy-six females (69.7%) and seventy-five males (47.8%) had fusion between first and second Ms OCs. Females and males always showed fusion after 11 and 17 years, respectively. Eighty-seven females (79.8%) and ninety-three males (60%) had fusion between second and third Ms OCs. The eldest individuals without fusion were a 17-year-old male and an 8-year-old female. Sixty-two females (92.5%) and ninety-six males (81.3%) had fusion between third and fourth Ms OCs. The maximum age without fusion was 12 in males and 3 in females. Fusion ratios were significantly higher in females (Table 3). Spearman correlation test showed significant correlation between age and vertical fusion (Table 4). All females older than 10 years of age, had fusion between second and third Ms OCs and third and fourth Ms OCs. Eldest male without fusion of first and second Ms OC was 19, second and third Ms OC was 17 and third and fourth Ms OC was 12 years old. Eldest females were 11, 8 and 3 years old, respectively. Sensitivity, specificity, positive predictive and negative predictive values were calculated depending on the cut-off values on ROC analysis, shown in Table 4. There was no statistically significant difference in cut-off values between males and females.

Discussion

Sternum can be recognized in the 6th week of in utero as two parallel mesenchymal bands, which fuse ventrolaterally and craniocaudally beginning at the 7th week. Sternum usually ossifies from six centers, which develop between the joint surfaces of costal cartilages. Ossification centers may be formed from several segments and it is reported that the ideal time to detect this pattern is last month in utero to 4 years [2]. With aging, the segments of ossifications centers fuse with each other and therefore ossification patterns cannot be recognized in the adulthood.

Manubrial, first and second Ms OCs were present in all of the individuals in our study, third Ms OC was absent only in three subjects, but fourth Ms OC was absent in 30.8% of the population which is similar to the previous studies [8]. It was also reported in previous studies that fourth Ms OC is found less frequently in females, similar to our results [4]. The more frequent occurrence of this

Table 4 Spearman correlation and ROC analysis of vertical fusion

	r	ROC analysis					
		AUC	Cut-off value (age)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Males							
Manubrio-mesosternal fusion	0.335[a]	0.864	12	100	64.8	19	100
Fusion of first and second MS OCs	0.746[a]	0.931	10	85.3	90.2	88.9	87.1
Fusion of second and third MS OCs	0.729[a]	0.929	9	79.6	95.2	96.1	75.6
Fusion of third and fourth MS OCs	0.553[a]	0.910	7	77.1	90.9	97.4	47.6
Females							
Manubrio-mesosternal fusion	0.334[a]	0.745	16	76.2	69.3	37.2	92.4
Fusion of first and second MS OCs	0.678[a]	0.926	6	89.5	84.8	93.2	77.8
Fusion of second and third MS OCs	0.578[a]	0.921	8	74.7	100	100	48.8
Fusion of third and fourth MS OCs	0.447[a]	0.990	3	95.2	100	100	62.5

Sensitivity, specificity, positive predictive value and negative predictive values were calculated depending on the cut-off value estimated by ROC analysis

r Spearman's rho, *AUC* area under curve

[a]Correlation is significant at the 0.01 level (two-tailed)

center in males may be one of the explanations for the difference between the sternal lengths of males and females. In our study, it was revealed that there are adults (older than 18 years old) without fourth OC, but it must be kept in mind that after the completion of mesosternal fusion, evaluating the presence of fourth Ms OC was difficult. Considering this difficulty and high ratio of its non-appearance, we think that age estimation based on or including the fourth OC may cause inaccurate results.

Our study showed horizontal fusion correlates with age (Table 2). Manubrial OCs were not segmented after 10 years, and Ms OCs were not segmented after 20 years. Our study revealed that females tend to have segmented ossification centers less frequently than males as it was implied previously [4] and there was significant difference in third and fourth Ms OCs between genders. Females also tend to complete the horizontal fusion earlier than males in our study. All females older than 10 years and males older than 13 years had horizontal fusion in our population. Sensitivity was low for both genders, which shows us that individuals younger than our cut-off ages also tend to have one segment. However, this is highly affected by nonsegmented ossification pattern that many individuals had nonsegmented form of ossification centers from the beginning. However, when we encountered an individual with segmented form, we can interpret that the individual is younger than our cut-off values with high specificity. High positive predictive values (PPV) indicate that individuals older than cut-off ages had vertical fusion completed. This results suggests that when a segmented OC is encountered, we can say that the person is younger than our cut-off values with high specificity, but when a nonsegmented form is present, we cannot interpret age accurately by depending on horizontal fusion.

Vertical fusion significantly correlates with age, but shows variability as it can be even present in the first year of life. Fusion of second and third, third and fourth Ms OCs was present in all females over 10 years old, and eldest males without fusion of second and third, third and fourth Ms OCs were 17 and 12 years old, respectively. These observations are consistent with previous results which revealed that fusion of these levels were fully complete in 16–20 years of age [4]. Vertical fusion was significantly more frequent in females, suggesting that it is developing earlier in females. But no difference is found between the cut-off values estimated by ROC analysis. AUC of ROC curves for both genders were high; sensitivity and specificity were higher than horizontal fusion (Table 4), suggesting that vertical fusion might be a better indicator. PPV was very low for manubriosternal junction in males, indicating that most of the males older than the cut-off ages did not have fusion in our population. Sensitivity and negative predictive values (NPV) were high, as there was no male younger than cut-off age with fusion in manubriosternal junction. Specificity and PPVs of mesosternal fusion were high, 100% for fusion of second and third Ms OCs, third and fourth Ms OCs in females, cause there was no female older than cut-off ages without fusion. NPVs were relatively lower though, which suggest that fusion is common under the cut-off ages. Considering these findings, we may predict age with higher accuracy if mesosternal fusion has not developed yet, but when mesosternal fusion is present, we cannot delineate age easily because fusion is also common at younger individuals.

Irregular or disturbed ossification and fusion in the sternum might lead to formation of various sternal variation like isolated single/multiple foramina [12] or a combination of foramina and clefts together [15]. Besides these, pectus excavatum, an anterior chest wall deformity which becomes apparent in two-thirds of the cases during puberty [7] with completion of the ossification and fusion of sternum, might cause cardiopulmonary complications in severe forms. In this regard, sternal variations were not noted in this study as a reflection of the young age of the study population, and exclusion of sternal anomalies such as pectus excavatum due to its risk of complications and accompanying anomalies [7]. On the other hand, xyphoid process has various shapes and configurations, but ossification usually starts in the adulthood and continues throughout life [20]; therefore xyphoid process maturation was not included in this study.

Studies in larger scales, including younger people, should be conducted to confirm our results and to estimate age accurately, and definition of age in months may be helpful for studying in detail. Also fusion is a process, starting in one point and spreading to the surface area. We did not consider the area of fusion and there is no staging system for fusion that has been developed until today. As previous studies revealed a correlation between area of ossification centers with age [14, 16], development of a staging system may help predicting age more accurately.

Conclusion

Sternum develops from a number of OCs with many different patterns. The vertical and horizontal fusions significantly correlate with age. Vertical fusion may be a better indicator of age, but as fusion is commonly seen in younger individuals too; large-scale studies including younger individuals should be conducted.

Author contributions EG: project development, data collection, data analysis, and manuscript writing. EA: data analysis and manuscript editing. OMA: project development and data analysis.

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Compliance with ethical stadards

Conflict of interest The authors declare that they have no conflict of interest.

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