Clinical Study

Quantitative analysis of the closure pattern of the neurocentral junction as related to preexistent rotation in the normal immature spine

Tom P.C. Schlösser, MD\textsuperscript{a}, Koen L. Vincken, PhD\textsuperscript{b}, Hamid Attech, MD\textsuperscript{a}, Hugo J. Kuijf, MSc\textsuperscript{b}, Max A. Viergever, PhD\textsuperscript{b}, Michiel M.A. Janssen, MD, PhD\textsuperscript{a}, René M. Castelein, MD, PhD\textsuperscript{a,*}

\textsuperscript{a}Department of Orthopaedics, University Medical Center Utrecht, G.05.228, P.O. Box 85500, 3508 GA Utrecht, The Netherlands
\textsuperscript{b}Image Sciences Institute, University Medical Center Utrecht, Q.S.459, P.O. Box 85500, 3508 GA Utrecht, The Netherlands

Received 12 December 2011; revised 5 June 2012; accepted 17 November 2012

Abstract

BACKGROUND CONTEXT: The normal spine is not a symmetrical structure. In recent studies, we demonstrated the presence of an axial rotational pattern that is similar to what is seen in the most prevalent curve patterns in idiopathic scoliosis at different ages. This suggests that if the spine starts to decompensate into scoliosis, it follows this preexistent rotational pattern. In scoliosis, the neurocentral junctions (NCJs) close asymmetrically, which leads to a different pedicle morphology in the convexity and concavity of the curve. The present study aimed to establish at which age the NCJ closes in different regions of the spine, whether it closes asymmetrically in the nonscoliotic spine as well and whether the closure pattern is related to the earlier demonstrated preexistent rotation.

PURPOSE: To evaluate the closure pattern and surface area of the left and right NCJs throughout the normal immature spine in relation to the preexistent spinal rotation at different ages.

STUDY DESIGN: Retrospective cohort study using a systematic, semiautomatic analysis.

PATIENT SAMPLE: Computed tomography (CT) scans of the thorax and abdomen of 199 non-scoliotic children (0–16 years old) were systemically analyzed. CT scans had been obtained for several reasons unrelated to this study, for example, recurrent respiratory infections, malignant disease (not involving the spine), or work up before bone marrow transplantation. Scans were categorized according to the criteria of the Scoliosis Research Society into infantile (0–3 years old), juvenile (4–9 years old), and adolescent (10–16 years old) age cohorts.

OUTCOME MEASURES: Closure, absolute surface area, and the angle between the longitudinal axis of the left and right NCJ and preexistent vertebral rotation at each spinal level.

METHODS: Transverse CT slices were systemically analyzed for closure and asymmetry of the absolute area of 4,992 NCJs from spinal levels T2–L5. The outcome measures were analyzed semiautomatically using custom-made software developed at our institution (ImageXplorer; Image Sciences Institute). Inter- and intraobserver reliabilities were calculated.

RESULTS: For all subjects, the entire thoracic area was available. Complete scans down to L5 of the lumbar spine were available in 43 cases. Closure of the NCJs was first observed in the lumbar spine, then in the high thoracic spine, and finally in the mid- and low thoracic spine. Closure occurred asymmetrically, left-right predominance depended on the age. In the mid- and low thoracic spine, the surface areas of the right NCJs were larger at the infantile age, whereas at the juvenile age the areas of the left NCJs were larger. This corresponded to the spine’s preexistent rotation. Rotation of the high thoracic vertebrae was to the left in all age cohorts. Rotation in the mid- and low thoracic spine was to the left in the infantile cohort but reversed to the right in the juveniles and even more so in the adolescents. The lumbar spine was rotated to the left at the infantile age and not significantly rotated at the juvenile and adolescent ages. Orientation of the NCJs in relation to the preexistent spinal rotation is shown in Figure 1.
to the vertebraes’ longitudinal axis was symmetrical, not dependent on age, and more transverse at the midthoracic levels than at other spinal levels.

**CONCLUSIONS:** This study focuses on the asymmetry and the regional pattern of closure of the NCJs at different ages. It suggests that preexistent rotation of the spine is related to the asymmetrical closure of the NCJs. Whether the asymmetry is the cause of or is caused by the preexistent rotation cannot be derived from this study. © 2013 Elsevier Inc. All rights reserved.

**Keywords:** Neurocentral junction; Normal immature spine; Preexistent vertebral rotation; Curve patterns in idiopathic scoliosis

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**Introduction**

The normal spine is not a symmetrical structure as has been appreciated for a long time [1–4]. More recently, we confirmed the presence of an axial rotational pattern that depends on age [5–7]. This rotational pattern is identical in direction—although less in magnitude—to the rotation that occurs in idiopathic scoliosis in different regions of the spine and at different ages. Apparently, once the spine starts to decompensate into scoliosis, it follows this preexistent rotational pattern.

The neurocentral junctions (NCJs) of the vertebrae connect the pedicles and laminae to the vertebral body bilaterally and allow for growth in the radial direction of the spinal canal. Asymmetric growth and closure of the NCJs occur in the development of pathological rotation of the spine as is known in naturally occurring scoliosis and in experimental scoliosis [1,8,9]. The timing and order at which the NCJs close in the normal, nonscoliotic spine are still under debate [10–16]. Its relation to the axial rotational patterns in the normal spine has not been established to the best of our knowledge. The aim of the present study was to analyze the closure patterns of the NCJs throughout the normal growing spine in relation to the preexistent spinal rotation at different ages.

**Subjects and methods**

Between 2005 and 2011, 755 children of the Dutch population under 16 years of age underwent computed tomography (CT) scanning of their thorax and abdomen for several indications unrelated to this study, for example, recurrent pulmonary infections, immune disorders, or before bone marrow transplantation, at the University Medical Center in Utrecht, The Netherlands. All medical information that has been documented in the electronic patient record, before and after the CT examination, were reviewed for the inclusion and exclusion criteria. A total of 80 children had at least good quality scans of their thoracic region. Frequently, thoracic scans also included levels L1 (n=118) and L2 (n=72). In total, 43 children had undergone CT examination of the abdomen as well and were, thus, available for the evaluation of both their complete thoracic and lumbar spine. All scans were made with a Philips Brilliance 16-P CT-scanner (Philips Medical Systems B.V., Best, The Netherlands). Pixel size varied between 0.25 and 0.50 mm and slice thickness varied between 3 and 5 mm.

The orientation and closure patterns of the NCJs as well as the vertebral axial rotation were evaluated in these 199 children and divided into three age cohorts according to the definition of the Scoliosis Research Society (SRS) [17]. There were 52 (26%) children between the age of 0 and 3 years (infantile), 69 (35%) between 4 and 9 years (juvenile), and 78 (39%) between 10 and 16 years (adolescent).

**CT measurement method**

All measurements were performed semiautomatically using in-house developed software (ImageXplorer; Image Sciences Institute, Utrecht, The Netherlands). Of all vertebrae, the midvertebral transverse slice on which the pedicles were best visible was selected. Measurements were performed at each available spinal level. Two types of measurements were performed:

I. Preexistent vertebral rotation.

II. Closure, absolute surface area, and orientation of the left and right NCJ.

ad I: At each spinal level, segmentation of the vertebra and spinal canal was performed. To evaluate the vertebral rotation at each spinal level, the same measurement method was used as in our previous studies; the intraclass correlation coefficients for inter- and intraobserver reliabilities were 0.96±0.06 and 0.99±0.01 (mean±SD), respectively [5–7,18,19]. With this method, vertebral rotation was defined as the angle between the longitudinal axis of the vertebra and the midline through the thorax in the transverse plane (Fig. 1). After segmentation, the centers of mass (COMs) of the spinal canal and anterior half of the vertebra were automatically calculated. The
longitudinal axis of the vertebra was calculated by a line through the COMs of the spinal canal and anterior half of the vertebra. The midline through the thorax was calculated by a line through the COMs of the canal and the sternum at level T5. Vertebral rotation to the left was defined as negative and to the right as positive [5–7,18,19].

ad II: First, at each spinal level, the left and right NCJs were determined as being open or closed. Neurocentral junction was defined as open when there was a low-density zone on the CT scan between the two regions with high density, similar to the density of the vertebral cortex. Open NCJs were manually segmented, which included partial volume effects; small NCJs consisting of only partial pixels were also segmented. The window level was standardized on bone window setting. A total of 4,992 NCJs, divided over the three age cohorts and 16 spinal levels, could be analyzed. Age of closing of the NCJ was, in line with Rajwani et al. [15,20,21], defined as the age at which 50% of the NCJs were closed at each spinal level. After segmentation of all open NCJs (Fig. 2, Left), absolute surface area data of all NCJs in square millimeters were determined automatically. Next, two best-fit lines were drawn through the NCJs at each level (Fig. 2, Right). To investigate the relation between the direction of a vertebra and the orientation of the NCJs, we calculated the angle between the longitudinal axis of the vertebra—as previously defined—and the corresponding NCJ line.

Interrater agreement for binominal data was calculated using Cohen kappa coefficient. Intraclass correlation coefficients for inter- and intraobserver reliabilities, including 95% confidence intervals (CIs), were calculated for continuous data.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA). Repeated measures analysis of variance with Greenhouse-Geisser significance was used to evaluate the differences in continuous data between the age cohorts. Because of the correlation of the data of different spinal levels within a single subject, intersegmental and left/right differences were defined as within factors and age cohort and gender as between factors. For post hoc analyses, a Bonferroni correction was applied. To test the relation between the NCJ asymmetry and rotational direction, Pearson chi-square was used. For all tests, a p value of <.05 was considered to be statistically significant.

Table
Subject characteristics for the infantile (0–3 years old), juvenile (4–9 years old), and adolescent (10–16 years old) cohorts

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Infants 0–3 years old</th>
<th>Juveniles 4–9 years old</th>
<th>Adolescents 10–16 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>52</td>
<td>69</td>
<td>78</td>
</tr>
<tr>
<td>Age in years (SD)</td>
<td>2.1 (1.1)</td>
<td>6.7 (1.6)</td>
<td>13.6 (1.7)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>20 (38)</td>
<td>25 (36)</td>
<td>27 (35)</td>
</tr>
<tr>
<td>Patients who underwent CT-thorax (%)</td>
<td>44 (85)</td>
<td>53 (77)</td>
<td>59 (76)</td>
</tr>
<tr>
<td>Patients who underwent CT-thorax and CT-abdomen (%)</td>
<td>8 (15)</td>
<td>16 (23)</td>
<td>19 (24)</td>
</tr>
<tr>
<td>Scan indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent pulmonary infections (%)</td>
<td>22 (42)</td>
<td>28 (41)</td>
<td>21 (27)</td>
</tr>
<tr>
<td>(Suspected) malignancy</td>
<td>10 (19)</td>
<td>15 (22)</td>
<td>26 (33)</td>
</tr>
<tr>
<td>Trauma</td>
<td>7 (13)</td>
<td>13 (19)</td>
<td>15 (19)</td>
</tr>
<tr>
<td>Immune disorder</td>
<td>5 (10)</td>
<td>7 (10)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>High fever</td>
<td>5 (10)</td>
<td>1 (1)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Postintervention</td>
<td>2 (4)</td>
<td>3 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

SD, standard deviation; CT, computed tomography.
The infantile, juvenile, and adolescent subgroups were created using the classification of the Scoliosis Research Society [17].

Fig. 1. Vertebral rotation—the angle between the longitudinal axis of the vertebra (spinal canal “C”–center of mass of anterior half of the vertebra “V”) and a midline through the thorax (spinal canal “C”–sternum “S”)—was semiautomatically measured on the transverse slices of computed tomography scans of normal children.
Results

NCJ closure

Neurocentral junction closure starts at lumbar levels L1–L3. At an average age of 4 to 5 years, 50% of all the NCJs at these vertebral levels were closed in both boys and girls. Thereafter, closure spreads to higher thoracic and lower lumbar levels, L4–L5, at the age of 6 to 7 years for both genders. Closure finishes in the mid- and low thoracic spine at the age of 6 to 9 years in girls and 7 to 11 years in boys (Fig. 3).

The mean surface area of the NCJs showed comparable results. Repeated measures analysis of variance showed that the surface area of the NCJs was dependent on the age, spinal level, and gender. The mean surface area of NCJs was 7.2 mm² (95% CI: 6.9, 7.3) in infants, 2.6 mm² (2.4, 2.8) in juveniles, and 0.5 mm² (0.5, 0.6) in adolescents (Fig. 4). At the adolescent age, 90% of NCJs were completely closed. The 10% of the NCJs that were determined to still open had a mean surface area of less than 1.0 mm².

As can be expected from the age of closure, the NCJs had a larger surface area at mid- and low thoracic levels as compared with high thoracic and lumbar levels at the same age (p=.009) (Fig. 4). The mean surface area of the NCJs throughout the spine was larger in boys than in girls in all age cohorts (p=.019).

NCJ asymmetry

The surface areas of the left and right NCJs were asymmetrical throughout the spine. In the thoracic spine at the infantile age, the right NCJ was predominantly larger than the left, whereas at the juvenile age, the left NCJ was predominantly larger than the right. Post hoc analysis showed that the differences in the NCJ asymmetry were largest between the infantile and juvenile age cohorts (p=.037) (Fig. 5). At the adolescent age, most levels (90%) were symmetrically closed. No significant differences in NCJ asymmetry were found between the genders at any age.

NCJ orientation

The angle between the longitudinal axis of the vertebra and the NCJs was symmetrical and not dependent on age. The NCJs showed a more horizontal orientation on transverse CT slices at the mid- and low thoracic levels than...
at high thoracic and lumbar levels in all age cohorts (p<.001) (Fig. 6).

Preexistent rotation

Mean vertebral rotation was significantly different between the age cohorts as well (p<.001) (Fig. 7). The spinal column was globally rotated to the left at all spinal levels of infantile children (p≤.05). At the juvenile age, level T3 was rotated to the left (p=.001) and levels T7, T8, and T10 to the right (p≤.035). Other thoracic and lumbar levels were not significantly rotated at the juvenile age. At the adolescent age, levels T3 and T4 were still rotated to the left (p≤.007), levels T6–T12 to the right, (p≤.004) and the spine reverted back to neutral around the thoracolumbar junction.

Furthermore, at the juvenile age, at the levels T4, T6, T7, and T10, there was a significant relation between the larger NCJ (left vs. right) and the direction of the axial rotation (p=.009, p=.004, p=.003, and p=.017, respectively). A larger right NCJ was associated with axial rotation to the left and a larger left NCJ with rotation to the right at these levels. This relation was not statistically significant at the other spinal levels and age cohorts.

Reproducibility

Interrater agreement on the closure of the NCJs was calculated according to Cohen kappa: 0.92±0.06 (mean±standard error). Intraclass correlation coefficients for inter- and intraobserver reliabilities were 0.96 (95% CI: 0.95, 0.96) and 0.99 (95% CI: 0.98, 1.00) for the absolute surface area measurements and 0.85 (95% CI: 0.80, 0.88) and 0.88 (95% CI: 0.85, 0.91) for the angle measurements, respectively.

Discussion

This study provides an in-depth analysis of the NCJ closure patterns related to age, gender, spinal level, left versus right side, and preexistent spinal rotation. Knowledge of the closure patterns of the NCJ during growth at different spinal levels is important for several reasons:

1. The use of transpedicular screw osteosynthesis has become a standard procedure potentially leading to premature growth arrest and spinal canal stenosis if performed at an age when that particular NCJ is still very active [22–25].
2. Closure of the NCJ has been shown to occur asymmetrically in scoliosis [1,3,4]. To determine whether this constitutes pathology, knowledge of closure patterns in the nonscoliotic spine is essential.
The asymmetrical closure of the NCJs in the normal mid- and low thoracic spine is consistent with the preexistent rotational patterns at the infantile, juvenile, and adolescent ages [5–7]. In the mid- and low thoracic spine of infants, the right NCJs were predominantly larger and the spine was rotated to the left, whereas in the mid- and low thoracic spine of juveniles, the left NCJ was predominantly larger and the spine was rotated to the right. The mid- and low thoracic spine of adolescents was rotated to the right, most NCJs were already closed and, therefore, unavailable for analysis.

The patterns of preexistent rotation that we described previously in the normal spine at different ages [5–7] were confirmed by this study. We are not aware of any other study that analyzed the asymmetry of the NCJ in relation to spinal rotation throughout the spine in such a semi-automated, systematic manner. Taylor [10] reported asymmetry of the NCJs in a cadaver study of normal, infantile, and juvenile spines based on observations only. More recently, Zhang et al. [16] did not observe asymmetry in the length and width of the NCJs of 34 pediatric patients without spinal deformity.

Age of closure of the NCJ appeared to be dependant on the spinal level. In the literature, the age and sequence of closure of the NCJs has been discussed in a number of studies [10–16]. Different study designs have been used, which might account for seemingly conflicting results. Rajwani et al. [15,20,21] studied the closure of the NCJs in the thoracic spine in the sagittal plane with magnetic resonance imaging (MRI). In our study, an identical definition for the age of closure was used as in the studies of Rajwani et al.: the age at which 50% of the NCJs are closed. They reported that the closure of the NCJs in the thoracic and lumbar spine takes place between 10 and 15 years of age [15]. In our study, closure of the NCJs was observed at a much earlier age, between 4 and 9 years, which may be accounted for by the differences between the CT and MRI in analyzing cartilaginous structures.

Additionally, this study demonstrated that the spinal levels with larger NCJs close at a later age than the levels with smaller ones. Thus, surface area may be considered a measure of the remaining epiphyseal activity, which suggests that larger NCJs will continue to grow longer than the smaller ones. The mean NCJ surface areas in our study were larger in boys than in girls, which may indicate the later closure in boys than in girls in accordance with their later skeletal maturity.

Zhang et al. [16] concluded that NCJ development is “age- and vertebral level-dependant.” In our study, the same sequence of spinal regions with closing NCJs were observed as reported by Vital et al. [11] and Zhang et al. [16] earlier: the normal sequence of ossification of the NCJ starts at the lumbar levels, followed by high thoracic levels. The ossification of the NCJs in the mid- and low thoracic spine occurred last in these studies. However, Rajwani et al. reported contrasting results. They showed that high thoracic levels close later than the mid- and low thoracic spine [15]. The major differences of the age and sequence of closure of the NCJs might—at least partly—be explained by several differences in study methods.

Firstly, for the epiphyseal plates in the peripheral skeleton, it has been reported that closure spreads in specific directions. For example, the ossification of the epiphyseal plate of the distal tibia expands slowly from anteromedial to posterolateral [30]. Rajwani et al. [15] and Zhang et al. [16] observed in MRI and cadaver studies, respectively, that the ossification of the NCJs starts in the middle of the NCJ and then expands into the superior and inferior parts of the growth plate. In the present study, CT images of the transverse plane were used. It was repeatedly observed that an NCJ was determined as closed on the selected slice, whereas more cranially or caudally the NCJs were still open. To evaluate both vertebral rotation and NCJ closure, we performed analyses on the transverse, midvertebral slices in which the pedicles were best visible. From the first signs of ossification of the growth plates, it might take months to years before the whole epiphyseal plate is closed [30]. Our results represent the age of closure of the NCJs at a midpedicular level and might, therefore, differ from the results of the studies performed in the sagittal plane.

Secondly, the other investigators used MRIs in the sagittal plane or cadaver specimens of Eskimos [10,11,15, 16,20,21,31]. In addition to the plane of analysis, the radiological technique may explain the variability in the reported age of closure. Recent MRI studies showed later age of closure than the CT and cadaver studies [14,15,20,31]. In epiphyseal trauma it is well known that an MRI provides additional information as compared with CT by imaging of the phases before the growth plate closure [32].
Thirdly, racial differences might explain the differences in the literature. Interracial differences in the age of closure of epiphyseal plates have been reported by Crowder and Austin [33] and Gilsanz et al. [34]. They showed that complete ossification of the epiphyseal plates occurs at an earlier age in Mexican-American and African males than in European-American males. Zhang et al. [16] reported the age of closure of the NCJs in 34 Eskimo skeletons, Rajwani et al. [15] in a Canadian population, and our study was performed in a Dutch population of pediatric patients. This variability of race within the study populations might partly explain the differences in the age of closure.

This study does not answer the question whether NCJ asymmetry causes the spinal rotation or is a consequence of a rotation that is caused by other factors. From the peripheral skeleton, it is known that growth plates may unilaterally lead to a discrepancy in pedicle length, progressive rotation, and possibly scoliosis similar to what was demonstrated in the experimental scoliosis by several investigators [8,9,22–25]. In this study, the larger NCJ was related to the direction of the axial rotation at thoracic spinal levels at the juvenile age. These results are consistent with the studies reporting NCJ asymmetry in scoliosis patients. Vital et al. [11] showed that asymmetry of the NCJs in a scoliotic population results in lengthening of the pedicle on the concave side, as was also demonstrated by Nicoladoni [1] and Taylor [10] at an earlier stage. If NCJ asymmetry is its cause, some still unknown mechanism must influence the neurocentral epiphyseal activity at the different ages.

On the other hand, Hueter-Volkman law implies accelerated closure of the epiphysis under compression and delayed closure under distraction [35,36]. Therefore, the changes in the preexistent rotation and NCJ asymmetry in the immature spine might be caused by another mechanism. During development of the child, the spine is subject to changes in mechanical load by motor development and physical growth (stature, weight, and shift in body proportions). In this study, no differences in axial rotation of the vertebrae between children of 0 to 18 months old (which are generally not able to stand and walk alone [37]) and 18 months to 3 years old (which are generally able to stand and walk alone) were observed, retrospectively. We previously showed that preexistent rotation is related to organ anatomy [19], and, therefore, the described changes in the NCJ asymmetry could very well be a passive phenomenon.

**Conclusion**

This study demonstrates that the age of closure of the NCJ depends on the spinal level, the left-right asymmetry depends on age and gender, and the asymmetry corresponds to the earlier demonstrated (and in this study confirmed) rotational patterns that preexist in the normal, nonscoliotic spine. Whether the asymmetry is the cause of or is caused by the preexistent rotation or is the cause of the convexity of the curve in idiopathic scoliosis cannot completely be derived from this study. This requires a longitudinal study setup, focused on the early changes in the three-dimensional morphology of the spine in an immature population at risk for the development of idiopathic scoliosis.

**Acknowledgments**

This study was supported by the Alexandre Suerman MD/PhD program and a Medtronic research grant.

**References**


