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Does the association between abnormal anatomy of the skull base and cerebellar tonsillar position also exist in syndromic craniosynostosis?

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Summary

Purpose: Cerebellar tonsillar herniation (TH) occurs frequently in syndromic craniosynostosis, however the exact pathogenesis is unknown. This study evaluates the association between skull base deformities and TH in syndromic craniosynostosis.

Methods: Retrospective study MRI study comparing syndromic craniosynostosis to controls. Measured parameters included clivus length, skull base angle, Boogards angle, foramen magnum area and cerebellar tonsillar position (TP). The association between skull base parameters and TP was evaluated with linear mixed models, correcting for age and risk factors for TH in craniosynostosis (hydrocephalus, intracranial hypertension, craniocerebral disproportion and lambdoid synostosis).

Results: 282 scans in 145 patients were included, and 146 scans in 146 controls. The clivus was smaller at birth and its growth was retarded in all syndromes. The skull base angle was smaller at birth in Apert and Crouzon, the evolution through time was normal. Boogards angle was smaller at birth in Apert, its evolution was disturbed in Apert and Saethre-Chotzen. The foramen magnum was smaller at birth in Crouzon and Saethre-Chotzen, its growth was disturbed in Apert, Crouzon and Saethre-Chotzen. TP was higher at birth in Apert, but lowered faster. In Crouzon, TP was lower at birth and throughout life. A smaller clivus and larger foramen magnum were associated with a lower TP in controls (p<0.001, p=0.007), in Crouzon this applied to only foramen magnum size (p=0.004).

Conclusion: The skull base and its growth are significantly different in syndromic craniosynostosis compared to controls. However, only foramen magnum area is associated with TP in Crouzon syndrome.

Keywords: tonsillar herniation, craniosynostosis, skull base, Chiari-I malformation
1. Introduction

Syndromic craniosynostosis arises in 0.9 per 10,000 live births (1, 2). Several brain anomalies have been described in syndromic craniosynostosis, including tonsillar herniation (TH)/Chiari I malformation (CM-I) (3-7). Factors influencing the development of TH in these patients include craniocerebral disproportion, venous hypertension, hydrocephalus and lambdoid suture synostosis (3-11). However, the exact pathogenesis remains unclear, and TH/CM-I is frequently asymptomatic in these patients (4, 5).

Previous studies in subjects with conditions other than craniosynostosis, showed that patients with an altered shape of the posterior fossa are more prone to develop a CM-I (12-14). Likewise, measures such as clivus length, foramen magnum size, skull base angle and Boogards angle have been significantly associated with cerebellar tonsillar position (TP) (12-14). To our knowledge, the association between these measures and cerebellar TP has not been studied in syndromic craniosynostosis before. In syndromic craniosynostosis, the skull base is often deformed because of the underlying genetic mutation (15-20). Similarly, the foramen magnum is smaller (21), and the sphenoid-occipital synchondrosis closes earlier in a substantial part of the patients (17, 19). These facts raise the question whether the association between skull base parameters and cerebellar TP also exists in syndromic craniosynostosis.

TH is an important clinical problem in syndromic craniosynostosis. Knowing its origin may help to prevent TH and its consequences such as syringomyelia and cerebrospinal fluid outflow obstruction. Generally prevention of TH is aimed at addressing raised intracranial pressure. If skull deformity would play an important role in the development of TH, this could influence treatment choices. Therefore, the objectives of this study were: 1) to determine the extent of the skull base deformation in syndromic craniosynostosis, by assessing skull base measures that are known to be related to TH, 2) to evaluate the association between these deformations and the cerebellar TP.

2. Materials/patients and methods
This study was conducted at the Dutch Craniofacial Center (Erasmus MC Sophia Childrens Hospital, Rotterdam, the Netherlands). It was approved by the IRB (MEC 2016-312), patient consent was not necessary due to the retrospective nature of the study. All patients with genetically confirmed syndromic craniosynostosis (Apert, Crouzon-Pfeiffer, Muenke and Saethre-Chotzen syndrome) who underwent MRI scanning in our treatment center between 2004 and 2017, were included in this study. In 2006, routine MR imaging studies pre-operatively and at the age of 4 years were added to our treatment protocol. Additionally, patients underwent MR imaging studies when indicated (i.e. when intracranial hypertension is suspected).

Cranial vault expansion is performed in the first year of life in all syndromic craniosynostosis patients. Apert and Crouzon patients undergo occipital expansion without distraction osteogenesis as the first intervention, anticipating on a fronto facial correction later on in life. Patients who present with severe exorbitism as a result of midface hypoplasia in the first year of life, undergo monobloc surgery with distraction osteogenesis. In Saethre-Chotzen and Muenke syndrome, fronto-supraorbital advancement without distraction osteogenesis is performed.

Atlanto-occipital decompression is performed in patients with a symptomatic Chiari-I malformation/syringomyelia. In this study, MR imaging studies performed after atlanto-occipital decompression were excluded, since this procedure alters the configuration of the craniocervical junction.

2.1 Measures

All measurements were performed on MR imaging studies, which were acquired on a 1.5T scanner (GE Healthcare, MR Signa Excite HD, Little Chalfont, UK). A 3D reformatting platform was used to align scans in all planes (AquariusNET; TeraRecon, Inc., Melbourne, Australia). Measurements included clivus length, skull base angle, Boogards angle, foramen magnum area and cerebellar TP .

See figure 1 for examples.

2.1.1 Clivus length, skull base angle, Boogards angle and foramen magnum area

The clivus length, skull base angle and Boogards angle were measured on midsagittal slices. For
clivus length (mm), a line was drawn along the posterior border of the clivus, from the basion to the
tip of the dorsum sellae. (13) Skull base angle (degrees) was defined as the angle between this line and
the line along the floor of the anterior cranial fossa. (22) Boogards angle (degrees) was defined as the
angle between the line across the posterior border of the clivus and a line from the basion to
opisthion. (22, 23) The foramen magnum area (mm²) was measured on axial planes, at the level
between the basion and opisthion.

2.1.2 Tonsillar position

The position of the lowest tonsil with respect to the foramen magnum was measured on midsagittal and
adjacent slices. The foramen magnum was defined by the line between the basion and opisthion. A
line perpendicular to the foramen magnum line was drawn to the tip of the cerebellar tonsils. A
positive position corresponded with tonsillar herniation, whereas a negative measurement indicated a
more rostral position of the cerebellar tonsil. (24) TP was analyzed as a continuous variable.

2.1.3 Correction for factors associated with cerebellar tonsillar position

Progressive ventriculomegaly (i.e. hydrocephalus), intracranial hypertension (ICH), craniocerebral
disproportion, and lambdoid synostosis are known to be correlated to cerebellar tonsillar herniation (3,
5, 8, 25, 26). Therefore, we corrected for these factors in our analysis.

2.1.3.1 Progressive ventriculomegaly

The size of the lateral ventricles was evaluated on axial planes of MRI scans, which were aligned in a
3D reformatting program as described above. The frontal occipital horn ratio (FOHR) was calculated,
the lateral ventricles were considered enlarged when the FOHR was > 0.40 (+ 1SD above the mean
for healthy children). Progressive ventriculomegaly was scored as present when ventricles were
progressively enlarged on ≥ 2 consecutive MRI or CT scans.

2.1.3.2 Papilledema, OFC curve deflection, lambdoid synostosis

A medical chart review was performed to check for (a history of) papilledema, which was examined
with fundoscopies. Additionally, the occipito-frontal head circumference (OFC) in SD was extracted
from medical charts. Growth curve deflection was defined as a ≥0.5 SD fall from baseline over 2 years. As OFC reliably predicts intracranial volume in syndromic craniosynostosis (27), OFC curve deflection indicates craniocerebral disproportion. The presence of lambdoid synostosis was reviewed on pre-operative CT scans, usually taken in the first year of life. Lambdoid synostosis flattens the occiput and is associated with the presence of cerebellar tonsillar herniation (3, 5).

2.2 Controls

The control group consisted of children who underwent MRI scanning in 2016 or 2017 for clinical reasons (e.g. cholesteatoma, insult, trauma, headaches), and there was no intracranial pathology on the MRI scan, or during the follow-up. An exception was made in patients with isolated cerebellar tonsillar herniation, as these patients were not excluded. MR images of controls and syndromic craniosynostosis patients were acquired using the identical MRI scanner.

2.3 Interrater reliability

To assess the interrater reliability, the intraclass correlation coefficient (ICC) was calculated for all skull base parameters. The measures were performed by the first and 3rd author, both have > 1 year experience in measuring skull base parameters in children with syndromic craniosynostosis, and were supervised by M.H.G.D., who is an experienced pediatric neuroradiologist.

2.4 Statistical analysis

The analysis was performed using R statistical software (version 3.6.1). To clarify the differences between syndromic craniosynostosis and controls, linear mixed models were developed, correcting for age. One model was developed for each skull base parameter in each syndrome, and thus all syndromes were evaluated separately. Additionally, the association between TP and skull base parameters was evaluated with one linear mixed model correcting for age and the above described factors. The correction was performed by adding these factors to the model as independent variables. A stepwise regression with forward variable selection was not performed to avoid multiple testing and as this would bias the results (28).

3. Results
282 scans in 145 patients were included, and 146 scans in 146 controls, see table 1 for the total prevalence of mild tonsillar herniation/CM-I in our study cohort, and table 2 for the means of the skull base parameters.

3.1 Interrater reliability

The ICC was 0.91 (95% CI 0.62-0.98) for clivus length, 0.89 (95% CI 0.60-0.97) for skull base angle, 0.92 (95% CI 0.70-0.98) for Boogards angle, 0.96 (95% CI 0.80-0.99) for foramen magnum area, and 0.95 (95% CI 0.81-0.99) for cerebellar TP.

3.2 Syndromic craniosynostosis compared to controls

As the growth/migration of the majority of the parameters was logarithmic over time (figure 2), a logarithmic scale was applied to age in all linear mixed models, except for the model with Boogards angle. Moreover, an interaction term between log(age) and syndrome (0 = controls, 1 = syndrome) was entered in the model to evaluate differences in growth between syndromic craniosynostosis and controls. The differences in skull base parameters between the two sexes were examined visually by plotting the data. This was performed for Crouzon syndrome, since the degrees of freedom in the model were sufficient in this syndrome only. No differences were observed.

The clivus length was significantly shorter at birth in all syndromes compared to controls, table 3, figure 3. Moreover, a significant growth retardation of the clivus was found in craniosynostosis, compared to controls (0.30mm growth retardation per 10% increase in age, p<0.001). The skull base angle in newborns with Apert and Crouzon syndrome was significantly smaller compared to controls, whereas the evolution of the angle throughout life was comparable to controls in all syndromes. Boogards angle at birth was significantly smaller in Apert, Saethre-Chotzen and Muenke syndrome, whereas the evolvement through time was significantly different in Apert and Saethre-Chotzen syndrome. The foramen magnum was smaller at birth in Crouzon and Saethre-Chotzen, and remained smaller throughout life. In Apert syndrome, the foramen magnum area at birth was normal, but the growth was disturbed. The TP at birth was significantly lower in Crouzon syndrome compared to controls. In Apert syndrome, the TP at birth was significantly higher, and the
migration of the tonsil was significantly different compared to controls (i.e. the tonsil migrated to a lower position faster), table 3.

### 3.3 Factors associated with tonsillar position

In controls, a larger foramen magnum and a shorter clivus were significantly associated with a higher degree of cerebellar tonsillar herniation. For each increase of 100 mm² in foramen magnum area, the additional tonsillar herniation was 1.1 mm (p<0.001). Moreover, for each 4.5 mm that the clivus was shorter, the TP was also 1 mm lower (p=0.007). The skull base angle and Boogards angle were not significantly associated with the TP (p=0.66 and p=0.76, respectively).

In syndromic craniosynostosis, the patient numbers were adequate to develop a linear mixed model in Crouzon syndrome only. Similar to controls, for each increase of 100 mm² in foramen magnum area, the TP was 1.3 mm lower (p=0.004). Skull base angle, Boogards angle and clivus length were not significantly associated with TP in Crouzon syndrome (p=0.23, p=0.11 and p=0.30, respectively).

### 4. Discussion

Understanding the origin of TH in syndromic craniosynostosis may help to prevent TH and its consequences such as syringomyelia and cerebrospinal fluid outflow obstruction. If skull base deformities would be involved in the development of TH this could influence treatment choices, since prevention of TH is generally focused in addressing ICH. In this study we evaluated the extent of the skull base deformities in syndromic craniosynostosis, and the association between these deformities and the cerebellar TP in Crouzon syndrome. We conclude that although patients with syndromic craniosynostosis have a deformed skull base, only the foramen magnum area is associated with the cerebellar TP in Crouzon syndrome.

Our analysis in controls revealed that a shorter clivus length and larger foramen magnum were associated with a lower TP, as previously reported by others (12, 13, 29). However, we found no association between skull base angle, Boogards angle and TP. An earlier study reporting on the association between skull base angle and TP, found that children with a CM-I have a larger skull base.
angle compared to controls without a CM-I (14). However, the patients in this study had symptomatic Chiari-I malformations, 53% of whom presented with syringomyelia (14). Another study in adults, found that a larger Boogards angle is associated with TH (13). The difference in the results between these studies and ours may be explained by a difference in patient population (13).

The analysis in Crouzon syndrome showed that the foramen magnum area in these children is smaller compared to controls, and the TP is lower. Moreover, a larger foramen magnum was associated with a significantly lower TP. An earlier study suggested that TH might contribute towards widening of the foramen magnum (30). However, due to the nature of the present study, we could not evaluate whether the foramen magnum area is a cause or a consequence of the TP, or whether they represent independent findings. Clivus length, skull base angle and Boogards angle were not associated with TP in our cohort. We therefore conclude that a lower TP is mostly associated with the high prevalence of ICH in Crouzon syndrome, rather than related to the existing skull base deformations (31).

In Saethre-Chotzen syndrome, the clivus length, Boogards angle and foramen magnum area were significantly smaller in comparison with controls. In contrast, the TP was comparable to controls. Although one could argue that the smaller foramen magnum prevents these patients from developing a CM-I, the higher prevalence of TH combined with the smaller foramen magnum in Crouzon syndrome contradicts this hypothesis. We therefore conclude that the skull base has no lowering effect on the TP in Saethre-Chotzen syndrome.

In Muenke syndrome, the TP did not differ significantly from controls, which might be due to the relatively low number of patients. An earlier study found that a higher ratio between volumes of cerebellum and posterior fossa is a predisposing factor for CM-I in craniosynostosis (32). However, patients with Muenke syndrome did not have a higher ratio (32). The prevalence of TH in these patients might be explained by an altered form of the posterior fossa, rather than a smaller volume, as suggested by others (14).
In Apert syndrome, the TP was significantly higher at birth compared to controls, and it lowered faster throughout life. As described in other children (14), the tonsillar position in these patients might be influenced by the disturbed growth of the skull base that we found. The exact interaction of factors remains unknown in these patients.

Limitations of this study included the small sample size in Apert, Saethre-Chotzen and Muenke syndrome, reflecting that these conditions are rare. Consequently, we could not develop multivariate linear mixed models with TP as the outcome, to evaluate the influence of the skull base on TP. An additional limitation included the nature of this study. Because we had MR imaging studies at different time points in all patients, we were only able to describe associations. The consecutive order and causative mechanism of events remains unknown (e.g. do patients have a larger foramen magnum, and tonsillar herniation as a consequence, or as a cause). Last, patients who underwent occipital expansion were included in this study. Although this procedure does not influence the clivus length, skull base angle, Boogards angle and foramen magnum area, it could potentially influence the posterior fossa volume. However, the posterior fossa volume was not associated with cerebellar TP in a previous study, and thus we believe that the influence of including these patients is minimal (32).

5. Conclusion

The skull base and its growth are significantly different in syndromic craniosynostosis compared to controls. All syndromes have a shortened clivus, whereas the skull base angle only differs in Apert and Crouzon, and Boogards angle in Apert, Muenke and Saethre-Chotzen. The foramen magnum area is reduced in Apert, Crouzon and Muenke. In Crouzon syndrome, a larger foramen magnum is associated with a lower tonsillar position. Whether this association is causal remains unknown.
Disclosures and declarations: There is no information to declare regarding sources of funding and financial or non-financial interests. This study was approved by the IRB (MEC 2016-312), patient consent was not necessary due to the retrospective nature of the study.

6. References


7. Figure legends

Fig 1 measured parameters in a patient with syndromic craniosynostosis. Above, left: clivus length. Above, right: skull base angle. Middle, left: Boogards angle, Middle, right: tonsillar position. Below: foramen magnum area.

Fig 2 Raw data plots for skull base measurements and tonsillar position in syndromic craniosynostosis and controls. A: clivus length, B skull base angle, C: Boogards angle, D foramen magnum area, E: tonsillar position.

Fig 3 Mean fitted values of the linear mixed models comparing skull base parameters between syndromic craniosynostosis (blue line) and controls (red line).
### Table 1: Prevalence of tonsillar descent < 5mm and Chiari-I malformations in our study population.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Tonsillar descent &lt;5 mm N (%)</th>
<th>CM-I&lt;sup&gt;1&lt;/sup&gt; N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls</strong></td>
<td>146</td>
<td>19 (13%)</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>

#### Craniosynostosis, patients

- **Apert**
  - 34 patients, 5 (15%) tonsillar descent, 5 (15%) Chiari-I malformation
- **Crouzon/Pfeiffer**
  - 57 patients, 11 (19%) tonsillar descent, 26 (46%) Chiari-I malformation<sup>2</sup>
- **Muenke**
  - 29 patients, 6 (21%) tonsillar descent, 3 (10%) Chiari-I malformation
- **Saethre-Chotzen**
  - 25 patients, 2 (8%) tonsillar descent, 0 (0%) Chiari-I malformation

#### Total

145 patients

<sup>1</sup> Tonsillar herniation ≥ 5 mm below the foramen magnum.

<sup>2</sup> Seven patients with Crouzon syndrome had a symptomatic Chiari-I malformation (12%), 2 also had a syringomyelia (3.5%). All these patients were treated with atlanto-axial decompression, and the scans performed after this procedure were excluded.

*Abbreviations: CM-I – Chiari-I malformation*
<table>
<thead>
<tr>
<th>N°</th>
<th>Mean age, yrs (range)</th>
<th>Mean CL, mm (range)</th>
<th>Mean SBA, degrees (range)</th>
<th>Mean BA, degrees (range)</th>
<th>Mean FMA, mm² (range)</th>
<th>Mean TP, mm (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>146</td>
<td>10.2 (0.01-20.11)</td>
<td>42.2 (21.9-58.1)</td>
<td>122.7 (106.8-137.5)</td>
<td>120.4 (102.4-146.8)</td>
<td>65.3 (139.6-1125.7)</td>
</tr>
<tr>
<td>Craniosynostosis, scans</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Apert</td>
<td>62</td>
<td>6.91 (0.02-21.32)</td>
<td>30.0 (16.0-40.6)</td>
<td>113.5 (90.2-145.1)</td>
<td>109.0 (90.3-137.1)</td>
<td>470.7 (165.5-963.0)</td>
</tr>
<tr>
<td>- Crouzon/ Pfeiffer</td>
<td>139</td>
<td>8.17 (0.24-20.54)</td>
<td>32.5 (20.1-45.0)</td>
<td>111.9 (84.9-141.2)</td>
<td>118.6 (98.9-143.9)</td>
<td>486.7 (204.3-843.2)</td>
</tr>
<tr>
<td>- Muenke</td>
<td>37</td>
<td>6.65 (0.26-24.13)</td>
<td>33.2 (23.3-44.8)</td>
<td>120.8 (106.5-150.3)</td>
<td>121.7 (108.9-134.5)</td>
<td>516.4 (201.5-757.2)</td>
</tr>
<tr>
<td>- Saethre-Chotzen</td>
<td>37</td>
<td>6.31 (0.21-24.16)</td>
<td>31.3 (22.8-41.5)</td>
<td>121.8 (104.7-148.8)</td>
<td>122.4 (108.5-148.8)</td>
<td>362.1 (115.3-603.8)</td>
</tr>
<tr>
<td>Total</td>
<td>275</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Patient characteristics.

1 Number of scans

Abbreviations: TP – tonsillar position, CL – clivus length, SBA – skull base angle, BA – Boogards angle, FMA – foramen magnum area
<table>
<thead>
<tr>
<th></th>
<th>Apert [β, [95%CI]]</th>
<th>Crouzon [β, [95%CI]]</th>
<th>Saethre-Chotzen [β, [95%CI]]</th>
<th>Muenke [β, [95%CI]]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clivus length (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At birth, compared to controls</td>
<td>-4.6 [-6.9, -2.4; p&lt;0.001]</td>
<td>-3.9 [-5.9, -1.9; p&lt;0.001]</td>
<td>-4.0 [-6.2, -1.7; p&lt;0.001]</td>
<td>-2.6 [-4.9, -0.27; p=0.03]</td>
</tr>
<tr>
<td>Growth (per 10% increase in age)(^1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Controls + patients(^2)</td>
<td>0.46 [0.39, 0.53; p&lt;0.001]</td>
<td>0.45 [0.39, 0.51; p&lt;0.001]</td>
<td>0.46 [0.39, 0.53; p&lt;0.001]</td>
<td>0.46 [0.38, 0.53; p&lt;0.001]</td>
</tr>
<tr>
<td>- Modification factor for patients</td>
<td>-0.30 [-0.39, -0.20; p&lt;0.001]</td>
<td>-0.22 [-0.31, -0.13; p&lt;0.001]</td>
<td>-0.23 [-0.33, -0.13; p&lt;0.001]</td>
<td>-0.19 [-0.32, -0.05; p=0.02]</td>
</tr>
<tr>
<td><strong>Skull base angle (degrees)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At birth, compared to controls</td>
<td>-9.2 [-13.2, -5.1; p&lt;0.001]</td>
<td>-11.2 [-15.2, -7.3; p&lt;0.001]</td>
<td>-1.5 [-5.6, 2.6; p=0.48]</td>
<td>-1.3 [-4.9, 2.3; p=0.47]</td>
</tr>
<tr>
<td>Growth (per 10% increase in age)(^1), mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Controls + patients(^2)</td>
<td>-0.18 [-0.30, -0.05; p=0.007]</td>
<td>-0.18 [-0.30, -0.06; p=0.004]</td>
<td>-0.18 [-0.30, -0.05; p=0.009]</td>
<td>-0.18 [-0.29, -0.06; p=0.009]</td>
</tr>
<tr>
<td>- Modification factor for patients</td>
<td>-0.06 [-0.23, 0.12; p=0.51]</td>
<td>-0.04 [-0.21, 0.14; p=0.57]</td>
<td>-0.13 [-0.34, 0.09; p=0.22]</td>
<td>-0.16 [-0.37, 0.05; p=0.12]</td>
</tr>
<tr>
<td><strong>Boogards angle (degrees)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At birth, compared to controls</td>
<td>-21.3 [-25.8, -16.8; p&lt;0.001]</td>
<td>-6.6 [-3.7, 2.4; p=0.069]</td>
<td>-6.2 [-10.2, -2.2; p=0.003]</td>
<td>-4.2 [-8.1, -0.4; p=0.03]</td>
</tr>
<tr>
<td>Growth (per year increase in age), degrees</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Controls + patients(^2)</td>
<td>-0.73 [-0.98, -0.48; p&lt;0.001]</td>
<td>-0.18 [-0.30, -0.06, p&lt;0.002]</td>
<td>-0.73 [-0.96, -0.50; p&lt;0.001]</td>
<td>-0.73 [-0.96, -0.50; p&lt;0.001]</td>
</tr>
<tr>
<td>- Modification factor for patients</td>
<td>1.21 [0.76, 1.66; p&lt;0.001]</td>
<td>0.16 [-0.42, 0.10; p=0.22]</td>
<td>0.84 [0.32, 1.36; p=0.005]</td>
<td>0.40 [-0.19, 0.98; p=0.15]</td>
</tr>
<tr>
<td><strong>Foramen magnum area (mm(^2))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At birth, compared to controls</td>
<td>-34.4 [-110.6, 41.8; p=0.37]</td>
<td>-99.4 [-165.8, -33.1; p=0.004]</td>
<td>-117.4 [-195.6, -39.1; p=0.003]</td>
<td>-30.4 [-103.6, 42.9; p=0.41]</td>
</tr>
<tr>
<td>Growth (per 10% increase in age)(^1), mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Controls + patients(^2)</td>
<td>9.91 [7.56, 12.27; p&lt;0.001]</td>
<td>9.36 [7.29, 11.43; p&lt;0.001]</td>
<td>9.91 [7.27, 12.55; p&lt;0.001]</td>
<td>9.91 [6.53, 13.29; p=0.003]</td>
</tr>
<tr>
<td>- Modification factor for patients</td>
<td>-5.16 [-8.27, -2.04; p=0.002]</td>
<td>-1.46 [-4.24, 1.33; p=0.30]</td>
<td>-5.60 [-9.43, -1.77; p=0.01]</td>
<td>-5.60 [-4.62, 3.50; p=0.69]</td>
</tr>
<tr>
<td><strong>Tonsillar position (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>At birth, compared to controls(^3)</td>
<td>-2.3 [-4.6, -0.1; p = 0.04]</td>
<td>4.5 [2.4, 6.7; p&lt;0.001]</td>
<td>-0.1 [-2.2, 2.02; p = 0.94]</td>
<td>1.1 [-1.1, 3.3; p=0.34]</td>
</tr>
<tr>
<td>Over time (descent per 10% increase in age)(^1), mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Controls + patients(^2)</td>
<td>0.10 [0.03, 0.16; p=0.008]</td>
<td>0.09 [0.02, 0.15; p=0.01]</td>
<td>0.10 [0.03, 0.16; p=0.007]</td>
<td>0.10 [0.02, 0.17; p=0.02]</td>
</tr>
<tr>
<td>- Modification factor for patients</td>
<td>0.15 [0.06, 0.25; p=0.003]</td>
<td>0.09 [0.001, 0.18; p=0.05]</td>
<td>0.08 [0.10, 0.11; p=0.87]</td>
<td>0.10 [-0.03, 0.23; p=0.12]</td>
</tr>
</tbody>
</table>

\(^1\) Corresponding to the logarithmic scale, the coefficients were expressed by an increase of 10% in age.

\(^2\) For example: if we calculate the clivus growth in a patient with Apert syndrome, the growth is 0.45 – 0.29 = 

Table 3: Predicted skull base parameters in syndromic craniosynostosis versus controls.
0.16 mm per 10% increase in age.

2 Apert + Controls in the first column, Crouzon + Controls in the second column, Saethre-Chotzen + Controls in the third column, and Muenke + Controls in the third column

3 A negative tonsillar position corresponds to a more rostral position of the cerebellar tonsil.