Skull base abnormalities in osteogenesis imperfecta: a cephalometric evaluation of 54 patients and 108 control volunteers

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Object. Osteogenesis imperfecta (OI), which usually results from mutations in type I collagen genes, causes bone fragility and deformities. The head is often abnormally shaped, and changes in skull base anatomy in the form of basilar impression and basilar invagination have been reported. The authors analyzed the skull base anatomy on standardized lateral cephalograms from 54 patients with OI (Types I, III, and IV) and 108 control volunteers. They were surprised to find that the previously used diagnostic measures for basilar abnormality in patients with OI were exceeded in 6.5 to 7.4% of the controls, and hence needed to be reevaluated.

Methods. The authors calculated the distance from the odontoid process to four reference lines, including a novel one, in the controls. The normal mean distances were exceeded by more than two standard deviations (SDs) in 28.3 to 35.2%, and by more than three SDs in 13.2 to 16.6% of the patients with OI. The latter figures reliably reflect the prevalence of basilar impression. As a sign of basilar invagination the odontoid process protruded into the foramen magnum or reached the foramen magnum level in 22.2% of the patients with OI, whereas none of the controls showed this feature.

Platybasia (an anterior cranial base angle > 146°) was present in 11.1% of the patients but in none of the controls.

Conclusions. Platybasia, basilar impression, and basilar invagination were often coexpressed, but each was also present as an isolated abnormality. These three abnormalities and wormian bones were predominantly found in OI Types III and IV as well as in patients exhibiting dentinal abnormality.

Key Words • osteogenesis imperfecta • basilar impression • basilar invagination • plastyasia • cephalometrics • skull base

OSTEGENESIS imperfecta is a genetic disease that in most patients results from mutations in either of the two genes coding for type I collagen. It causes bone fragility as well as deformities in the osseous structures such as the skull and spine. Flattening of the anterior skull base and protrusion of the uppermost vertebrae into the foramen magnum with associated compression of the brainstem have been described in OI as well as in other conditions characterized by soft bone. The brainstem compression can be asymptomatic or can lead to a variety of neurocognitive symptoms and even death; therefore, it is important to screen for anomalies of the craniovertebral junction in patients with OI. Although these anomalies are best visualized on computed tomography scans or MR images, lateral radiographs are widely used for screening purposes and in epidemiological studies. Notably, the anatomical structures from which measurements are made to reveal skull base pathophysiology lie in the midsagittal plane, and the essential information about their relationships in a given patient is independent of the imaging modality.

In previous studies, abnormal relationships among the anterior skull base, posterior skull base, and cranial vertebrae have been classified as basilar impressions or invaginations; normal relationships among these structures have also been determined. In several studies of patients with OI, basilar abnormality has been diagnosed when the tip of the odontoid process was located more than 5 mm above the Chamberlain line (joining the dorsal hard palate/posterior nasal spine and the posterior lip of the foramen magnum) or more than 7 mm above the McGregor line (joining the posterior nasal spine and the lowest point of the posterior skull base). Note, however, that other criteria based on lateral radiographs obtained in patients with OI have also been used to diagnose basilar invagination and/or impression.

Abbreviations used in this paper: MR = magnetic resonance; OI = osteogenesis imperfecta; SD = standard deviation.
Unfortunately, earlier studies often lack information on the radiographic magnifications as well as parallel structural measurements in control volunteers.

In the present study we analyzed the skull base anatomy on lateral cephalograms obtained in mostly adult patients with OI and control volunteers. Based on these analyses we proposed separate definitions for basilar impression and basilar invagination. We also tested the applicability of a number of linear and angular measurements, including a novel one, in diagnosing basilar impression and invagination. We found that the threshold measurements previously used to diagnose basilar impression in patients with OI are too low; these values were exceeded in a significant proportion of the controls in the present study. Based on the results in this control population, we confirmed an earlier suggestion that basilar invagination can be diagnosed when the entire odontoid process is not situated below the level of the foramen magnum. For basilar impression we propose new diagnostic limits to be used in the adult population, independent of the imaging modality.

Clinical Material and Methods

Patients and Control Volunteers

At the institutes of dentistry at the universities of Helsinki and Turku, Finland, standardized lateral cephalograms were obtained as part of a medical or follow-up evaluation in 54 patients with OI. The patient population is described in more detail in Table 1. None of these patients had been treated with bisphosphonates. When several cephalograms had been obtained in a patient, we used only the latest one. Among the 54 patients with OI, 29 (22 females and seven males) had Type I (dominantly inherited, mild type with blue sclerae), five (two females and three males) had Type III (progressively deforming type), 19 (13 females and six males) had Type IV (moderately severe type), and one (one female) had a form of the disease that could not be distinguished between Types III and IV. Patients with OI Type I or IV were further classified into subtype A if their teeth appeared normal and into subtype B if a dentinogenesis imperfecta–dental abnormality was diagnosed. A clinical geneticist (I.K.) had diagnosed the disease in most of the patients and had classified the disease type in all of them. For additional information on the OI subtypes, we refer the reader to Rauch and Glorieux’s review.1

For control data we used previously collected lateral cephalograms from 51 unselected adults and 57 adults who had sought an orthodontic consultation because of occlusal problems. These persons were otherwise healthy, and with respect to the anatomy of the craniovertebral junction, they could be categorized as unselected controls. The ethics committee of the Institute of Dentistry, University of Helsinki, and the joint ethical committee of the Helsinki University Central Hospital approved the study protocol.

Cephalometric Analysis

Lateral cephalograms were obtained using a rigid cephalostat (Wehmer 517; BF Wehmer Co., Lombard, IL). The film-focus distance was 154 cm, and the linear enlargement was 10% for structures situated in the median plane. The points traced and the variables measured are illustrated in Fig. 1. Measurements were obtained from tracings to the closest 0.5 mm or 0.5° by an oral radiologist (O.K.); in all uncertain cases, an orthodontist (J.W.S.) helped to reach a consensus. When points were difficult to trace, information from all available radiographs in a patient (previous lateral and posteroanterior cephalograms) was utilized. Original magnifications were converted to actual sizes for description purposes and for statistical analysis of the results.

Statistical Analysis

Dependencies were evaluated using a correlation analysis of the linear measurements in both the OI and control groups. The between-group differences in the linear measurements and the severity of basilar abnormality were analyzed using two-sample t-tests and cross tables (contingency tables), respectively. In the latter case the Fisher exact test was used to determine the statistical significance of the dependencies.

Results

Pooling of the Results

We first compared the results between male and female control volunteers and found no statistically significant differences in the mean values or variances between the sexes. Because of the relatively small sample size, patients with OI were divided into two categories: those with Type I and those with Type III, III/IV, or IV. Within the OI Type I group, there were no statistically significant differences in the mean values or variances between female and male patients. Neither were there such differences in the group with the more severe types of OI, with the exception of the craniovertebral angle’s size, which showed significantly greater variation among female patients. Note, however, that the mean values were not statistically significantly different. Thus, we grouped together the results for females and males (Table 2). A similar lack of any significant difference between the sexes has been documented previously.10

Foramen Magnum Line

The foramen magnum line, which is the same as the McRae line, was traced from the anterior to the posterior lip of the foramen magnum. The McRae measure was the perpendicular distance to the tip of the odontoid process (dens point) from the McRae line (Fig. 1). The value of this measure was positive when the dens point lay above the line. In all control volunteers the entire odontoid process was situated below the foramen magnum line, and the mean McRae measure was −5 mm. Among the patients with OI the mean McRae measure was −2.7 mm. In 10 patients, the odontoid process partly protruded into the foramen magnum and thus the dens point was situated above the foramen magnum line; in two other patients the dens point touched the line. Among these 12 patients (22.2% of those with OI), two females had Type IA OI, one female had Type IB, two females and one male had Type III, one female had Type IVA, and four females and one male had Type IVB.

The Chamberlain Line

The modified Chamberlain line was traced from the pos-
Skull base abnormalities in osteogenesis imperfecta

### TABLE 1

**Summary of characteristics in 54 patients with OI***

<table>
<thead>
<tr>
<th>OI Type</th>
<th>Total</th>
<th>Females</th>
<th>Males</th>
<th>Age (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>IA</td>
<td>24</td>
<td>18</td>
<td>6</td>
<td>39.9</td>
</tr>
<tr>
<td>IB</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>37.0</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>36.4</td>
</tr>
<tr>
<td>III/IV</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>31.0</td>
</tr>
<tr>
<td>IVA</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>32.9</td>
</tr>
<tr>
<td>IVB</td>
<td>12</td>
<td>9</td>
<td>3</td>
<td>31.4</td>
</tr>
<tr>
<td>total</td>
<td>54</td>
<td>38</td>
<td>16</td>
<td>36.4</td>
</tr>
</tbody>
</table>

* NA = not applicable.

The McGregor line was traced from the posterior nasal spine to the lowest point of the occipital curve. The McGregor measure was the perpendicular distance to the tip of the odontoid process (dens point) from this line (Fig. 1); its value was positive when the dens point lay above the line. The mean McGregor measure was 2.3 mm among all the control volunteers and was greater than 7 mm in 6.5% of the volunteers. The mean measure was 7 mm among patients with OI and greater than 7 mm in 21 of them (39.6%). In only one of these 21 patients (a female patient with OI Type IB) was the Chamberlain line more than 5 mm above the line in eight controls (7.4%). The odontoid process was entirely below the Chamberlain line in only 9.4% of the patients with OI, and the mean Chamberlain measure was 4.7 mm. The dens point exceeded the line by more than 5 mm in 22 patients (40.7%); in 10 of these patients the dens point also reached or exceeded the level of the foramen magnum. Among these 22 patients, six females and one male had OI Type IA, one female and one male had Type IB, two females and one male had Type III, two females and one male had Type IVA, and five females and two males had Type IVB.

The McGregor Line

The McGregor line was traced from the posterior nasal spine to the lowest point of the occipital curve. The McGregor measure was the perpendicular distance to the tip of the odontoid process (dens point) from the McGregor line (Fig. 1); its value was positive when the dens point lay above this line. The mean McGregor measure was 2.3 mm among all the control volunteers and was greater than 7 mm in 6.5% of the volunteers. The mean measure was 7 mm among patients with OI and greater than 7 mm in 21 of them (39.6%). In only one of these 21 patients (a female patient with OI Type IB) was the Chamberlain line more than 5 mm below the line. The McGregor line was perpendicular to the nasion–sella line and drawn through the most caudal point of the posterior cranial base (M); the D-M distance—a novel variable—measuring the perpendicular distance from D to a line parallel to the nasion (N)–sella (S) line and drawn through M; and 7, anteroposterior relation of the odontoid process to the clivus (odontoid process axis runs anterior to, posterior to, or through the Ba); and 8, wormian bones (present, not present, or not present with certainty). The higher the D is situated in relation to the reference lines 1 to 4, the greater the (positive) measured value.

The D-M Distance and Correlations With the Linear Variables

We tested the applicability of a novel measurement to evaluate the craniovertebral anatomy without using the posterior nasal spine as a reference point. One reason for this strategy was the recognition that the posterior nasal point moves in patients having maxillary orthognathic surgery, which is not particularly uncommon in patients with OI, and thus an alternative method is required on the follow-up evaluation. Moreover, we found that patients with OI exhibit alterations in the size and structure of their faces; therefore, the position of the posterior nasal spine as well as other reference points may differ from those in controls.23

Measuring the D-M distance required assessment of a line coursing parallel to the nasion–sella line and through the most caudal point of the posterior cranial bone (the M point, which is also used for the McGregor line). The D-M distance was measured as the perpendicular distance between the dens point and this line (Fig. 1). The value of this measure was positive when the dens point lay above the line. In the control population the D-M distance ranged from −10.9 to 7.3 mm (mean ± SD, −1.3 ± 3.6 mm). In the patients with OI the D-M distance ranged from −7.7 to 25.9 mm (mean 4.3 ± 7 mm).

Within both the control and OI groups, the distance to the dens point from the foramen magnum line, the Chamberlain...
line, the McGregor line, and the D-M distance strongly correlated with each other. In fact, all six linear combinations in both groups had a probability value of 0.000 (Fig. 2 and Table 3).

**Anterior Cranial Base Angle**

We measured the anterior cranial base angle (nasion-sella-basion angle) by using the geometric sella point, which is a standard cephalometric reference point (Fig. 1). This angle varied from 113.5 to 142° (mean 129.8 ± 5.5°) in the controls and from 119.5 to 166° (mean 133.9 ± 10.3°) in the patients with OI. There was no correlation between the anterior cranial base angle and the McRae measure in healthy volunteers (p = 0.57), but there was a borderline correlation in patients with OI (p = 0.052). This angle correlated statistically significantly with the Chamberlain and McGregor measures in both the OI and control groups (p < 0.05).

Thus, in individuals with a large cranial base angle, the dens point generally was situated high above the Chamberlain and McGregor lines.

**Craniovertebral Angle**

For our purposes the craniovertebral angle was located between the continuation of the nasion–sella line and the visually estimated longitudinal axis of the odontoid process (Fig. 1). The mean value of this angle was almost identical in the control and OI groups (92.1° and 92.5°, respectively) but showed a significantly greater range and variation in patients with OI (range 61–147.0°, SD ± 13.2°) than in the controls (range 70–115.5°, SD ± 8.3°). The craniovertebral angle displayed a statistically significant negative correlation with all linear variables (p < 0.05), except for the McRae measure in patients with OI (p = 0.053) and the Chamberlain measure in controls (p = 0.08). Thus, in persons with a small craniovertebral angle, the odontoid process tended to be cranially positioned.

Note that both the craniovertebral and cranial base angles correlated positively in patients and controls (p = 0.050 and p = 0.019, respectively), indicating that when the anterior cranial base angle was large, the odontoid process tended to be anteriorly inclined (Fig. 3).

<table>
<thead>
<tr>
<th>Measure (mm)</th>
<th>Age (yrs)</th>
<th>McRae</th>
<th>Chamberlain</th>
<th>McGregor</th>
<th>D-M Distance (mm)</th>
<th>Cranial Base Angle (°)</th>
<th>Craniovertebral Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control (108 volunteers)</td>
<td>mean</td>
<td>32.8</td>
<td>-5.0</td>
<td>0.7</td>
<td>2.3</td>
<td>-1.3</td>
<td>129.8</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>10.3</td>
<td>2.4</td>
<td>3.3</td>
<td>3.2</td>
<td>3.6</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>min</td>
<td>18</td>
<td>-11.4</td>
<td>-8.2</td>
<td>-6.4</td>
<td>-10.9</td>
<td>113.5</td>
</tr>
<tr>
<td></td>
<td>max</td>
<td>59</td>
<td>-0.5</td>
<td>7.3</td>
<td>9.1</td>
<td>7.3</td>
<td>142.0</td>
</tr>
<tr>
<td>OI (54 patients)</td>
<td>mean</td>
<td>36.4</td>
<td>-2.7*</td>
<td>4.7*</td>
<td>7.0*</td>
<td>4.3*</td>
<td>133.9*</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>12.2</td>
<td>3.9*</td>
<td>4.8*</td>
<td>6.4*</td>
<td>7.0*</td>
<td>10.3*</td>
</tr>
<tr>
<td></td>
<td>min</td>
<td>16</td>
<td>-10.0</td>
<td>-5.5</td>
<td>-3.6</td>
<td>-7.7</td>
<td>119.5</td>
</tr>
<tr>
<td></td>
<td>max</td>
<td>69</td>
<td>9.1</td>
<td>15.5</td>
<td>35.0</td>
<td>25.9</td>
<td>166.0</td>
</tr>
<tr>
<td>OI Type I (29 patients)</td>
<td>mean</td>
<td>39.4</td>
<td>-3.73</td>
<td>4.15</td>
<td>5.74</td>
<td>3.50</td>
<td>130.6</td>
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<tr>
<td></td>
<td>SD</td>
<td>13.2</td>
<td>2.60</td>
<td>4.11</td>
<td>4.45</td>
<td>5.16</td>
<td>6.8</td>
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<tr>
<td></td>
<td>min</td>
<td>18</td>
<td>-10.00</td>
<td>-2.73</td>
<td>-1.36</td>
<td>-3.64</td>
<td>119.5</td>
</tr>
<tr>
<td></td>
<td>max</td>
<td>69</td>
<td>1.36</td>
<td>12.73</td>
<td>17.27</td>
<td>16.82</td>
<td>148.0</td>
</tr>
<tr>
<td>OI Types III, III/IV, &amp; IV (25 patients)</td>
<td>mean</td>
<td>32.8</td>
<td>-1.51†</td>
<td>5.42</td>
<td>8.47</td>
<td>5.34</td>
<td>137.8†</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>10.0</td>
<td>4.79‡</td>
<td>5.48</td>
<td>8.02‡</td>
<td>8.79‡</td>
<td>12.30‡</td>
</tr>
<tr>
<td></td>
<td>min</td>
<td>16</td>
<td>-9.09</td>
<td>-5.45</td>
<td>-3.64</td>
<td>-7.73</td>
<td>121.0</td>
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<tr>
<td></td>
<td>max</td>
<td>54</td>
<td>9.09</td>
<td>15.45</td>
<td>35.00</td>
<td>25.91</td>
<td>166.0</td>
</tr>
</tbody>
</table>

*p < 0.001, compared with controls. Magnification converted.
†p < 0.05, compared with OI Type I group.
‡p < 0.01, compared with OI Type I group.
**Anteroposterior Position of the Odontoid Process**

We also noted how the continuation of the odontoid process axis was related to the anterior lip of the foramen magnum (Fig. 1). In 59.2% of the controls the axis ran anterior to the basion point; in 20.4%, through it; and in 20.4%, posterior to it. Corresponding figures in the patients with OI were 70.4, 1.8, and 27.8%. Thus, a significantly larger proportion of the patients with OI compared with controls had an anteriorly positioned or angulated odontoid process (p = 0.005).

**Differences Between OI Groups**

In patients with OI Type I, the vertical position of the odontoid process was closer to its normal position than it was in those with the more severe types of OI; only the McRae measure was statistically significantly different (p = 0.005). The mean craniovertebral angle was quite similar in these two groups. The anterior skull base angle was the most significantly different, being larger in the group with the severe OI types than in the group with Type I (p = 0.0122). It is notable that there was significantly more variation in almost all linear and angular variables among the group with severe OI types than in the Type I group (Table 2). Whether this result is due to interindividual variation within a specific disease subtype or simply follows from the fact that OI Types III and IV were pooled must be clarified with a larger patient sample.

**Correlations With Age**

The linear and angular variables did not significantly correlate with age in the control volunteers, and only the cranial base angle correlated with age in the patients with OI (p = 0.030; Table 3), although only in a negative way. Given that the cranial base angle was larger in the patients with severe OI than in those with Type I, the correlation may indicate that either the angle actually diminishes with age or that the patient material was biased—that is, those with severe forms of OI were younger than those with the milder type.

Because the age difference in patients with OI Type I compared with those with Type III or IV did not appear to be statistically significant, one could conclude that an age-related change in the cranial base structure may occur.

**Wormian Bones**

Supernumerary sutural bones were not seen in any of the controls. They were observed in patients with severe types of OI more often than in those with the milder Type I (p = 0.000). Of the five patients with OI Type III, wormian bones appeared in four and their presence could not be ruled out in one. Of the 19 patients with OI Type IV, wormian bones were present in 17 (89.5%), none were in one, and their

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**Table 3**

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>McRae Measure</th>
<th>Chamberlain Measure</th>
<th>McGregor Measure</th>
<th>D-M Distance</th>
<th>Cranial Base Angle</th>
<th>Craniovertebral Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>OI (54 patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>1</td>
<td>-0.145</td>
<td>0.700*</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McRae measure</td>
<td></td>
<td>-0.038</td>
<td>0.910*</td>
<td>0.899*</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chamberlain measure</td>
<td></td>
<td>-0.157</td>
<td>0.630*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McGregor measure</td>
<td></td>
<td>-0.031</td>
<td>0.561*</td>
<td></td>
<td>0.456*</td>
<td>0.124</td>
<td></td>
</tr>
<tr>
<td>D-M distance</td>
<td></td>
<td>-0.295†</td>
<td>0.266</td>
<td>0.270†</td>
<td>0.380*</td>
<td>0.522*</td>
<td>0.268†</td>
</tr>
<tr>
<td>cranial base angle</td>
<td></td>
<td>-0.102</td>
<td>-0.264</td>
<td>-0.455*</td>
<td>-0.380*</td>
<td>-0.522*</td>
<td>0.268†</td>
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<tr>
<td>craniovertebral angle</td>
<td></td>
<td>0.089</td>
<td>-0.213†</td>
<td>-0.169</td>
<td>-0.190</td>
<td>-0.265*</td>
<td>0.225</td>
</tr>
</tbody>
</table>

* p < 0.001.  †p < 0.05. ‡p < 0.001. § p < 0.05.

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**Fig. 3.** Graph displaying the distribution of measures for the anterior cranial base angle and craniovertebral angle in patients with OI and in controls. The anterior cranial base angle tends to be larger in patients with OI than in controls, and angles 146° or greater are indicative of platybasia. The craniovertebral angle in patients with OI may deviate from the control mean by more than three SDs in any direction. These two angles show a statistically significant positive correlation with each other in both patients (p = 0.050) and controls (p = 0.019).
presence was uncertain in one. Wormian bones were also present in 44% of the patients with OI Type I. Note that their presence in this group did not statistically significantly correlate with age.

Developmental Dentinal Abnormality

We determined how the presence of skull base anomalies correlated with the abnormal development of dentin by subdividing patients with OI Types I and IV into two categories: A, those with normal-appearing teeth; and B, those with a dentinogenesis imperfecta–like phenotype, with discolored and fragile teeth. Of the 24 patients with OI Type IA, three (12.5%) had basilar abnormality. Of the five with OI Type IB, one (20%) had basilar abnormality. Of the seven with Type IV and the 12 with Type IVB, one (14.3%) and six (50%), respectively, had basilar abnormality. Hence, among OI Types I and IV, basilar abnormality was more often found in patients with abnormal teeth, and this difference reached statistical significance (p = 0.0362). This result is mainly based on the difference between Types IA and IVB (p = 0.0362).

Discussion

Applicability of Cephalometric Findings

The anatomical landmarks for analysis of basilar abnormalities (Fig. 1) are similarly located on lateral skull radiographs and midsagittal computed tomography scans or MR images. Therefore, the value of the findings regarding anatomical relationships in the craniovertebral junction does not depend on the imaging modality.

Cranial Base Structure in Healthy Populations

In his 1939 article on platybasia and basilar impression, Chamberlain drew a baseline extending from the dorsal hard palate to the dorsal surface of the posterior margin of the foramen magnum. This “Chamberlain line” has in some later studies been drawn from the most posterior point of the hard palate to the anterior margin of the occipital bone, and this modification has been used in the present study. Chamberlain claimed that normally all parts of the atlas and axis lie caudal to this line. It was Saunders who first published the normal values for the Chamberlain measure, however. His material comprised lateral radiographs obtained in 100 unaffected, probably American, individuals. The mean Chamberlain measure was −0.9 ± 3.6 mm. A negative value indicates here and in the following discussion that the dens point was below the observed reference line. Bull and associates studied lateral radiographs from 120 patients in London, with each decade between the ages of 10 and 69 years being represented by 10 male and 10 female persons. The mean Chamberlain measure was −2.9 ± 3 mm. In the controls in the present study the mean was 0.7 ± 3.3 mm. Closest to this latter measure is the one reported by Poppel and coworkers, which was based on 102 predominantly male persons with a mean Chamberlain measure of 0.1 ± 3.3 mm.

McGregor established his baseline as the one joining the posterior edge of the hard palate and the most caudal point of the occipital curve. He measured the distance of the dens point from this line on 204 lateral radiographs obtained in African Bantu persons, mostly young adults. The corrected mean for 164 men was −1.5 ± 2.5 mm; and for 39 women, −0.4 ± 2.8 mm. A mean distance of −0.4 ± 3.0 mm was reported by Bull and coworkers. The mean McGregor measure of 2.3 ± 3.2 mm in the present study was markedly greater than previously reported values. Note that the healthy sample in the study by Bull, et al., included individuals whose growth was not completed.

The third frequently used reference line, the foramen magnum or McRae line, runs from the anterior to the posterior border of the foramen magnum. Normally, the entire odontoid process is described as being situated below this line. Our observations in the present study were completely in line with that observation.

Findings in healthy populations have been used to make a distinction between normal and pathological linear and angular measures. According to Saunders, the probability of a Chamberlain measure greater than 7 mm is one in 64 in a healthy population, and only reasonably large deviations from this value are indicative of abnormality. Although the McGregor line lies more caudal than the Chamberlain line, McGregor suggested that if the tip of the odontoid process lies 4.5 mm above his baseline, abnormality must be considered. This statement was based on an estimation that this measure would be reached by one in 75 persons. Notably, however, the incidence of basilar impression or invagination has been approximated to be at least one in 3000 or one in 1500. According to Bull and colleagues, an anomaly is surely present when the measurement differs from the mean value by three SDs. Hence, they suggested that the radiological criteria for basilar impression would be a dens point at least 7 mm above the Chamberlain line or at least 9 mm above the McGregor line.

Radiological Criteria for Basilar Impression or Invagination

Table 4 lists studies in which the frequency of a basilar abnormality was evaluated as well as the radiological criteria used in each study. The lowest thresholds for establishing a diagnosis has been a dens point more than 2.5 mm above the Chamberlain line or more than 4.5 mm above the McGregor line. A McGregor measure greater than 5 mm has been used by Elies and Plester as well as by Charlton and Marini. In studies on patients with OI the most frequently used diagnostic limit has been a dens point more than 5 mm above the Chamberlain line or more than 7 mm above the McGregor line.

We found that in more than one half of the controls part of the odontoid process projected above the modified Chamberlain line, and the commonly used 5-mm threshold value for abnormality was exceeded in 7.4% of unselected individuals. Without correcting for the magnification, the ratio of pathological findings in our controls would increase to 11.1%. Moreover, the McGregor measure was greater than 4.5 mm in 28.7% of the controls and greater than 7 mm in 6.5%, with the magnification corrected. Although the McRae measure did not reveal any surprising results, the Chamberlain and McGregor measures were unexpectedly high in the controls. It is notable that the threshold values repeatedly used in earlier OI studies would have indicated basilar abnormality in a marked share of the controls.
Skull base abnormalities in osteogenesis imperfecta

There are several possible explanations for the differences between these results and those from previous studies in control populations. The ways of constructing the reference lines differ, as already described. Radiographic magnifications may also differ, and the anode–film or anode–patient distances have been mentioned in only a few articles. Of course, the magnification does not affect angular measurements, and with regard to the foramen magnum line, the odontoid process either lies completely below it or it does not. However, for the Chamberlain and McGregor measures, for instance, the magnification does affect the results. Moreover, the ethnic origin of the healthy control population may be important. Three geographically distinct populations from Europe, Africa, and Asia have recently been shown to exhibit differences in cranial base orientation and posterior cranial base length. Parallel measurements of the craniovertebral junction have not been performed in ethnically or geographically distinct groups.

Definitions of Platybasia, Basilar Impression, and Basilar Invagination

The mixed use of the terms “platybasia,” “basilar impression,” and “basilar invagination” and the differences in their diagnostic criteria have made it very difficult to compare results of the various studies. Based on what we observed in the control population and in those affected with OI, we used the following terms and diagnostic criteria. “Platybasia” is a morphological abnormality consisting of an anterior or cranial base angle (nasion-sella-basion angle) that is flat, as previously suggested by, for example, McGregor. The angle limit was set at 146° (study mean + 3 SDs), which is close to the 148° limit that has been considered as highly suggestive of abnormality. We found statistically significant correlations between this angle, and the Chamberlain and McGregor measures in both patients with OI and controls. Six patients had a cranial base angle of 146° or larger; these patients included one female with OI Type IA, one female and one male with Type III, two females with Type IVB, and one female with Type III/IV. Each of these patients also had wormian bones, and four had an abnormal McGregor measure.

The terms “basilar impression” and “basilar invagination” have been widely used synonymously. We found, however, that partial protrusion of the odontoid process into the foramen magnum sometimes occurs without notable infolding of the osseous margins of the foramen. Moreover, in patients with a markedly convex posterior skull base or invaginated posterior margin of the foramen magnum, the odontoid process did not necessarily protrude into the foramen (Fig. 4). Therefore, we found it necessary to define these two conditions distinctly. We defined basilar invagination as a protrusion of the odontoid process into the foramen magnum. This anomaly is apparent from the relation of the dens point to the foramen magnum line (McRae line). Negative values for the McRae measure (the dens point below this line) are normal, whereas values greater than or equal to 0 indicate more or less severe basilar invagination. According to this definition, none of the controls—but 12 of the patients (22.2%)—fulfilled the radiological criteria for basilar invagination.

Basilar impression is a condition in which the odontoid process is positioned far above the caudal borders of the skull. Again, determining which measures are deviant enough for a diagnosis is somewhat subjective. Nonetheless, it has become very clear from material in the present study that at least in this Caucasian population, the previously used limits would lead to a vast number of false-positive results.

### TABLE 4

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>OI Type I</th>
<th>OI Type III</th>
<th>OI Type IV</th>
<th>Criteria for Basilar Abnormality†</th>
</tr>
</thead>
<tbody>
<tr>
<td>studies w/ unselected sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charnas &amp; Marini, 1993</td>
<td>0/4 (0)</td>
<td>6/33 (18),</td>
<td>2/31 (6)</td>
<td>d&gt;5 mm above M</td>
</tr>
<tr>
<td>Sillence, 1994§</td>
<td>(10) II</td>
<td>(30) II‡</td>
<td>(5) II</td>
<td>d&gt;5 mm above C or &gt;7 mm above M</td>
</tr>
<tr>
<td>Jensen &amp; Lund, 1997</td>
<td>1/35 (3)</td>
<td>4/100 (100)</td>
<td>5/13 (38)</td>
<td>d&gt;5 mm above C or &gt;7 mm above M</td>
</tr>
<tr>
<td>Engellert, et al., 1998</td>
<td>0/17 (0)</td>
<td>7/16 (44)</td>
<td>1/14 (7)</td>
<td>using the McGregor line</td>
</tr>
<tr>
<td>Janus, et al., 2003</td>
<td>0/85 (0)</td>
<td>7/21 (33)</td>
<td>1/24 (4)</td>
<td>diagnosis based on MRI</td>
</tr>
<tr>
<td>Kuurila, et al., 2003‡‡</td>
<td>3/18 (17), II</td>
<td>2/5 (40),</td>
<td>1/7 (14), II</td>
<td>d not entirely below foramen magnum line</td>
</tr>
<tr>
<td>&amp;‡‡‡‡ Patients in these studies partly overlap.</td>
<td>0/3 (0)**</td>
<td>0/1 (0)§§</td>
<td>3/8 (38)**</td>
<td>or ≥10 mm above C</td>
</tr>
<tr>
<td>present study‡‡</td>
<td>3/24 (12), II</td>
<td>3/5 (60),</td>
<td>1/7 (14), II</td>
<td>d not entirely below foramen magnum line,</td>
</tr>
<tr>
<td>&amp;‡‡‡‡ Patients in these studies partly overlap.</td>
<td>1/5 (20)**</td>
<td>0/1 (0)§§</td>
<td>6/12 (50)**</td>
<td>&gt;10.5 mm above C, or &gt;11.9 mm above M, or D-M distance &gt;9.4 mm</td>
</tr>
<tr>
<td>study w/ preselected sample III</td>
<td>2/18 (11)</td>
<td>10/18 (56)</td>
<td>6/18 (33)</td>
<td>d&gt;2.5 mm above C, &gt;4.5 mm above M, or not entirely below foramen magnum line</td>
</tr>
</tbody>
</table>

* C = Chamberlain line or its modification; d = tip of odontoid process; M = McGregor line.
† On lateral skull radiographs, although additional criteria and diagnostic tools may have been used.
‡ Eight patients had signs of OI Types II and III.
§ These authors reported on 87 patients with OI.
II Subtype A.
** Subtype B.
‡‡ Patients had signs of OI Types III and IV.
‡‡‡‡ Patients in these studies partly overlap.
III Patients had OI and basilar abnormality on selection.
positive diagnoses. If a value three SDs from the mean is a sign of abnormality, then seven (13.2%) of 53 patients with OI in the present sample had basilar impression based on a Chamberlain measure greater than 10.5 mm, the same seven patients had it based on a McGregor measure greater than 11.9 mm, and nine (16.6%) of 54 patients had it based on a vertical D-M distance greater than 9.4 mm. According to these criteria, none of the controls had basilar impression. The area beneath the normal variation curve between the limits covers 99.7% of the total, and theoretically one in 800 unselected individuals would exceed the upper limit.

Among the 10 patients with measures exceeding any of the aforementioned diagnostic criteria for basilar impression, three females had OI Type I, two females and one male had Type III, and three females and one male had Type IV. In six of these patients all three criteria were simultaneously fulfilled. Notably, however, in two of these 10 patients, the dens point was 3.6 and 3.2 mm below the foramen magnum line. Similarly, of the 12 patients with an odontoid process touching or intersecting the foramen magnum line, only eight definitely exhibited basilar impression. In one man with OI Type IV, the dens point was 4.5 mm above the foramen magnum level, but he showed no sign of basilar impression (all measures were less than the mean + 1.5 SDs). Thus, although basilar impression and basilar invagination are often coexpressed, each is a distinct type of aberration (Fig. 4A–C).

Screening Criteria for Clinical Use

Patients with OI who are displaying neurological signs or symptoms as well as those with measures differing from the population mean by two or more SDs should be closely examined and followed up for eventual development of medullary compression. The area under the normal variation curve between the −2 and +2 SD limits covers 95.5% of the total. Supposing that our controls are representative of normal variation, the appropriate screening limit for the Chamberlain measure would be 7.2 mm and that for the McGregor measure would be 8.7 mm, with magnification corrected. Of the 108 controls in our study two men and one woman had Chamberlain measures that exceeded the aforementioned limit; the McGregor measure also exceeded the limit in this woman. Similarly, the screening limit for the new D-M distance would be 5.8 mm, and this distance was exceeded in only one female control volunteer. The two SDs from the mean were exceeded in patients with OI: 30.2% for the Chamberlain measure, 28.3% for the McGregor measure, and 35.2% for the vertical D-M distance. The fact that our novel D-M distance measure selects a higher number of patients exceeding the two-SD limit for screening...
Skull base abnormalities in osteogenesis imperfecta

than do the older measures (the McGregor and Chamberlain measures) indicates its sensitivity.

Using the two-SDs rule, patients with an anterior cranial base angle larger than 140° might also be selected for further evaluation. The greatest value among the controls in our study was 142°, and only in this female volunteer was it more than 140°. Platybasia in itself may be insignificant as a cause of neurological problems, although this anomaly has been found to be frequently associated with basilar impression.17 Indeed, in six patients with OI and platybasia only two had no basilar impression or invagination (Fig. 4D–F). The cranial base angle measurement may be clinically important, for instance, when the dens point is difficult to locate on the radiograph.

Correlations With Age

It has been documented that changes in the McGregor measure between the ages of 10 and 69 years are small, and some have concluded that age does not need to be considered.1 We also observed that there are no statistically significant correlations between age, and the linear and angular variables measured in controls. Nevertheless, we must acknowledge that mostly adults (only two adolescents) were included in our study. To our knowledge there are no publications on basilar skull structures in unaffected young adolescents. However, radiological criteria have been used uniformly in studies of patients with OI whose ages have ranged from 4 months to 65 years as well as from 1 to 16 years.25

Correlations Between the Variables

The strong correlation between the McRae, Chamberlain, and McGregor measures and the D-M distance is not an unexpected finding given that they all describe the superoinferior position of the odontoid process. The lowest correlations were found in those linear combinations in which the McRae measure was included. This result indicates that the dens point can be situated at different distances from the skull base, which itself shows anatomical variation (upward folding of the posterior margin of the foramen magnum and/or increased convexity of the basiocciput). A new measurement ignoring the dens is needed to study separately the grade of caudal flexure of the posterior skull base. Previously, we observed that measuring the height of the posterior skull base beneath the nasion–sella level does not resolve the question; consider, for example, that in patients with a soft skull, the sella itself is also ventrally depressed due to the weight of the brain.23

The anterior cranial base angle and the vertical position of the odontoid process have been found to correlate poorly.16 Data in the present study, however, show that in both patients and controls the flexure of the anterior skull base and the grade of the basilar impression, but not necessarily basilar invagination, correlate. Less attention has been paid to the craniovertebral angle, yet this measure correlated significantly with most of the other measurements. It correlated negatively with the linear indicators of basilar abnormality, which means that patients with an acute craniovertebral angle risk developing intrusion of the odontoid process beyond the reference levels. This angle correlated positively with the cranial base angle. Hence, persons with a flat cranial base have a tendency toward an obtuse craniovertebral angle. This result means that when the clivus rotates posteriorly, the cervical spine rotates anteriorly. These apparently opposite correlations support our observation of the existence of two extremes in cranial base configuration. In the pure type of basilar invagination, the craniovertebral angle may be very small and the dens point slips into the foramen magnum. In the pure type of basilar impression, both angles become large as the odontoid process bends anteriorly under the horizontal clivus and the posterior skull sinks caudally. Notably, however, most of the patients with basilar abnormality exhibit features of both impression and invagination (Fig. 4).

In the 12 patients with an odontoid process intruding into the foramen magnum, the axis always ran posteriorly to the basion point (posterior tip of the clivus). This notation is in line with McRae’s 1953 observation that neurological symptoms and signs are usually found in patients with a posteriorly angulated odontoid process.17 Note, however, that we found this structure to be situated posteriorly in the majority of patients (and controls), and thus this orientation alone does not predict pathological development. In the two patients exhibiting basilar impression and an odontoid process situated below the foramen magnum, the axis was situated anteriorly. A significantly larger proportion of the patients compared with controls had an anteriorly positioned or angulated odontoid process. This feature appears to prevent protrusion of the odontoid process into the foramen magnum even if the skull base is clearly impressed (Fig. 4B). Although the odontoid process does not intrude the foramen magnum but rather bends anteriorly under the horizontal and truncated clivus, the brainstem may be distorted.10 Indeed, McRae documented 10 symptomatic cases in which the dens point was 5 to 25 mm above the Chamberlain line but below the foramen magnum.17

Basilar Abnormality and the OI Phenotype

It has been reasoned that in OI the weight of the cranium and its contents exceeds the load-bearing capacity of the soft bones at the skull base, deforming them gradually and leading to basilar abnormality.1 This explanation agrees with most others favoring the idea that basilar abnormality is most prevalent in Type III and least prevalent in Type I (Table 4) and that it appears earlier in patients with severe disease. Moreover, infants with the lethal OI Type II reportedly do not show basilar abnormality, a finding related to the missing upright position and weight bearing on the upper cervical spine.23 Another explanation is that basilar abnormality could be associated with microfractures in the region of the foramen magnum, and thus predominantly occurs in patients with OI Type I or IV.20 In the present study, of the 29 patients with Type I disease, three (10.3%) undoubtedly had some form of basilar abnormality; of the five with Type III, three (60%) displayed an anomaly; and of the 19 with Type IV, seven (36.8%) had an anomaly. These prevalence figures support the first explanation of progressive deformity.

We found that wormian bones are present in patients with basilar abnormality more frequently than in those with a normal-appearing skull base. The predictive value of wormian bones is limited, however. Consider that of the 33 patients with wormian bones, only one third had basilar abnormality; of those without, one fifth had a skull base ab-
normality. Notably, the type of OI correlated more significantly than basilar structure with the presence of wormian bones.

Engelbert and coworkers\(^6\) found spinal complications, especially basilar abnormality, in patients with OI and dentogenesis imperfecta more often than in those with OI and normal-appearing teeth. Note, however, that this result may be associated with the fact that seven of the eight patients with basilar abnormality had Type III disease, in which dental abnormality is frequent. Thus, we were particularly interested in testing whether basilar abnormality was more frequent in OI Types IB and IVB (abnormal dentin) than in Types IA and IVA (normal-appearing teeth). We found that basilar abnormality was present statistically significantly more often in patients with abnormal teeth within OI Types I or IV.

Conclusions

Fortunately, a large number of radiologically demonstrated cases of basilar abnormality are clinically asymptomatic.\(^1\) This observation may be partly associated with the previously used radiological criteria, which, as shown in the present study, have been remarkably low. Surgically managed cases of neurologically significant basilar abnormality among patients with OI have exhibited an axial translation of the odontoid process of at least 20 mm,\(^7,\)\(^,\)\(^8\) or high McGregor measures such as 62 and 30 mm.\(^7,\)\(^1\)\(^3\) None of the patients included in this study and with a maximum McGregor measure of 35 mm has required operative management.

Our control and patient populations were composed mostly of adults. Corresponding cephalometric normal values in children are lacking, as are comparative longitudinal data in unaffected children and in those with OI. Based on data in the present study, it is important to screen separately for an intrusion of the odontoid process into the foramen magnum and the development of an impressed cranial base. To determine the latter, the novel D-M distance was shown to be a sensitive measure.

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References


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