ORIGINAL ARTICLE

JBMR

Cranial Base Abnormalities in Osteogenesis Imperfecta: Phenotypic and Genotypic Determinants

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ABSTRACT

Cranial base abnormalities are an important complication of osteogenesis imperfecta (OI), a hereditary bone fragility disorder that in most patients is caused by mutations affecting collagen type I. To elucidate which clinical characteristics are associated with the occurrence of cranial base abnormalities in OI, we compared cephalometric results of 187 OI patients (median age 12.0 years, range 3.4 to 47 years; 96 female) with those of 191 healthy subjects and related findings to clinical descriptors of the disease. Overall, 41 patients (22%) had at least one unambiguously abnormal skull base measure. Multivariate logistic regression analysis in patients with OI types I, III, and IV ($n = 169$) revealed that height *Z*-score [odds ratio (OR) = 0.53, 95% confidence interval (CI) 0.43–0.66, $p < .001$]—but not age, gender, scleral hue, lumbar spine areal bone mineral density, or a history of bisphosphonate treatment—was a significant independent determinant of skull base abnormalities. Among patients with a height *Z*-score below –3, 48% had a skull base abnormality regardless of whether they had received bisphosphonate treatment in the first year of life or not. Genotype-phenotype correlations were evaluated in patients with detectable mutations in *COL1A1* or *COL1A2*, the genes coding for collagen type I ($n = 140$). Skull base abnormalities were present in 6% of patients with haploinsufficiency (frameshift or nonsense) mutations, in 43% of patients with helical glycine substitutions caused by *COL1A1* mutations, in 32% of patients with helical glycine substitutions owing to *COL1A2* mutations, and in 17% of patients with splice-site mutations affecting either *COL1A1* or *COL1A2*. However, multivariate logistic regression analysis showed that height *Z*-score but not the type of collagen type I mutation was independently associated with the prevalence of skull base abnormalities. In conclusion, this study shows that clinical severity of OI, as expressed by the height *Z*-score, was the strongest predictor of skull base abnormalities. We did not find evidence for the hypothesis that bisphosphonate treatment protects against skull base abnormalities. © 2011 American Society for Bone and Mineral Research.

KEY WORDS: BASILAR IMPRESSION; BASILAR INVAGINATION; COLLAGEN TYPE I; OSTEOGENESIS IMPERFECTA; PLATYBASIA

Introduction

Osteogenesis imperfecta (OI) is a hereditary disease characterized by bone fragility and short stature.[1] The clinical spectrum represents a continuum ranging from perinatal lethality to nearly asymptomatic individuals with occasional fractures and normal stature. Most individuals with a clinical diagnosis of OI have an identifiable mutation in *COL1A1* or *COL1A2*, the genes that encode the two collagen type I α chains, α1(I) and α2(I).[1] OI patients with collagen type I mutations can be classified into four clinically defined types. OI type I comprises patients with absence of bone deformities and normal or near-normal stature. Type II is lethal in the perinatal period. OI type III is the most severe form in children surviving the neonatal period and leads to extremely short stature. Patients with mild to moderate bone deformities and variably short stature are classified as having OI type IV.

Two broad categories of collagen type I mutations result in OI types I to IV.[2] The first are haploinsufficiency mutations that are caused by the failure to synthesize the products of one *COL1A1* allele and consistently result in a clinical picture of OI type I. The second class of mutations consists of those which result in the synthesis of collagen molecules with structural abnormalities. This is caused most frequently by the substitution of glycine by another amino acid in the helical domain of either the α1(I) or the α2(I) chain. Helical glycine mutations can lead to the whole spectrum of clinical severity of OI, from mild OI type I to lethal OI type II, depending on the type of α chain affected, the type of amino acid substituting for glycine, and the position of the mutation within the α chain.[3]

Received in original form February 18, 2010; revised form August 3, 2010; accepted August 6, 2010. Published online August 18, 2010.
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Journal of Bone and Mineral Research, Vol. 26, No. 2, February 2011, pp 405–413
DOI: 10.1002/jbmr.220

Apart from these "classic" types of OI, three conditions known as OI types V, VI, and VII have been identified over the past decade.[1] OI types V to VII resemble OI types I, III, or IV on clinical grounds but also have some distinguishing features and are not caused by *COL1A1* or *COL1A2* mutations.

Cranial base abnormalities are an important complication of OI and can lead to compression of the structures of the posterior fossa, Chiari malformation, spinal cord syrinx formation, and hydrocephalus.[4,5] In the clinical setting, lateral skull radiographs usually are used to screen for cranial base abnormalities, and MRI is performed when abnormalities are found.

The literature on skull base abnormalities can be hard to evaluate because terms such as *basilar invagination*, *basilar impression*, *platybasia*, and others often have been used interchangeably. However, as pointed out by Kovero and colleagues, protrusion of the odontoid process into the foramen magnum (basilar invagination), position of the odontoid process far above the caudal borders of the skull (basilar impression), and a flat anterior cranial base angle (platybasia) can occur independent of each other and therefore should be regarded as clearly separate entities.[6]

At present, there is little information on which clinical characteristics are associated with the occurrence of cranial base abnormalities in OI. In this study we therefore examined 187 pediatric and adult OI patients for the presence of cranial base abnormalities and related findings to patient characteristics such as type of collagen type I mutation, age, clinical phenotype, bone density, and treatment with intravenous bisphosphonates. This study thus addresses two questions that are highly relevant for the clinical management of OI patients. First, what are the clinical and genetic risk factors that predispose to the occurrence of cranial base abnormalities in OI? Second, can bisphosphonate treatment prevent the occurrence of such abnormalities?

Subjects and Methods

Healthy subjects

The healthy control group consisted of 191 subjects (103 female, 88 male; ages 3 to 59 years) who had participated in two previously described studies,[6,7] both conducted at the Institute of Dentistry, University of Helsinki, Finland. These studies were approved by the Ethics Committee of the Institute of Dentistry, University of Helsinki, and the Joint Ethical Committee of the Helsinki University Central Hospital.

OI patients

The study population consisted of patients with a clinical diagnosis of OI who were examined at the Shriners Hospital for Children in Montreal between October 1999 and April 2008 and for whom at least one lateral skull radiograph had been obtained at the age of 3 years or older. The rationale for this age cutoff was that cephalometric reference data were not available for children younger than 3 years of age. When more than one skull X-ray was available, the most recent radiograph was used for the cross-sectional analyses presented here. A total of 187 patients (96 female, 91 male; age at the time of the most recent skull radiograph: median 12.0 years, range 3.4 to 47 years) fulfilled these criteria and were included in the analysis. The study was approved by the Shriners Hospital Institutional Review Board. Informed consent was obtained from the legal guardians and/or patients.

In 62 patients, at least one other previous skull X-ray was available that had been obtained at the age of 3 years or older. The first and most recent skull X-rays of these patients were used for longitudinal analyses.

The diagnosis of OI type (based on clinical assessment), bisphosphonate treatment history, height, weight, presence of dentinogenesis imperfecta or blue sclera, and results of mutation analysis were obtained from the medical chart of each patient.

Of the 187 patients included in this study, 169 were affected by one of the OI types that are usually caused by mutations in collagen type I (OI type I, III, or IV). DNA sequence analysis was performed in 149 of these patients. The remaining 20 patients did not undergo DNA testing mostly because they or, in children, their parents were not interested in having this analysis performed. In 9 patients, no mutation was found by full sequence analyses of all exons and exon-intron boundaries of the *COL1A1* and *COL1A2* genes. The 140 patients who were positive for a mutation in *COL1A1* or *COL1A2* were included in the analysis of the relationship between genotype and skull base abnormalities.

Cephalometric analyses

Lateral skull radiographs were obtained using standard films placed in close contact with the head so as to minimize object-film distance. Film focus distance was 100 cm. These radiographs were used to determine cranial base measures (Fig. 1).

The McRae measure represents the perpendicular distance from the tip of the dens to the McRae line (ie, the line joining the anterior and posterior margins of the foramen magnum). The Chamberlain measure represents the perpendicular distance of the tip of the dens to the Chamberlain line (ie, the line from the posterior nasal spine to the posterior lip of the foramen magnum). The McGregor measure represents the perpendicular distance of the tip of the dens to the McGregor line (ie, the line joining the posterior nasal spine to the most caudal portion of the posterior cranial base). The DM distance represents the perpendicular distance of the tip of the dens from a parallel line to the nasion-sella line passing through the most caudal part of the posterior cranial bone.[6] Any distance of the dens above the respective line used for each measure was denoted as a positive value. Measurements were obtained from radiographs to the closest 1 mm or 1 degree by two independent observers, and the average result of the two observers was used for further analysis. Observer disagreement (defined as a difference of >2 mm for distance measures and >5 degrees for angles) was resolved by a radiologist specialized in pediatric bone disease.

To estimate the mean distance of the median plane structures from the film and thereby their enlargement in the radiographs, we analyzed the head widths measured directly on the skull of 36 Finnish patients with OI types I, III, and IV aged 3.4 to 69 years (this study was approved by the Ethics Committee of the Institute of Dentistry, University of Helsinki, and the Joint Ethical Committee of the Helsinki University Central Hospital). The

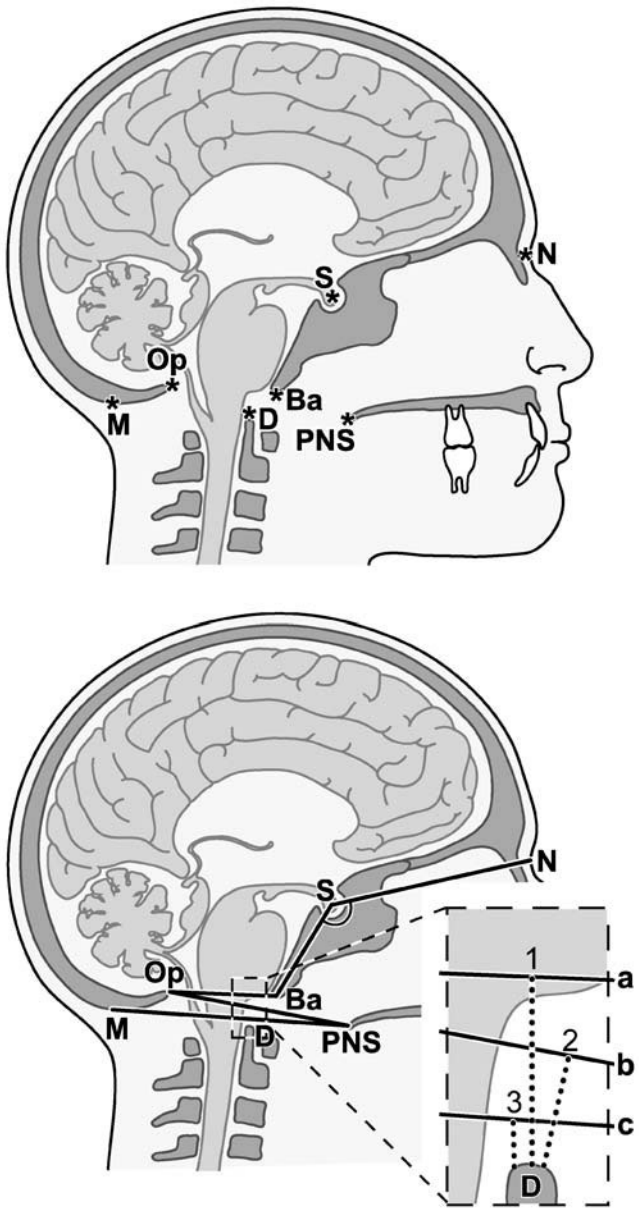

Fig. 1. (*Above*) Landmarks for measurements. Ba = basion or tip of clivus denoting the anterior lip of the foramen magnum; D = dens or tip of odontoid process; M = lowest part of posterior cranial vault; N = nasion; Op = opisthion or posterior lip of the foramen magnum; PNS = posterior nasal spine; S = middle of sella turcica. (*Below*) Lines, measures, and angles. McRae line joining Ba-Op (indicated as *a* in the *inset*), Chamberlain line joining PNS-Op (*b*), and McGregor line (*c*) joining PNS-M. Measurements are taken as the perpendicular distance from the tip of the odontoid process (*D*) to these lines, *D* above the line is positive; *D* below is a negative value. The number 1 in the inset indicates the McRae measure, 2 represents the Chamberlain measure, and 3 shows the McGregor measure. N-S-Ba = cranial base angle. The DM distance is not indicated to maintain the clarity of the drawing.

measured head widths were well in line with those documented for Danish OI patients[8] and yielded an estimated radiographic magnification ranging from 7.2% to 9.3%, with a mean of 8.5%. In these analyses, all results of linear measures made on radiographs therefore were divided by 1.085 to correct for the magnification error.

Control material was divided into age groups: 3 to 4 years, 5 to 6 years, 7 to 8 years, and 9 years and older, and OI patients' findings were compared with the relevant control group. The need for age-specific controls for young children was based on earlier observations that most of the skull base measures vary with age during childhood but remain constant in healthy subjects aged 9 years and older.[9]

We used the definitions and diagnostic criteria established by Kovero and colleagues[6] (Fig. 2):

- *Basilar invagination*—the protrusion of the odontoid process into the foramen magnum. The radiographic criterion for basilar invagination is a McRae measure at or above 0.
- *Basilar impression*—a condition in which the odontoid process is positioned far above the caudal borders of the skull. The radiographic criteria for basilar impression are fulfilled if the Chamberlain measure, the McGregor measure, or the DM distance are elevated by more than 3 SDs above the average of age-matched healthy controls.[6]
- *Platybasia*—a flat anterior cranial base angle (nasion-sella-basion angle). Platybasia was diagnosed when the anterior

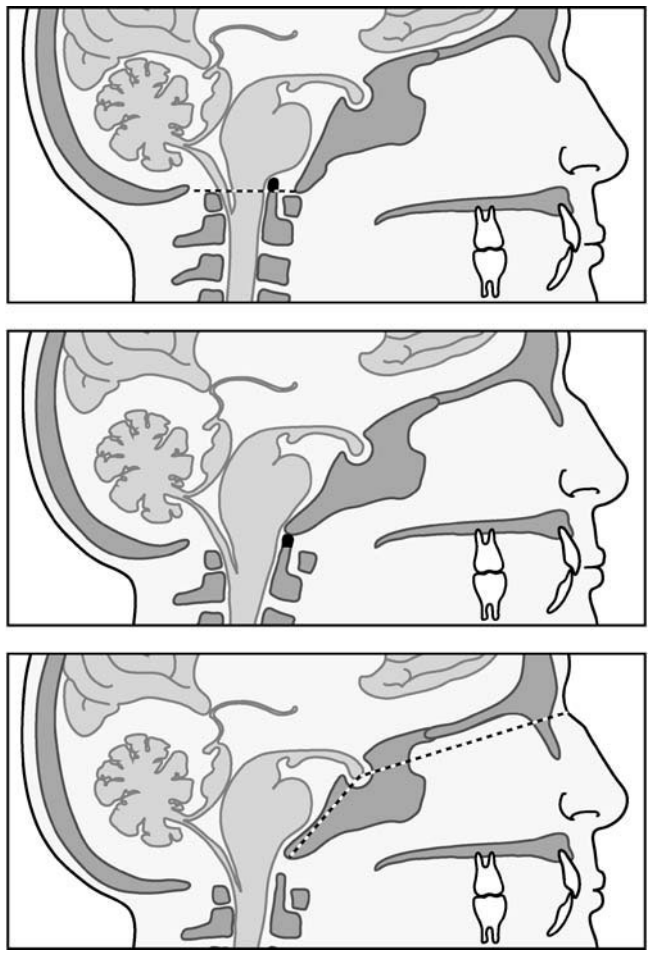

Fig. 2. Schematic representation of the various cranial base abnormalities. (*Above*) Basilar invagination. The tip of the dens (marked in *black*) is protruding into the foramen magnum (McRae line indicated). (*Center*) Basilar impression. The tip of the dens (marked in *black*) is located in an abnormally high position but does not protrude into the foramen magnum *C*. (*Below*) Platybasia. The anterior cranial base angle (nasion-sella-basion angle) is flat.

cranial base angle was more than 3 SDs above the average of healthy controls.
- Patients who had at least one of these diagnoses were said to have a *skull base abnormality*.

Bone densitometry

Lumbar spine (L_1–L_4) areal bone density (LS aBMD) was determined by dual-energy X-ray absorptiometry (DXA; Hologic QDR 2000W or 4500A, Hologic, Inc., Waltham, MA, USA) in the posteroanterior direction. Results were transformed to age-specific *Z*-scores combining reference data from Salle and colleagues[10] and data provided by the densitometer manufacturer.

Collagen type I mutation analysis

Total genomic DNA was isolated from peripheral blood using the QIAamp DNA Blood Mini Kit (Qiagen, Inc., Mississauga, Ontario, Canada). All exons of the *COL1A1* and *COL1A2* genes, including the exon-intron boundaries, were amplified by PCR using primers described previously.[11] The sequencing reaction was performed using a BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA), and the nucleotide sequence was determined using an Applied Biosystems 3100 DNA sequencer. Mutations in *COL1A1* causing frameshifts or point mutations creating termination codons were predicted to lead to haploinsufficiency. Even though some splice-site mutations also may result in haploinsufficiency, the effect of such mutations on mRNA processing is often complex and cannot be predicted on the basis of DNA analysis alone.[12] Therefore, patients with splice-site mutations were not included in the haploinsufficiency group.

Statistical analysis

Height and weight measurements were converted to age- and sex-specific *Z*-scores on the basis of reference data published by the Centers for Disease Control and Prevention.[13] In the control population, differences between age groups were evaluated for significance using analysis of variance (ANOVA). Post hoc comparisons between age groups were performed using Bonferroni's adjustment.

The age dependency of cranial base measures in OI patients was evaluated using linear regression analysis. Logistic regression analysis was used to evaluate the relationship between patient characteristics and the presence of skull base abnormalities. Results were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). The effect of potential predictor variables was assessed initially in univariate models and then in stepwise multivariate models. To assess the effect of prior bisphosphonate therapy, bisphosphonate treatment status at the time of the radiograph was included as a dichotomous variable (no/yes). OI type I was selected as the reference category for the analyses of OI types because this group of patients constitutes one end of the spectrum of disease severity.

All tests were two-tailed. *p* Values below .05 were considered significant. Calculations were performed using PASW Statistics Software Version 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Healthy population

In the 191 healthy controls, none of the skull base measures was significantly different between sexes, and results from both sexes therefore were pooled (Table 1). Statistically significant differences between age groups were found for the McRae measure, the Chamberlain measure, the McGregor measure, and DM distances (Table 1). However, after the age of 9 years, these measurements remained constant, as described in detail elsewhere.[9] Cranial base angle did not vary significantly with age. The McRae measure was negative in all controls.

Analysis by clinical OI type

The clinical characteristics of OI patients are indicated in Table 2. Age- and OI type-dependent results of all patients are shown in Fig. 3. Whereas the distance measures did not vary significantly with age, cranial base angle decreased with age ($p < .001$). This negative association between age and cranial base angle also was seen when the analysis was limited to the most frequently observed OI types (OI types I, III, and IV). In that group, the negative partial correlation coefficient between age and cranial base angle remained statistically significant ($p < .001$) when OI type, height *Z*-score, gender, and LS aBMD were included into the regression model.

Table 1. Results of Skull Base Measurements in Healthy Controls

Age group	3–4 years	5–6 years	7–8 years	≥9 years	*p*
N	10	30	25	126	
Age	4.5 (0.5)	5.7 (0.5)	7.7 (0.6)	30.0 (11.8)	
McRae (mm)	−7.6[a,b] (2.6)	−6.2[a] (2.9)	−4.7 (1.9)	−4.9 (2.3)	<.05
Chamberlain (mm)	−4.5[a,b] (2.9)	−3.0[a] (3.5)	−1.2 (2.5)	+0.4 (3.2)	<.05
McGregor (mm)	−2.6[a,b] (3.0)	−0.9[a] (3.5)	+0.8 (2.5)	+2.1 (3.1)	<.05
DM (mm)	−4.6[a,b] (3.4)	−1.6 (4.5)	−0.4 (3.2)	−1.3 (3.6)	<.05
Cranial base angle (degrees)	131.1 (4.4)	129.2 (5.3)	130.8 (4.9)	129.5 (5.4)	NS

NS = not significant.
[a] $p < .05$ for difference to ≥9 years.
[b] $p < .05$ for difference to 7–8 years.

Table 2. Clinical Characteristics of the OI Patient Population

	OI-I	OI-III	OI-IV	OI-V	OI-VI	OI-VII	All
N (M/F)	88 (41/47)	30 (16/14)	51 (27/24)	11 (5/6)	4 (2/2)	3 (0/3)	187 (91/96)
Age (years)	13.9 (8.7)	10.0 (4.1)	13.0 (5.3)	17.8 (10.8)	15.3 (10.1)	15.4 (1.2)	13.3 (7.5)
Height (*Z*-score)	−1.2 (1.2)	−6.7 (1.9)	−3.5 (2.2)	−2.6 (2.0)	−4.4 (3.7)	−2.1 (1.6)	−2.9 (2.6)
Weight (*Z*-score)	−0.5 (1.2)	−2.6 (1.7)	−1.4 (1.5)	−0.9 (1.5)	−0.6 (2.4)	1.7 (0.9)	−1.1 (1.6)
aBMD (*Z*-score)	−2.3 (1.0)	−3.3 (1.2)	−2.6 (1.2)	−2.0 (2.1)	−1.9 (1.8)	−2.1 (1.3)	−2.5 (1.2)
Dentinogenesis imperfecta, *n* (%)	15 (17%)	26 (87%)	26 (51%)	0 (0%)	0 (0%)	0 (0%)	67 (36%)
Blue sclerae, *n* (%)	72 (82%)	24 (80%)	29 (57%)	2 (18%)	0 (0%)	0 (0%)	127 (68%)
Wormian bones, *n* (%)	32 (36%)	30 (100%)	42 (82%)	8 (73%)	0 (0%)	2 (67%)	114 (61%)
Bisphosphonate treatment, *n* (%)	40 (46%)	28 (93%)	49 (96%)	9 (82%)	4 (100%)	3 (100%)	133 (71%)

Table 3 provides the number of patients with unambiguously abnormal results, defined as a result above 0 for the McRae measure or a result >3 SD above the age-appropriate average in controls for the other measures. The McRae measure was above 0 in seven patients, who thus fulfilled the radiographic criterion for the diagnosis of basilar invagination. Eleven patients had abnormal results indicative of basilar impression, defined as an abnormal result in one of the following: Chamberlain measure, McGregor measure, or DM distance. All these patients had an abnormal DM distance, three patients also had an abnormal Chamberlain measure, and two had an abnormal McGregor measure. The anterior cranial base angle was abnormally large in 29 patients, who thus were diagnosed as having platybasia.

Overall, 41 patients (22%) had at least one unambiguously abnormal skull base measure. Four patients had isolated basilar invagination, 7 patients had isolated basilar impression, and 25 patients had isolated platybasia, whereas 4 patients had a combination of two of these conditions, and 1 patient was positive for all three.

To elucidate clinical characteristics associated with skull base abnormalities, logistic regression analyses were performed (Table 4). These analyses were limited to the group of 169 patients with OI types I, III, and IV because the other OI types were too rare for detailed statistical evaluation. Thirty-seven (22%) of these patients were positive for a skull base abnormality. Univariate analyses showed that the odds of having a skull base abnormality were significantly higher in patients who had dentinogenesis imperfecta or Wormian bones. A diagnosis of OI type I as well as higher *Z*-scores for height, weight, and LS aBMD were significantly associated with lower odds for a skull base abnormality. Age, gender, scleral hue, and a history of bisphosphonate treatment were not significantly related with the presence of skull base abnormalities.

To find out which of these factors were independently associated with skull base abnormalities, they were entered into a stepwise logistic regression model. The final model included only height *Z*-score (OR = 0.53, 95% CI 0.43–0.66, $p < .001$) as a significant independent determinant of skull base abnormalities. This reflected the fact that only 2 of the 44 patients (5%) with a height *Z*-score above –1 had a skull base abnormality, whereas 6 of the 64 patients (9%) with a height *Z*-score between –1 and –3 and 29 of 61 patients (48%) with a height *Z*-score below –3 had a skull base abnormality.

Even though a history of prior bisphosphonate treatment had no discernible effect on skull base abnormalities in the logistic regression analysis, we hypothesized that intravenous pamidronate treatment started in the first year of life might prevent the development of skull base abnormalities in the most severely affected children. However, in the group of patients with a height *Z*-score below –3, the prevalence of skull base abnormalities was similar to that in patients who had received pamidronate in the first year of life (8 of 17 patients corresponding to a prevalence of 47%) and in patients who had received bisphosphonates at a later age or not at all (21 of 44 patients, prevalence 48%, $p = .96$ by chi-square test).

Analysis by genotype

The association between skull base abnormalities and the type of collagen type I mutation underlying OI was investigated in the 140 patients with OI type I, III, or IV who had a known mutation in either the *COL1A1* or *COL1A2* gene (Table 5). Skull base abnormalities were present in 6% of the patients with haploinsufficiency mutations, in 43% of patients with helical glycine substitutions in α1(I), in 32% of patients with helical glycine substitutions in α2(I), in 17% of patients with splice-site mutations affecting either *COL1A1* or *COL1A2*, in two of the five patients with C-propeptide mutations, and in one of the five patients with in-frame deletions.

Further statistical assessment was performed in the group of 107 patients with either haploinsufficiency mutations or helical glycine substitutions because propeptide mutations and deletions were too rare for statistical analysis, and the effect of splice-site mutations on gene transcription cannot be judged on the basis of DNA analyses alone. Stepwise logistic regression analysis was performed to evaluate which of a set of variables (ie, type of collagen mutation, age, sex, height *Z*-score, weight *Z*-score, lumbar spine aBMD *Z*-score, presence of dentinogenesis imperfecta, presence of blue sclerae, presence of Wormian bones, or history of bisphosphonate treatment) were independently associated with skull base abnormalities. The final model included only height *Z*-score (OR = 0.48, 95% CI 0.37–0.64, $p < .001$) as a significant independent predictive factor of skull base abnormalities.

Longitudinal analysis

The preceding analyses were performed on the last available skull radiograph of each patient. However, in 62 patients, at least one previous skull X-ray was available that had been obtained at

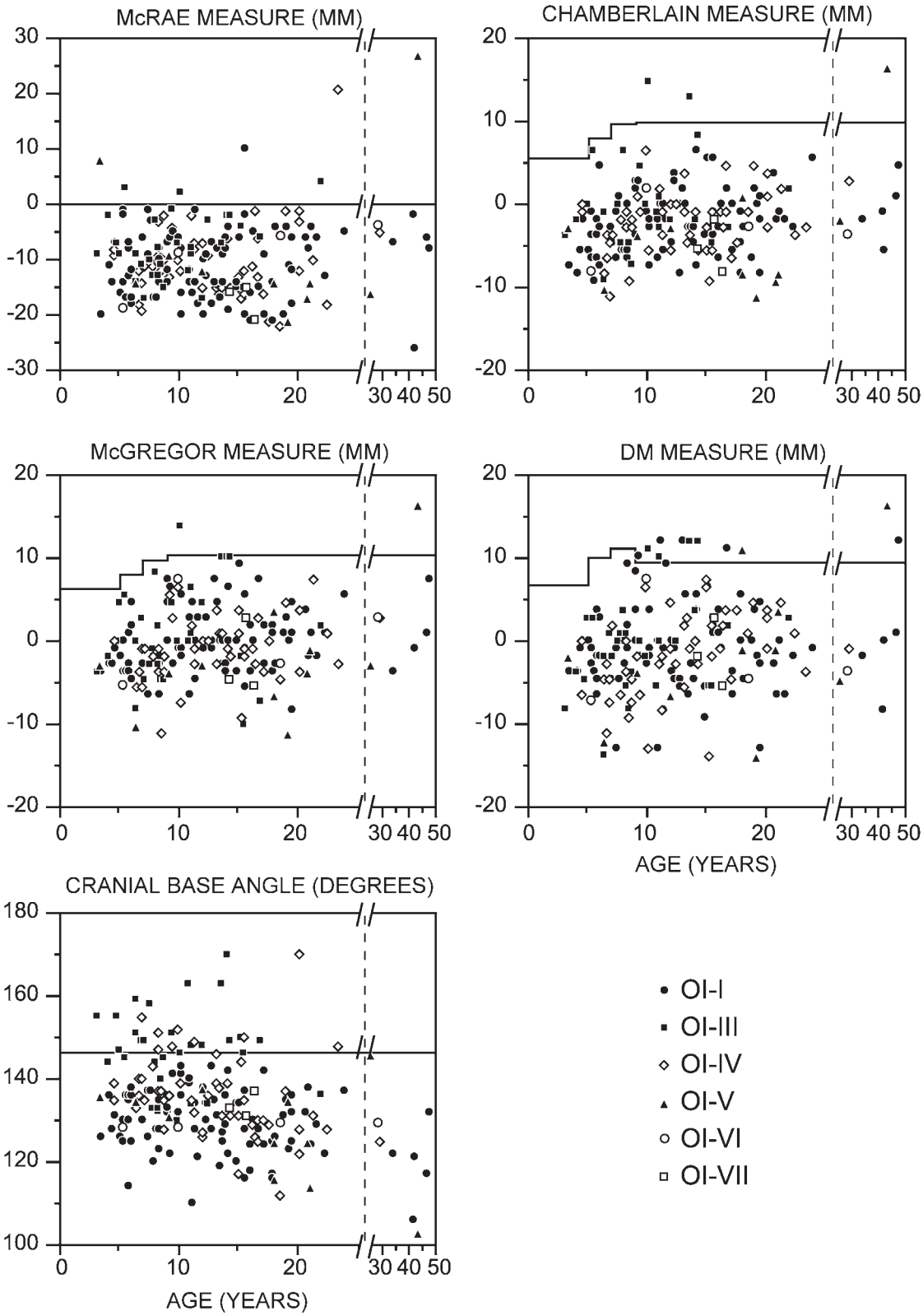

Fig. 3. Individual results of skull base measurements in patients with OI. The cutoff values for diagnosing skull base abnormalities are indicated by drawn lines.

the age of 3 years or older. This allowed for the evaluation of changes in skull base abnormalities. The first skull radiograph had been obtained at a median age of 7.3 years (range 3.1 to 23 years), and the median time interval between the first and the last skull X-ray was 6.8 years. The first radiograph showed a skull base abnormality in 9 of the 62 (15%) patients (basilar impression in 4, platybasia in 5 patients). At the time of the second radiograph, none of the 4 patients with basilar impression on the

Table 3. Number and Percentage of All OI Patients With a Positive McRae Value or a Measurement Value > 3 SD Above the Average Value of the Age-Appropriate Healthy Control Group

OI type	OI-I ($n = 88$)	OI-III ($n = 30$)	OI-IV ($n = 51$)	OI-V ($n = 11$)	OI-VI ($n = 4$)	OI-VII ($n = 3$)	All ($n = 187$)
McRae	1 (1%)	3 (10%)	1 (2%)	2 (18%)	0 (0%)	0 (0%)	7 (4%)
Chamberlain	0 (0%)	2 (7%)	0 (0%)	1 (9%)	0 (0%)	0 (0%)	3 (2%)
McGregor	0 (0%)	1 (3%)	0 (0%)	1 (9%)	0 (0%)	0 (0%)	2 (1%)
DM distance	5 (6%)	4 (13%)	0 (0%)	2 (18%)	0 (0%)	0 (0%)	11 (6%)
Cranial base angle	0 (0%)	18 (60%)	10 (20%)	1 (9%)	0 (0%)	0 (0%)	29 (16%)
Any abnormality	6 (7%)	21 (70%)	10 (20%)	4 (36%)	0 (0%)	0 (0%)	41 (22%)

Table 4. Univariate Logistic Regression Analysis of Factors Associated With the Presence of Any Skull Base Abnormalities in Patients With Clinical Type I, Type III, or Type IV OI

	n	OR (95% CI)	*p*
Gender (F/M)	169	1.06 (0.51–2.2)	.88
OI type (I versus III and IV)	169	0.30 (0.10–0.88)	.03
Age (years)	169	0.99 (0.94–1.04)	.67
Height (*Z*-score)	169	0.57 (0.47–0.68)	<.001
Weight (*Z*-score)	169	0.54 (0.41–0.72)	<.001
LS aBMD (*Z*-score)	160	0.61 (0.43–0.87)	.005
Dentinogenesis imperfecta (yes/no)	169	7.4 (3.2–17.2)	<.001
Blue sclera (yes/no)	169	1.1 (0.48–2.6)	.79
Bisphosphonate treatment (yes/no)	169	2.2 (0.90–5.4)	.08
Wormian bones (yes/no)	169	3.4 (1.4–8.2)	.008

CI = confidence interval; LS aBMD = lumbar spine areal bone mineral density; OR = odds ratio.

Table 5. Abnormal Results According to the Type of COL1A1 or COL1A2 Mutation

OI type	Haplo-insufficiency ($n = 35$)	Helical α1(I) mutation ($n = 28$)	Helical α2(I) mutation ($n = 44$)	Splice-Site Mutation ($n = 23$)	C-Propeptide mutation ($n = 5$)	Deletion ($n = 5$)	All ($n = 140$)
McRae	0 (0%)	2 (7%)	2 (5%)	1 (4%)	0 (0%)	0 (0%)	5 (4%)
Chamberlain	0 (0%)	1 (4%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)
McGregor	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)
DM distance	2 (6%)	2 (7%)	2 (5%)	2 (9%)	0 (0%)	0 (0%)	8 (6%)
Cranial base angle	0 (0%)	9 (32%)	13 (30%)	1 (4%)	2 (40%)	1 (20%)	26 (19%)
Any abnormality	2 (6%)	12 (43%)	14 (32%)	4 (17%)	2 (40%)	1 (20%)	35 (25%)

initial film fulfilled criteria for basilar impression any longer. In contrast, platybasia persisted in all 5 patients who had this diagnosis in the first skull radiograph. At the time of the second X-ray, an additional 7 patients (who had been between 3 and 15 years of age at the time of the first radiograph) had developed platybasia, and 6 had newly acquired basilar impression. Basilar invagination was not observed in this group at either time point.

Discussion

In this study we found skull base abnormalities in all OI types except for the rare OI types VI and VII. Overall, 22% of patients were positive for at least one skull base abnormality. Platybasia was by far the most prevalent diagnosis, affecting 16% of patients, whereas basilar impression and basilar invagination were noted in 6% and 4% of patients, respectively. We observed a clear genotype-phenotype correlation: Patients with haploinsufficiency mutations (which lead to a milder phenotype) were less likely to have skull base abnormalities than patients with helical glycine substitutions. However, the strongest predictor of skull base abnormality was not the type of collagen mutation underlying OI but the clinical severity of the disorder, as expressed by the height *Z*-score.

To our knowledge, the presence of skull base abnormalities in OI type V has not been reported before. For the other OI types, the prevalence of skull base abnormalities found in this study appears to be within the range reported in the literature, even

though comparisons with most other studies are made difficult by differences in diagnostic criteria. For example, Janus and colleagues suspected basilar invagination in 10% of their 130 pediatric OI patients based on "protrusion of the odontoid above Chamberlain's or McGregor's line" on lateral skull radiographs.[14] In our study population, a much higher proportion of patients, 37%, would have fulfilled these criteria. In contrast, the prevalence of skull base abnormalities in our study was clearly lower than suggested by Sillence, who reported that "25% of a relatively random group of clinic patients with OI had basilar invagination," based on a Chamberlain measure above 5 mm or a McGregor measure above 7 mm.[15] When applying these cutoff values, only 11% of our study population would be classified as having abnormal results.

The only study that used the same definitions and diagnostic criteria as this analysis found that 22% of 54 adult OI patients had basilar invagination (defined as a McRae measure at or above 0). In this study, only 4% of patients had basilar invagination based on this definition, even though the distribution of OI types was similar between the two studies. The discrepancy in the prevalence of basilar invagination between the two studies may be due to the age difference between study populations. Most of our patients were children and adolescents, and the median age of participants was 12 years, whereas Kovero and colleagues examined adults with an average age of 36 years. These observations suggest that basilar invagination, as defined in this study, develops predominantly during adulthood.

Our finding that skull base abnormalities are more frequent in more severely affected patients confirms earlier studies.[6,15] A new observation of this study is that height *Z*-score is the strongest predictor of skull base abnormalities. Indeed, once height *Z*-score was included in the logistic regression model, it "crowded out" OI type and type of collagen type I mutation and other clinical characteristics as predictors of skull base abnormalities. This is probably due to the fact that height *Z*-score as a continuous measure provides more precise information about disease severity than clinical OI type, type of collagen mutation, or dichotomous clinical characteristics such as presence or absence of dentinogenesis imperfecta. Therefore, the presence of a cranial base abnormality should be suspected, especially in short patients who present with suggestive signs and symptoms, such as headache, facial numbness, nystagmus, dysphagia, and ataxia.[4]

Although little is known about the mechanisms leading to skull base abnormalities in OI, many authors assume that they are caused by the "softness" of the skull bone.[4,5] This view is corroborated by the observation that skull base abnormalities occur not only in OI but also in other conditions that decrease the mechanical resistance of bone, such as osteomalacia, Hajdu-Cheney syndrome, and Paget disease.[4,5] However, bone in OI is not "soft" but on the material level is even harder than normal bone, which makes OI bone more brittle.[16] Thus it appears more plausible to assume that repeated microcracks rather than "bone softness" lead to skull deformation in OI.

If decreased mechanical resistance of bone tissue is the underlying cause of skull base abnormalities in OI, one might assume that bisphosphonate treatment might have a preventative effect. However, our logistic regression analyses indicated that a history of bisphosphonate treatment did not have an independent effect on the prevalence of skull base abnormalities. In addition, in patients with very short stature (and thus a high risk of skull base abnormalities,) treatment with intravenous pamidronate in the first year of life did not have a detectable influence on the prevalence of skull base abnormalities in later life. It is still possible that bisphosphonate treatment has an effect on the development of skull base abnormalities in ways that escaped detection in this study. For example, as discussed earlier, it appears that basilar invagination develops mostly during adulthood. However, basilar invagination was rare in this study, and long-term follow-up into adulthood would be necessary to assess whether bisphosphonate treatment during childhood decreases the risk of developing basilar invagination in later life.

In this study, we followed the definitions and diagnostic criteria established by Kovero and colleagues.[6] For two of the diagnoses pertaining to the skull base, basilar invagination and platybasia, the diagnostic criteria remain unchanged from 3 years of age to adulthood and are independent of the radiographic magnification factor. This is so because basilar invagination at all ages is defined as protrusion of the odontoid process into the foramen magnum, corresponding to a McRae measure of 0 or greater. Platybasia is diagnosed on the basis of the anterior cranial angle, which in our healthy population did not vary between 3 years of age and adulthood.[6,9] Interestingly, however, the cranial base angle decreased with age in the OI population, which suggests that craniofacial growth is altered in OI.

In contrast to basilar invagination and platybasia, the measures used to diagnose basilar impression vary with age in the healthy population and depend on the radiographic magnification factor. During facial growth, the palate changes its position relative to the craniovertebral junction, and consequently, measures using the palate (Chamberlain and McGregor lines) increase age-dependently, as seen in our control population. The third measure defining basilar impression, the DM distance, changes less with age because it uses the anterior skull base as a reference structure, which stabilizes earlier during growth than the midface. Apart from changing less with age, the DM measure also seems to be the most sensitive indicator of basilar impression. Indeed, all OI patients with an abnormal DM measure also had abnormal Chamberlain and McGregor measures. Similar observations had been made by Kovero and colleagues in adults.[6] It thus appears that in future studies it would be sufficient to determine the DM measure alone to diagnose basilar impression.

To our knowledge, this is the first study to include longitudinal data on skull base abnormalities in OI. In the subgroup of 62 patients in whom two skull radiographs could be evaluated, we found that platybasia persisted in all patients who had this diagnosis at the first time point and that some patients developed platybasia during follow-up. Thus platybasia did not have the tendency to "outgrow itself." In contrast, a few patients who were diagnosed with basilar impression based on the first radiograph no longer fulfilled the criteria for this diagnosis at the time of the second radiograph. This indicates that either the measurements that are used for diagnosing basilar impression

are more variable or that the basilar skull deformity itself can self-correct in some cases.

The strength of this study is that it provides information on skull base abnormalities in a well-characterized group of OI patients. The main limitation is that it is based entirely on lateral skull radiographs. Even though MRI was performed in a number of patients, as clinically indicated, these tests were not obtained systematically, and therefore, it is not possible to assess the extent to which radiographic findings correlate with the results of MRI. Nevertheless, we believe that lateral skull radiographs can provide useful information about the epidemiology of skull base abnormalities in patients with OI.

In conclusion, this study showed that skull base abnormalities were present in about a fifth of OI patients and that platybasia was the most frequent finding. Patients with very short stature are at the highest risk of developing skull base abnormalities. We did not find evidence for a protective effect of bisphosphonate treatment.

Disclosures

All the authors state that they have no conflicts of interest.

Acknowledgments

We thank Guylaine Bédard and Mark Lepik for preparation of the figures and Alberto Carli for contributing to the cephalometric evaluation. FR is a Chercheur-Boursier Clinicien of the Fonds de la Recherche en Santé du Québec. This study was supported by the Shriners of North America and the Fonds the la Recherche en Santé du Québec.

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