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Juliana Marulanda

Jean-Marc Retrouvey

Brendan Lee

V Reid Sutton

Frank Rauch

See next page for additional authors

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Cranio-Cervical Abnormalities in Moderate to Severe Osteogenesis Imperfecta – Genotypic and Phenotypic Determinants

Juliana Marulanda[1,2], **Jean-Marc Retrouvey**[3], **Brendan Lee**[4], **V. Reid Sutton**[4], **Members of the BBD Consortium**, **Frank Rauch**[1,2], **Michelle Briner**[3]

[1] Shriners Hospital for Children, Montreal, Qc, Canada

[2] Department of Pediatrics, McGill University, Montreal, Qc, Canada

[3] University of Missouri-Kansas City, Kansas City, MO, USA

[4]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

Abstract

Background: Cranio-cervical anomalies are significant complications of osteogenesis imperfecta (OI), a rare bone fragility disorder that is usually caused by mutations in collagen type I encoding genes.

Objective: To assess cranio-cervical anomalies and associated clinical findings in patients with moderate to severe OI using 3D cone beam computed tomography (CBCT) scans.

Approach: Cross-sectional analysis of CBCT scans in 52 individuals with OI (age 10 to 37 years; 32 females) and 40 healthy controls (age 10 to 32 years; 26 females). Individuals with a diagnosis of OI type III (severe, n = 11), type IV (moderate, n = 33) and non-collagen OI (n = 8) were recruited through the Brittle Bone Disorders Consortium. Controls were recruited through the orthodontic clinic of the University of Missouri-Kansas City (UMKC).

Results: OI and control groups were similar in mean age (OI: 18.4 (SD:7.2) years, controls:18.1 (SD:6.3) years). The cranial base angle was increased in the OI group (OI: mean 148.6° (SD:19.3), controls: mean 130.4° (SD:5.7), $p = 0.001$), indicating a flatter cranial base. Protrusion of the odontoid process into the foramen magnum (n=7, 14%) and abnormally located odontoid process (n=19, 37%) were observed in the OI group but not in controls. Low stature, expressed as height z-score (p=0.01), presence of DI (p=0.04), and being male (p=0.04) were strong predictors of

Corresponding author: **Michelle Briner, DDS**, Oral and Maxillofacial Radiologist, Assistant Professor, Department of Oral Pathology, Radiology and Medicine, University of Missouri – Kansas City, School of Dentistry, 650 East 25th Street, #3101, Kansas City, MO 64108.

Authors' roles

Study design: JM, JMR and FR. Data collection: JM, MB. Data interpretation: JM and FR. Drafting manuscript: JM, MB. Revising manuscript content and approving final version of manuscript: all authors. JM and FR take responsibility for the integrity of the data analyses.

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platybasia, whereas height z-score (p=0.049) alone was found as positive predictor for basilar impression as per the Chamberlain measurement.

Conclusion: The severity of the postcranial skeleton phenotype in OI, as expressed by the height z-score, correlates with the severity of cranial base anomalies such as platybasia and basilar impression in moderate to severe OI. Screening for cranial base anomalies is advisable in individuals with moderate to severe OI, with special regards to the individuals with a shorter stature and DI.

Introduction

Osteogenesis imperfecta (OI) is a hereditary condition characterized by low bone mass and bone fractures (1). Disease severity varies widely, ranging from lethal in the perinatal period, to very mild without bone fractures. OI can be accompanied by extraskeletal manifestations, such as blue sclera, dentinogenesis imperfecta (DI), hearing impairment and hyperlaxity of ligaments and skin (1). Height is inversely associated with the severity of the phenotype, as individuals with mild OI typically have a height within normal limits, whereas those with severe OI have marked height deficits (2).

About 85-90% of individuals with OI have pathogenic variants in either of the two collagen type I encoding genes *COL1A1* and *COL1A2*. Substitutions of glycine by another amino acid in the triple helical domain of either of the two collagen type I alpha chains are the most common mutations (3).

The treatment of OI depends on the severity, varying from bone fracture management to complex orthopedic rehabilitation where long bone deformities, vertebral compression fractures, scoliosis and mobility is compromised. The standard treatment of OI includes intravenous infusions with drugs from the class of bisphosphonates (4-6).

Craniofacial malformations are common findings in the OI population with the moderate to severe form. A higher incidence of class III malocclusion with anterior and posterior open bites has been reported (7). Bending of the cranial base and a counterclockwise rotation of the mandible, vertical underdevelopment of the dentoalveolar bone and condylar processes are thought to lead to a relative mandibular prognathism characteristic of OI (8). Likewise, facial asymmetries in the transversal plane, hypoplastic and retrognathic maxilla and insufficient airway dimension has been reported (9).

Cranio-cervical abnormalities are also important complications in OI. They mostly consist of flattening of the anterior base of the skull and protrusion of the vertebra C2 into the foramen magnum, causing brain stem compression, Chiari malformation, spinal cord syrinx formation and hydrocephalous (9-11). A variety of neurological symptoms have been reported, such as trigeminal neuralgia, imbalance, head and neck pain, weakness in legs and arms and bladder disorder (12, 13).

Cone beam-CT scan (CBCTs) is an X-ray technique that produces a volume of data that can be reconstructed for visualization in 3D. This technique allows clinicians to extract more reliable information on the patient, such as unerupted teeth, supernumerary teeth,

assessment of root resorption, airways, asymmetries, etc. Since the cranio-cervical region is also visible in large volume CBCTs, and since pathologies in this region are prevalent in the OI population, here, we assess the cranio-cervical abnormalities and associated clinical findings in a cohort of 52 patients with moderate to severe OI using 3D cone beam computed tomography (CBCT) scans.

Materials and Methods

Subjects

68 individuals with moderate to severe OI were recruited through the Brittle Bone Disorders Consortium (BBDC) (https://www.rarediseasesnetwork.org/cms/BBD) and evaluated at the Shriners Hospital for Children in Montreal. The consortium is a Rare Disease Clinical Research Network that is funded by the National Institutes of Health. Dental assessments were performed in the context of a natural history study that aims to describe the clinical features of all types of OI. CBCT scans were performed as part of a craniofacial study that focused on moderate to severe OI. All study participants or their legal guardians provided informed consent. Additionally, CBCT scans from 40 age- and sex-matched controls were obtained from the University of Missouri-Kansas City School of Dentistry (UMKC). These CBCT scans had been performed for clinical orthodontic assessments between 2015 and 2022. Ethics approval was granted by McGill University and UMKC.

Cone Beam CT Scans

CBCT scans for the OI group were acquired with a 3D Accuitomo 170 (Morita Inc, Kyoto, Japan) CBCT machine in a 170 mm × 120 mm field-of-view and a 250 μm voxel size. The exposure settings included a tube voltage of 90 kV and a tube current of 4.5 mA for 17.5 seconds. CBCT scans for the control cases were taken using the I-CAT FLX machine with 120kVp, 5mA and 14 seconds of exposure. The field of view was 17x12 centimeters. To be included in this study, all the images had to show the nasion, sella turcica, clivus, second cervical spine and opisthion. Patients with syndromes or pathologies (besides OI) that would modify the bony anatomy of the head and neck, or images with artifacts that would impair accurate measurements, were excluded from the study.

Craniometry

CBCT scans were analyzed by an Oral and Maxillofacial Radiologist (MB) using Anatomage InVivo 6 (Invivo Dental; Anatomage, San Jose, CA) software. The measurements were done using the ruler (in millimeters) and compass tools of the software. To ensure standardization, the images were aligned adjusting the midsagittal and Frankfort horizontal planes perpendicular and parallel to the floor, respectively. The measurements performed were the following: Distance between the Chamberlain, McGregor, McRae, bimastoid and digastric lines to the dens, base of the skull and clivoaxial angle (Table 1 and Figure 1).

Platybasia was diagnosed by a cranial base angle greater than 140°(14, 15), *basilar invagination* by a McRae line to Dens greater than 0mm (14, 16), and *basilar impre*ssion

by Chamberlain-Dens greater than 5mm and McGregor-Dens greater than 7mm (10, 16, 17)(Table 1).

Clinical assessment

Height was measured using a Harpenden stadiometer (Holtain Limited, Crymych, UK). Presence or absence of dentinogenesis imperfecta was recorded from the dental exams obtained in the context of the BBDC natural history study that aims to describe the clinical features of OI. Results of genetic testing were obtained from the BBD study database. Patients with mutations in genes other than *COL1A1* and *COL1A2* were clustered together in a group called Non-Col OI.

Statistical Analysis

Height measurements values were converted to age- and sex-specific z-scores according to the reference data published by the Center for Disease Control and Prevention (18). Group differences were evaluated using t-test, ANOVA and X^2. Logistic regression analysis was used to evaluate the relationship between clinical characteristics and the presence of cranio-cervical abnormalities. Results are expressed as odds ratios (ORs) with 95% CI. All tests were two tailed, and p values <0.05 were considered significant. Calculations were preformed using SPSS software, version 28.0 (SPSS Chicago, IL, USA) and graphs were generated using GraphPad Prism, version 9.5.1 (GraphPad software, San Diego, California USA).

Results

CBCT scans were performed in 68 individuals with OI, but the scans of 16 participants were excluded from analysis, due to poor visibility of posterior cranial structures or poor positioning during the CBCT acquisition, as many patients had limited mobility.

Comparison between OI and control groups

Demographics: CBCTs of 52 OI patients and 40 controls were analyzed. There were no differences between OI and control group with regard to age (OI: 18.4 (SD: 7.2) years, control: 18.1 (SD: 6.3) years, $p = 0.73$) and sex distribution (Female/Male OI: 34/18, Control: 26/14 $p= 0.99$).

Cranio-cervical abnormalities: More than half of the OI patient cohort (56%) presented with platybasia, as compared to only 3 controls (7%) ($p <0.001$) (Figure 2A). Regarding the position of the dens in relation to the foramen magnum, 14% of the OI patients and none of the controls were diagnosed as having basilar invagination ($p <0.001$), defined by a Dens-McRae measurement above 0 mm (Figure 2B). Basilar impression assessed by the Dens-Chamberlain, Dens-McGregor, and Dens-Bimastoid measurements, was diagnosed in about 30% of the patients with OI and none in the control group ($p <0.001$ in all cases). The clivo-axial angle was decreased in 10 OI patients as well ($p <0.001$) (Figure 2 C-F and Table 2).

Analysis by OI type

Sample demographics: CBCT results were compared between OI groups (Table 3). Differences in height z-score were statistically significant between groups, with OI type III individuals being the most affected. None of the Non-Col OI patients presented with DI, whereas 82% of the OI type III and 45% of OI type IV groups were diagnosed with having DI. Other clinical characteristics such as sex and age were similar between groups. (Table 3).

Cranio-cervical abnormalities: Platybasia was present in 100% of the patients with OI type III, while 58% of the patients with OI type IV presented a flat cranial base. In contrast, none of the patients with OI due to mutations in genes other than *COL1A1* and *COL1A2* had platybasia. Basilar invagination and basilar impression were assessed according to OI types. (Figure 3 and Table 4). Basilar invagination was seen in 27% of the patients with OI type III and basilar impression was detected in more than half of the OI type III group. In contrast, 30% of the patients with OI type IV had basilar impression, and 12% of them had basilar invagination. The patients in the non-Col OI group were the least affected, with only one patient having signs of basilar invagination based on the increased Dens-Chamberlain and Dens-Bimastoid measurement. The clivo-axial angle was affected in 21% of the patients with moderate to severe OI, while 82% of the severe OIs presented with an increased Dens-Bimastoid distance (Table 4).

Next, we compared the severity of the craniofacial phenotype by the gene mutated, as determined by genetic testing. There was no difference in the severity of the cranio-cervical phenotype between patients with mutations in *COL1A1*, *COL1A2* and other genes known to cause moderate to severe OI (Other) (Table 5).

Correlation between clinical characteristics and cranio-cervical abnormalities: We next examined whether clinical characteristics could be predictors of platybasia in the population with moderate to severe OI. Univariate and multivariate logistic regression analysis indicated that presence of DI, the height z-score and sex were strong predictors of a flat cranial base, but not age (Table 6). Yet, there were not enough cases with basilar invagination (McRae greater than 0mm) to assess whether any of the clinical characteristics could act as a predictor for such an abnormality. Height z-score was the only predictor for basilar impression as per Dens-Chamberlain measurement (Chamberlain greater than 5mm). Conversely, the presence of DI, age and sex did not show any correlation with basilar impression (Table 7).

Correlation between platybasia and other cranio-cervical abnormalities: Since a flat cranial base is the more prevalent cranio-cervical abnormality in our OI cohort (56%), we asked whether it correlates with the other abnormalities assessed. We found that platybasia correlates significantly with basilar impression and basilar invagination, which may have important clinical implications when diagnosing cranio-cervical pathologies (Table 8).

Discussion

In the present study, we assessed the prevalence of cranio-cervical abnormalities in a cohort of patients with moderate to severe OI and compared it to healthy controls by CBCTs. We found that more than half of the population with OI have some form of cranio-cervical malformation, whereas only 3 individuals in the control group were diagnosed with platybasia. Moreover, we evaluated clinical characteristics that could act as predictors of cranio-cervical pathology and compared the severity of the cranio-cervical involvement within OI groups.

Several studies assessed cranio-cervical abnormalities in OI (8-11, 13). However, these studies use mainly lateral cephalograms to assess the cranial base angle, basilar invagination, and basilar impression. Although the anatomical landmarks are similar on lateral skull radiographs, CBCTs and MRIs, superimposition of images, the inability to visualize the mid sagittal plane, the radiographic magnification and extreme osteoporotic skull bones and altered cranial base anatomy, can lead to landmark misinterpretation and measurement errors (15, 19, 20).

It has been hypothesized that the brain weight placing pressure over poorly mineralized bones might cause caudal sinking of the occipital bone and depression of the sella, causing an alteration of the base of the skull angle and McGregor line measurements in OI patients (8). This phenomenon might be the responsible for the flat base of the skull and increased incidence of basilar impression in the OI population, as reported here and by others (9-11, 21).

We found platybasia in 100% of patients with OI type III, 58% of the patients with OI type IV, 7% of the control cases and none of the non-col type OI. Most affected patients were thus those with severe form of OI. This finding was consistent with a previous CBCT study done by Reznikov in 2019 (9) using the same database of OI patients as the current paper. Noteworthy to mention that the severity of the craniocervical involvement was statistically significant between the different OI types (III, IV and non-Col), regarding platybasia and basilar impression. Conversely, basilar invagination measured by Dens-McRae, did not differ between OI types.

Similar findings were reported in a cephalometric study (8), where a mean base of the skull angle of 140° was reported in patients with OI type III and IV, whereas none of the control cases presented platybasia. In the other hand, in our study, we found 3 control patients with platybasia, two of which had cranial angle measurements negligibly altered as their measurements were slightly above the normal limit. The base of the skull alterations seen in these control cases were minimal compared to the OI patients, and it was considered clinically irrelevant as it was an isolated finding, and the patients were asymptomatic. It is important to mention that platybasia can occur in a variety of disorders or congenital craniofacial anomalies, other than OI (15, 22).

Basilar invagination and basilar impression are craniovertebral junction anomalies, where the odontoid process of C2 prolapses into the foramen magnum. The term basilar impression is used when there is an abnormal softening of the bone, like in cases of OI. In the literature,

the prevalence of these anomalies in OI patients varies, averaging approximately 25% (13) and 37% (10) which is consistent with our findings.

The findings regarding basilar invagination and impression were correlated with body height, as a short stature is a known feature affecting individuals with OI, especially those with OI type III and IV. In our study, patients with OI type III were statistically significantly shorter than those with OI type IV and other non-Col types. This finding was expected, as patients with OI type III are more severely affected. The reason for a short stature is still unknown. It has been hypothesized in a mouse model that it is caused by dysfunctional hypertrophic chondrocytes. However, this theory has not be proven in humans (6). Other theories such as the impact of the long-term use of bisphosphonates on linear growth has been studied without conclusive answers (23). In our study, we analyzed whether a shorter stature would correlate with basilar impressions or invaginations. Indeed, a lower height z-score and presence of DI were positive predictors of OI severity and were associated with platybasia. Moreover, we found that lower stature also increased the odds of having basilar impression, but not basilar invagination.

Since the diagnosis of OI was confirmed in our population by genetic testing, we asked whether the severity of the cranio-cervical phenotype would differ regarding the gene mutated. We found no difference in the cranio-cervical pathology between patients with mutations in *COL1A1* and *COL1A2* chains of the collagen type I and other genes, grouped all together. Other papers have reported that genetic variants are good predictors of dental phenotype, however, in this case, patients with OI type I (haploinsufficient, mild OI) were compared together with patients with glycine substitutions, that are the moderate to severe cases (24). In the current study, that only includes moderate and severe forms of OI, the genotype did not predict the severity of the cranio-cervical phenotype.

We showed here that more than 90% of the patients that have basilar impression and/or basilar invagination, also have platybasia. This observation has important clinical implications, since the cranial base angle is routinely measured in the orthodontic consult as part of a basic cephalometric analysis. However, the cranio-cervical analysis that define basilar invagination and basilar impression are not regularly performed, and overlooked in many cases. Thus, if platybasia is detected in an OI patient, a detailed analysis of the cranio-cervical anatomy is warranted.

Conclusion

This study shows that cranial-base abnormalities are highly prevalent in the population with moderate to severe OI, with platybasia being diagnosed in more than half of the population. Short stature and DI are predictors of a flat cranial base and basilar impression. Platybasia is significantly associated with basilar impression and invagination, therefore making it an important diagnostic criteria in the craniofacial exam of patients with moderate to severe OI and shorter stature.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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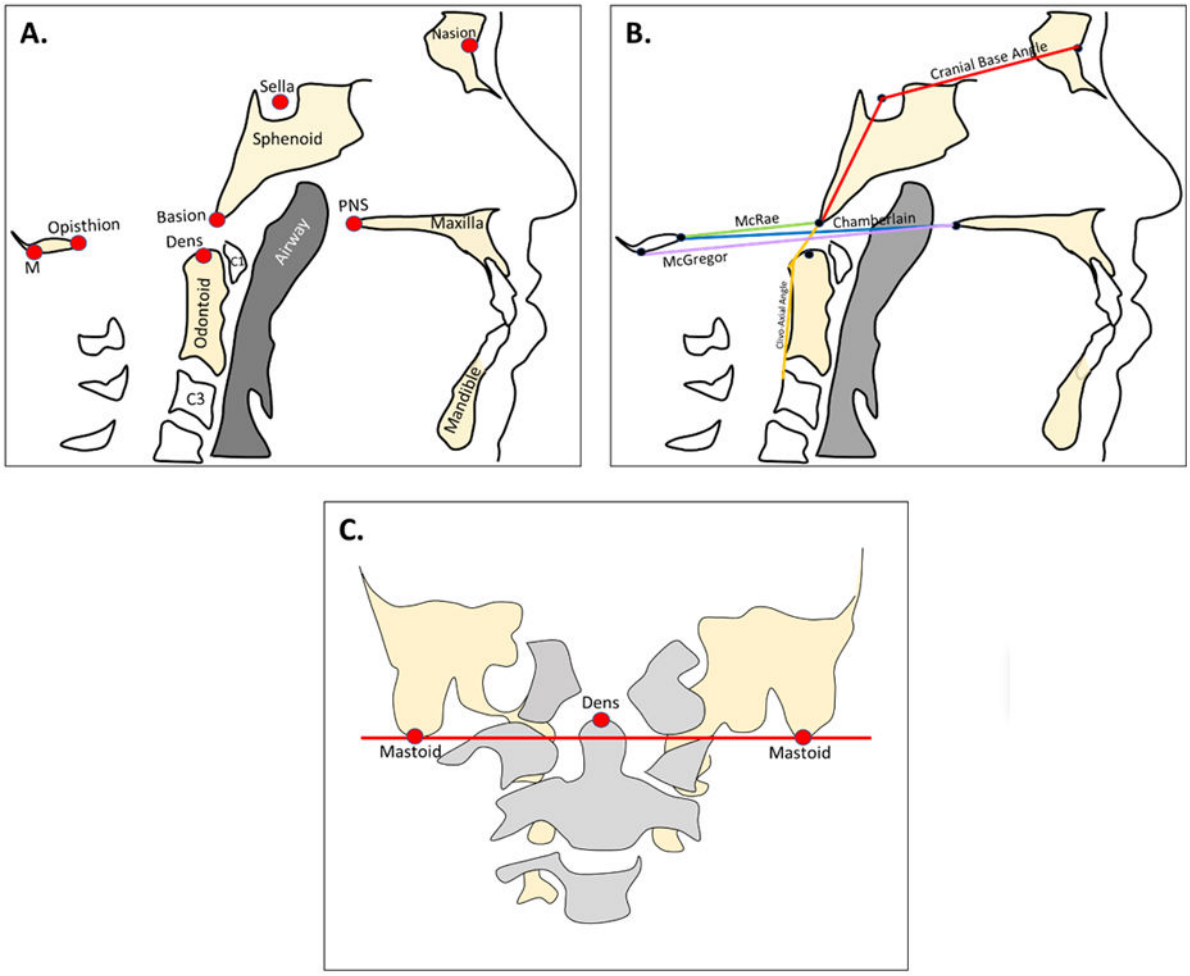

Figure 1: Landmarks and measurements.

A. Cranio-cervical landmarks identified in CBCTs in sagittal view. **B.** Reference lines to measure angles (Cranial base angle, Clivoaxial angle) or distances between point Dens to the respective line. **C.** Landmarks and reference line for the Bimastoid-Dens measurement in the coronal view. The two-colored bones represent two different coronal planes. Refer to Table 1 for measurement definitions.

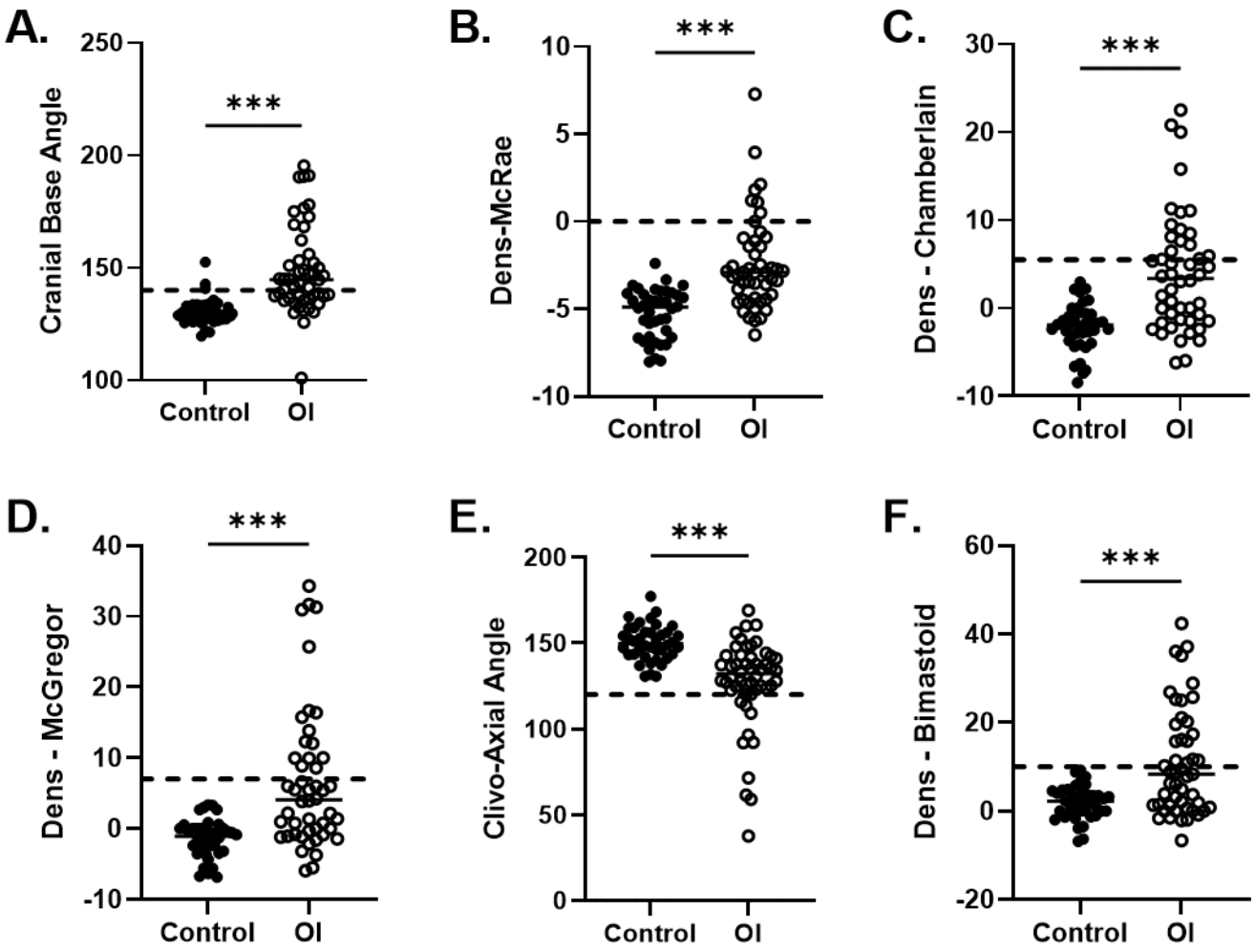

Figure 2:

Cranio-cervical abnormalities in control and OI group. SEM denoted with continuous line among each dataset, dotted line across datasets describes cutoff value for each measurement. $p = 0.001$*** by T-Test.

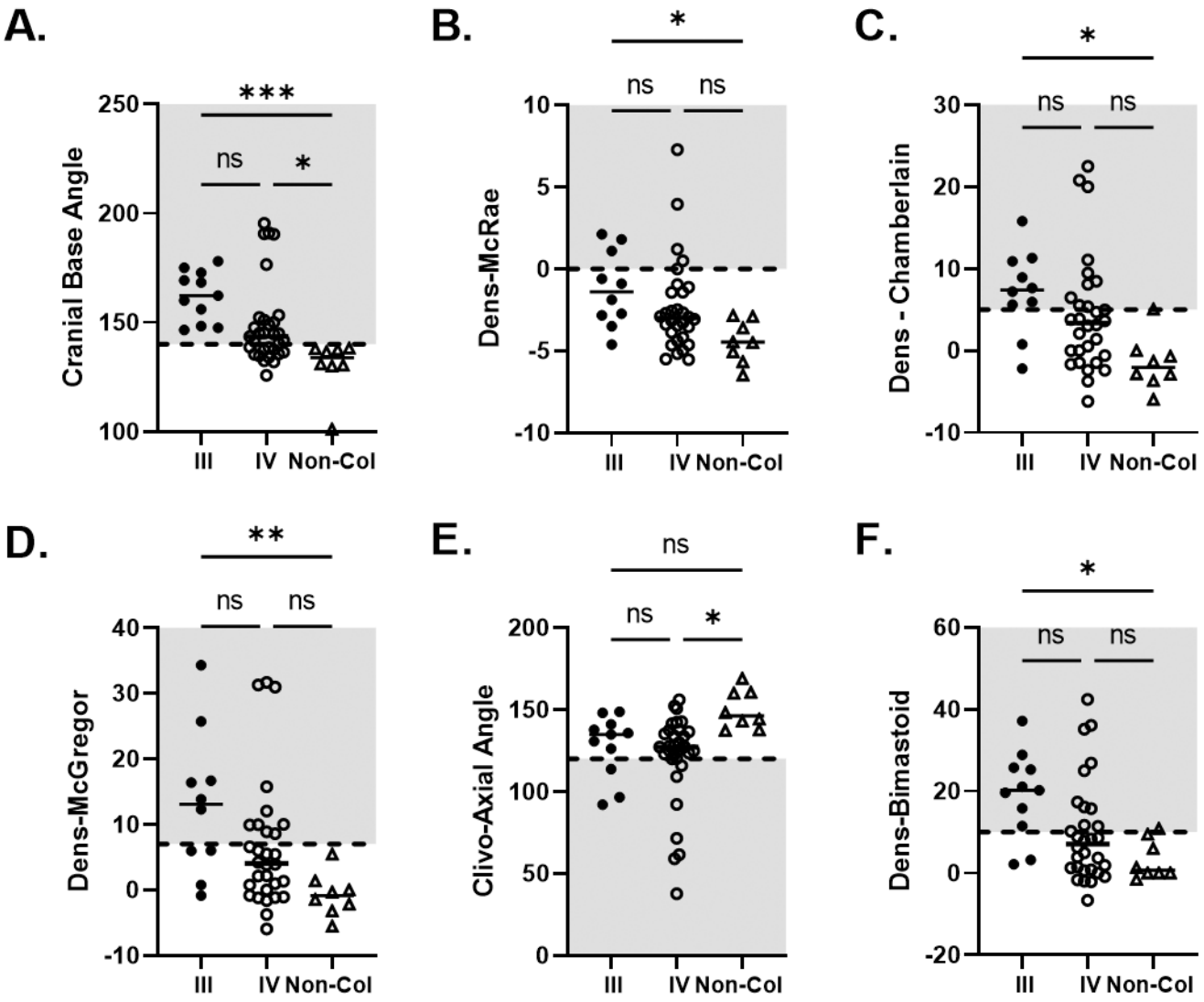

Figure 3:

Cranio-cervical abnormalities by OI type. SEM denoted with continuous line among each dataset, gray shadow represents the pathological measurements above or below the cutoff value. *p*= 0.05*, 0.005**, 0.001***NS: Not significant by ANOVA.

Table 1:

Craniometry in CBCT scans. Negative values are indicated below the reference line.

Landmark	Definition	Normal measurements	Abnormal measurements
Chamberlain line	Runs from the posterior nasal spine (PNS) to the opisthion	The tip of the odontoid process should be positioned +− 3.3 mm around this line.	Extends more than 5mm above this line (14, 16)
McGregor line	Runs from the posterosuperior margin of the hard palate (PNS) to the lowest point on the occipital curve (M)	The tip of the odontoid process extends no more than 4.5 mm above this line	Extends more than 7 mm above this line (14, 16)
McRae line	Runs from basion to the opisthion	The tip of the odontoid process should be below this line by approximately −4 to −5 mm.	Extends beyond this line by more than 5 mm (14, 16, 17)
Cranial Base Angle	Lines drawn from the nasion (N) to the center of the pituitary fossa (S), and from S to the midpoint on the anterior border of the foramen magnum (basion, Ba)	It is 132° on average and considered normal when less than 140°	Platybasia is defined by an angle greater than 140°(14)
Clivoaxial angle (CXA)	Angle formed by the intersection of a line extending from the top of the dorsum sellae to the basion, and a line extending from the infero-dorsal to the most superodorsal part of the dens	This angle has a normal range of 145° to 160° in neutral neck position, 150° in flexion to 180° in extension.	The CXA angle in patients with basilar invaginations averages 120° (25).
Bimastoid line	Drawn between the inferior tips of the mastoid process bilaterally	The tip of the odontoid process projects approximately 5.15mm above this line, with a standard deviation of +/−4.86mm.	The dens projects 10 mm above this line (16)

Table 2:

Number of patients and percentage with craniovertebral anomalies in control and OI groups.

	Control (n=40)	OI (n=52)
Cranial base angle	3 (7%)	29 (56%)
Dens-McRae	0 (0%)	7 (14%)
Dens-Chamberlain	0 (0%)	19 (37%)
Dens-McGregor	0 (0%)	16 (31%)
Clivo-axial angle	0 (0%)	10 (19%)
Dens-Bimastoid	0 (0%)	21 (40%)

Table 3:

OI group according to OI type

	All	OI type III	OI Type IV	Non-Col OI	*p*
n (%)	52	11 (21)	33 (63)	8 (16)	
Male/Female (%)	18/34 (35/65)	3/8 (27/73)	14/19 (42/58)	1/7 (12/88)	0.25
Age (mean, SD)	18.4 (7.24)	18.4 (7.2)	18.3 (7.4)	18.8 (7.5)	0.89
Dentinogenesis Imperfecta *n*, (%)	24 (46.2%)	9 (82%)[b]	15 (45%)[c]	0 (0%)	0.001
Height Z-score (mean, SD)	−4.68 (2.90)	−8.0 (2.9)[a,b]	−3.8 (2.9)	−4.2 (3.0)	<0.001

Abbreviations: SD: Standard deviation

p value compares the 3 OI sub-groups by ANOVA. Multiple comparisons are calculated with Bonferroni post-hoc test and significance is denoted by superscript.

[a] $p < 0.05$ for OI type III vs IV

[b] $p < 0.05$ for OI type III vs Non-Col

[c] $p < 0.05$ for OI type IV vs Non-Col

Table 4:

Number of patients and percentage with positive craniovertebral anomalies by OI type.

	OI III (n=11)	OI IV (n=33)	Non-Col OI (n=8)	*p*
Cranial base angle	11 (100%)[ab]	19 (58%)[c]	0 (0%)	<0.001
Dens-McRae	3 (27%)	4 (12%)	0 (0%)	0.20
Dens-Chamberlain	8 (73%)[ab]	10 (30%)	1 (12%)	0.01
Dens-McGregor	6 (55%)[b]	10 (30%)	0 (0%)	0.04
Clivo-axial angle	3 (27%)	7 (21%)	0 (0%)	0.31
Dens-Bimastoid	9 (82%)[ab]	11 (33%)	1 (12%)	0.003

p value compares the 3 OI sub-groups by ANOVA. Multiple comparisons are calculated with Bonferroni post-hoc test and significance is denoted by superscript.

[a] $p < 0.05$ for OI type III vs IV

[b] $p < 0.05$ for OI type III vs Non-Col

[c] $p < 0.05$ for OI type IV vs Non-Col

Table 5:

Distribution of OI cases with cranial base abnormalities by gene mutation

	Total *n* (%)	***Col1A1* *n***	***Col1A2* *n***	**Other *n***	**Not found *n***	***p***
Cranial base angle (Platybasia)	32 (62)	13	15	1	3	0.82
McRae (Basilar Invagination)	7 (13)	5	2	0	0	0.57
Chamberlain (Basilar Impression)	19 (37)	9	5	2	3	0.93
McGregor (Basilar Impression)	16 (31)	7	6	0	3	0.97
Clivoaxial Angle (Basilar Invagination)	10 (20)	4	6	0	0	0.10
Bimastoid (Basilar Invagination)	21 (40)	9	9	2	1	0.56

p value determined by ANOVA and Bonferroni post-hoc test

Table 6:

Clinical characteristics associated with Platybasia

	No Platybasia* ***n*=20**	**Platybasia*** ***n*=32**	**OR (95% CI) Univariate**	***p***	**OR (95% CI) Multivariate**	***p***
Presence of DI (y/n)	4/16	20/12	6.00 (1.60, 22.38)	0.008	6.16 (1.09, 34.82)	0.04
Height z-score	−4.5 (−8.1, 0.2)	−4.6 (−10.8, − 0.7)	0.66 (0.50, 0.87)	0.004	0.68 (0.50, 0.92)	0.01
Age (years)	16.6 (10.5, 37.8)	16.8 (10, 35.3)	1.055 (0.92, 1.08)	0.90	1.01 (0.90, 1.13)	0.89
Sex (m [=0] / f [=1])	3/17	15/17	0.23 (0.05, 0.95)	0.04	0.11 (0.02, 0.84)	0.03

*Values represent *n* or median (min, max)

Table 7:

Clinical characteristics associated with Basilar Impression

	No Basilar Impression* **n=33**	**Basilar Impression*** **n=19**	**OR (95% CI) Univariate**	***p***	**OR (95% CI) Multivariate**	***p***
Presence of DI (y/n)	13/20	11/8	2.61 (0.79, 8.59)	0.11	2.12 (0.50, 9.09)	0.31
Height z-score	−4.5 (−9.7, 0.2)	−4.8 (−10.8, −0.4)	0.75 (0.59 – 0.96)	0.02	0.78 (0.60, 1.00)	0.049
Age (years)	16.6 (10.5, 37.8)	17.05 (10, 35.3)	1.01 (0.93 – 1.10)	0.81	1.02 (0.91, 1.14)	0.77
Sex (m [=0] / f [=1])	21/12	13/6	0.83 (0.23 – 2.92)	0.77	0.99 (0.20, 4.92)	0.99

*Values represent *n* or median (min, max)

Table 8:

Association between platybasia and other cranio-cervical anomalies in OI

	Total	Platybasia n (%)	No platybasia n (%)	*p*
McRae (Basilar Invagination)	7	7 (100)	0 (0)	0.035
Chamberlain (Basilar Impression)	19	18 (95)	1 (5)	<0.001
McGregor (Basilar Impression)	16	0	16	<0.001
Clivoaxial Angle (Basilar Invagination)	10	10 (100)	0 (0)	0.008
Bimastoid (Basilar Invagination)	21	19 (90)	2 (10)	<0.001

Total represents all the OI patients positive for the craniofacial abnormality. Significance calculated by Fisher's exact test.