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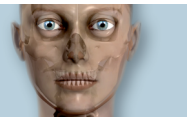

ORIGINAL ARTICLE

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Morphological characteristics of frontal sinus and nasal bone focusing on bone resorption and apposition in hypophosphatemic rickets

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Structured Abstract

Objectives – To characterize the size and the morphology of the frontal sinus (i.e., structure evolved by bone resorption) and the nasal bone (i.e., structure evolved by bone formation) in adults with hypophosphatemic rickets (HR) compared with controls.

Setting and sample population – Thirty-six patients with HR (12 males and 24 females) aged 21–74 years were included. The control group comprised 49 healthy individuals (23 males and 26 females) aged 20–79 years.

Material and methods – Profile cephalograms were obtained and the following measurements were included: height and width of the frontal sinus; length, width, and area of the nasal bone. The morphology of the nasal bone was assessed. Linear regression analyses were used to compare HR patients with controls.

Results – In HR patients, the size of the frontal sinus was unaffected ($p = 0.406$ to $p = 0.862$). The proximal width of the nasal bone, and the ratio between the proximal width and the axial length of the nasal bone were increased in HR patients ($p < 0.05$).

Conclusions – The size of the frontal sinus was unaffected, indicating a normal ability of bone resorption within the bone. The morphology of the nasal bone was abnormal indicating a disturbance in bone formation during growth. The disturbances in nasal bone modeling were mainly expressed in the proximal part supported by structures of cartilaginous origin.

Key words: bone formation; bone resorption; frontal sinus; hypophosphatemic rickets; nasal bone

Introduction

Hypophosphatemic rickets (HR) is a rare disease characterized by insufficient mineralization of the bones due to abnormal renal wasting of phosphate (1). The most predominant type of HR is inherited in a dominant X-linked fashion, caused by mutations in the gene encoding for the phosphate-regulating endopeptidase homolog, X-linked (*PHEX,* MIM 300550) (XLHR, MIM 307800) (2). XLHR is a fibroblast-growth-factor-23 (FGF23)-associated HR, and FGF23 is a potent phosphaturetic factor, being the principal regulatory hormone of the phosphate homeostasis. In addition, FGF23 is suggested to have a direct effect on bone cells (3).

The skeletal symptoms of HR include impact upon cranial bones in humans (1, 4–8), and in animals (9, 10). In a cephalometric study, including 53 individuals with X-linked HR, we recently reported an increased thickness of the theca compared with controls (11). During normal development of the skull, the sutural growth of the flat bones is combined with internal (i.e., endosteal) resorption and external (i.e., ectocranial and endocranial) apposition of bone (12). The increased thickness of theca in the HR patients indicates a disturbance in the bone modeling of the skull, but the former study (11) did not reveal if it was a matter of excess bone formation (apposition) or lack of bone resorption. Generally, high levels of FGF23 cause hypophosphatemia, and impair bone modeling (i.e., the reshaping of bone by the independent action of osteoblasts and osteoclasts during the development of bony structures) as well as bone remodeling (i.e., resorption of bone tissue and simultaneous deposition of new bone by coupling between bone cells), and based on animal models of HR, the disturbances in bone modeling and remodeling might be explained by both an alteration in osteoblast function and a reduced number of osteoclasts (13).

All anatomical structures in a developmental field are evolved from the same origin (14). In a specific developmental field (e.g., the nasofrontal field), the morphology of some osseous structures may evolve primarily by bone resorption and others primarily by apposition. In the nasofrontal field, the frontal sinus is a structure not present in newborns. The frontal sinus develops by resorption of bone and appears radiographically around the age of five (15). The final size of the frontal sinus varies considerably (16). The growth of the nasal bone is extensive from 2–17 years of age, and the growth occurs both in the nasofrontal suture and appositional at the nasal tip along with a bone modeling occurring at the superior and the inferior borders (17). Thus, in this study, the frontal sinus and the nasal bone were chosen as the structures for studying bone resorption and formation, respectively.

Focusing on bone resorption and apposition, the aim was to analyze the size of the frontal sinus and evaluate the morphology and the size of the nasal bone, in patients with XLHR compared with healthy controls. Furthermore, the aim was to examine the interrelationship between the nasal bone morphology and the severity of general skeletal impact of HR.

Materials and methods

Study population

A total of 36 adults (age > 18 years.) with X-linked HR participated in this study. The HR diagnosis was based on biochemical analyses and was genetically verified (1). In three cases, the genetic verification was not possible. According to the criteria of skeletal impact of HR defined by Beck-Nielsen et al. (1), the skeletal impact in 14 HR patients was categorized as ‘mild’, and in 22 patients as ‘severe’ impact. The control group consisted of 49 healthy adults with a minimum of 24 permanent teeth and with a neutral occlusion or only minor deviations of the morphological occlusion. In both groups, the distribution according to gender was tabulated (Table 1).

Methods

Standardized profile radiographs were obtained as described by Solow (18), using the digital radiographic equipment Planmeca Promax© (Planmeca Oy, Helsinki, Finland). The sensor-focus distance

Table 1. **Number of HR patients and controls according to gender**

	HR		Controls	
	Female	Male	Female	Male
N	24	12	26	23
Mean age (SD)	41.2 (14.6)	42.4 (18.7)	42.3 (15.4)	39.5 (15.9)
Age range	21.0–74.5	18.8–73.2	23.0–74.5	20.7–72.6

Age in years.

was 1.50 m and the enlargement factor 1.13. During exposure, the head of the patient was fixed in a rigid cephalostat, and the participants were instructed to keep their teeth in occlusion. The head posture was adjusted to the best fit of the borders of the X-ray sensor.

The analysis of the radiographs was performed using software for cephalometric analysis, Pordios® (Institute of Orthodontic Computer Science, Aarhus, Denmark). The first author performed the digitizing of all the radiographs after randomization in order to blind the observer to the health status of the individuals.

The structures which had to be analyzed (i.e., the frontal sinus and the nasal bone) were both located in the nasofrontal developmental field (Fig. 1).

Cephalometric analysis, the frontal sinus

The landmarks for the analysis of the frontal sinus were as follows: Sella (S), the midpoint of the sella turcica; Nasion (N), the most anterior point of the nasofrontal suture; Glabella (Gla), the most prominent point above the supraorbital ridge; the most inferior (Sl), and the most superior (Sh) points of the contour of the frontal sinus. In addition, posterior (Spo^) and anterior (Sa^) landmarks were defined on the contour of the sinus at the level of the greatest transverse dimension perpendicular to the axis of the frontal sinus (Sl-Sh). Posterior (Spo) and anterior (Sa) landmarks were defined as the intersection between the line S-Gla and the contour of the frontal sinus (Fig. 2).

The projection height of the frontal sinus perpendicular to the line S-N (Sh-Sl^), the absolute

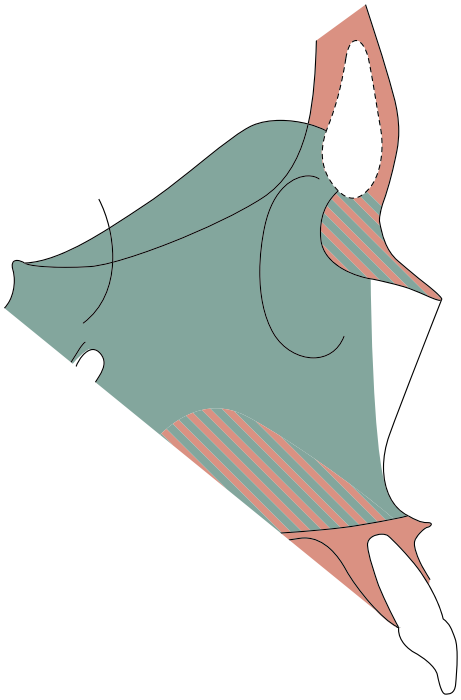


Fig. 1. Drawing of the fronto-nasal field. The bony origins of osseous structures are marked schematically. The cranial base and the upper part of the nasal septum are cartilaginous developed (green). The nasal bone and vomer are structures of intramembranous origin developed upon a scaffold of cartilage (the cartilaginous nasal capsule and the nasal septum) (red/green). Only the proximal part of the nasal bone is supported by structures of cartilaginous origin. The other bony structures are intramembranous developed (red) (14). The drawing shows the fronto-nasal field as a section of Fig. 2 in the former report by Gjørup et al. (11).

height of the frontal sinus (Sh-Sl), the width of sinus (Spo^-Sa^; Spo-Sa), and the angle S-N-Gla were calculated by the software in accordance with the definitions by Brown et al. (15), Ertürk (19), and Dostalova et al. (20).

Cephalometric analysis, the nasal bone

The main landmarks for the analysis of the nasal bone were as follows: Sella (S); Nasion (N); and Nasal-apex (Na): the most anterior point of the nasal bone (Fig. 3). The length of the nasal bone and the angulation of the nasal bone in relation to the cranial base (S-N) were measured in accordance with the definition by Solow (18). The nasal bone morphology was assessed by measuring the transversal dimensions of the nasal bone by lines perpendicular to the axis of the nasal bone. The axis of the nasal bone was defined by the midpoint of a line N-N^ (Nmi) and Na. The point N^ was

defined as the intersection of the lower border of the nasal bone and a perpendicular line to N-Na through N. N-N^ was regarded as a constructed fronto-nasal suture. Perpendicular to the nasal axis, lines were constructed with a distance of 3 mm between lines. The lines were numbered from 0 to 11: proximally, line '0' was the baseline passing through N (L0-N) and distally, line '11' was near the apex of the nasal bone (Na). The intersections between the perpendicular line and the upper and lower border were used as landmarks (U1-U11 and L0-L11, respectively). The distances from the N-Na line to the upper and lower border, and the transversal dimensions (L0-N, L1-U1, L2-U2, etc.) were calculated by the software. In addition, the ratio between the length of the basal line and the length of the nasal axis was calculated (base/axis: L0-N/Nmi-Na), and the area of the polygon defined by the multiple landmarks on the upper and the lower borders of the nasal bone was calculated. The ratio (L0-N / Nmi-Na) was defined as 'low' when below 0.5 and 'high' when above 0.5.

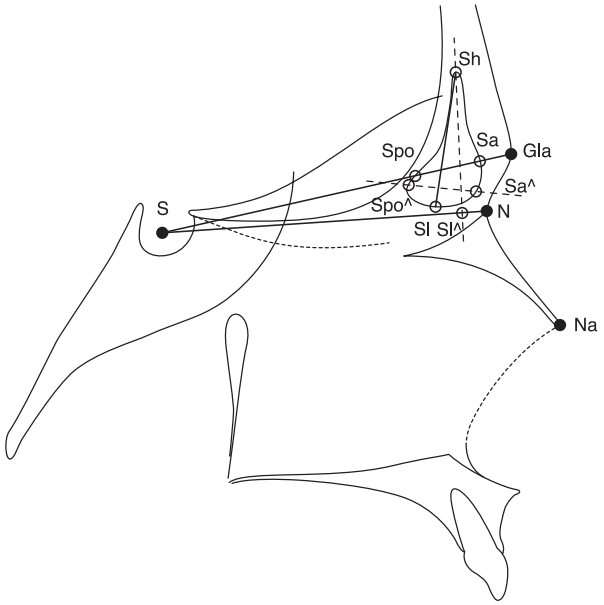


Fig. 2. Landmarks and cephalometric variables. The frontal sinus: Sh-Sl: the absolute height of the sinus; Spo^-Sa^: the greatest anterior–posterior width perpendicular to the axis (Sh-Sl); Spo-Sa: the anterior–posterior width at the line S-Gla; Sh-Sl^: the projection height, *that is*, the distance between Sh and Sl^ (i.e., the projection of Sh on S-N line). The nasal bone: N-Na: the length of the bone; S-N-Na: the inclination (degree) of the nasal bone (N-Na) in relation to the anterior cranial base (S-N).

Reliability

To test the intra-examiner reliability, the first author digitized 22 randomly selected radiographs twice. The radiographs selected for redigitizing were included in the overall randomization of radiographs in order to blind the observer to whether the radiographs were read before. Except for three of the 11 variables describing the transversal dimension of the nasal bone, the differences for none of the variables were significantly different from zero ($p > 0.05$). For each of the cephalometric variables, the random error (S) was calculated as described by Dahlberg (21). S ran-

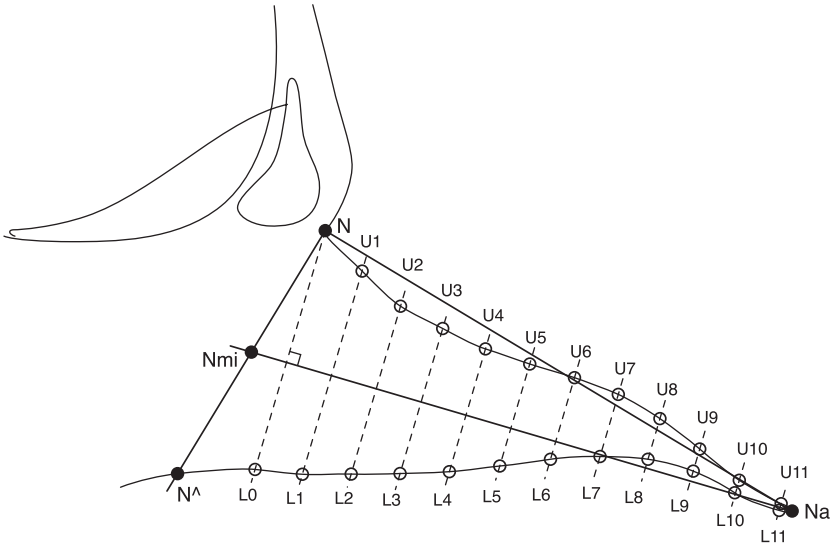


Fig. 3. Analysis of the morphology of the nasal bone. N-N^: line perpendicular to line N-Na. Nmi: the midpoint of the line N-N^; Nmi-Na: the axis of the nasal bone; N-L0: the base of the nasal bone perpendicular to the axis (Nmi-Na). Line numbers 1–11 are perpendicular to the axis (Nmi-Na), with 3-mm interline distance, and crossing the upper and lower border of the nasal bone in U1-U11 and L1-L11, respectively.

ged from 0.01 to 2.29 in the case of variables of the nasal bone and from 0.64 to 4.38 in the case of variables of the frontal sinus. The coefficient of reliability (R) was estimated according to Houston (22). In the case of variables describing the transverse dimensions of the nasal bone, R ranged from 0.74 to 0.97, and in the case of the other variables, R ranged from 0.92 to 0.99.

Statistical analyses

Irrespective of age, the gender distribution in HR group and in control group was compared by the two-sided chi-squared test. For each gender, the age distribution in the two groups was compared with the unpaired *t*-test. In both the HR group and the control group, the cephalometric measurements underwent a visual examination for normality using Q-Q plots and histograms, and a normal distribution was found in both groups. The effect of the health status (i.e., HR or control), age, and gender upon the cephalometric measurements was assessed by a linear regression analysis. To allow for familiar dependence, the regression estimates were adjusted for clustering. Potential interactions between the effect of the age and the health status and between the effect of the gender and the health status were assessed in the regression analysis.

The cephalometric data are presented according to the gender. Means and standard deviations were used as descriptive statistics and *p*-values equal to or below 0.05 were considered statistically significant.

The proportion of high-ratio base/axis (L0-N/Nmi-Na) according to skeletal severity impact was compared by a two-sided chi-squared test.

Data analysis was performed using STATA® 11.0 (StataCorp, College Station, TX, USA).

Ethics

The study was approved by the Regional Scientific Ethical Committees for Southern Denmark (M-2678-05) and by the Danish Data Protection Agency (2009-41-3613). Written informed consent was obtained from all patients before entering the study.

Results

The distribution of the participants according to the health (HR patients and controls) and the gender is presented in Table 1. The proportion of females in the HR group (67%) did not significantly exceed the proportion of females in the control group (53%) ($p = 0.208$). Irrespective of gender, the mean age of the HR group and the control group was not significantly different.

The height and width of the frontal sinus were not significantly different in HR patients and controls ($p = 0.406$ to $p = 0.863$) (Table 2). Five HR patients (13.9%) and 3 controls (6.1%) had no visible frontal sinus, but this difference was not statistically significant ($p = 0.116$). According to the regression analysis, the cephalometric variables of the frontal sinus were not significantly affected by age.

Hypophosphatemic rickets patients showed, in comparison with controls, a tendency toward a reduced mean length of the nasal bone and an increased mean area of the nasal bone was found, but this did not reach a significant level (Table 2). Regression analysis with the nasal bone length (N – Na) as outcome variable, revealed a negative regression-coefficient for the effect of HR (coefficient = −1.73; 95% CI: −4.94, 0.48), which indicated a reduced nasal bone length in HR patients. Proximal, the width of the nasal bone was greater in HR patients compared with controls. The significant differences were restricted to the four proximal lines, the differences in width being: L0: 1.06 ($p = 0.014$), L1: 1.04 ($p = 0.005$), L2: 0.081 ($p = 0.002$), and L3: 0.59 ($p = 0.007$). The morphology of the nasal bone was illustrated by the mean distances from the line N-Na to the upper and the lower border of the nasal bone (Fig. 4). In addition, examples of the radiographic appearance of the nasal bone in HR patients and in controls have been depicted (Fig. 5). According to the regression analysis, the cephalometric variables of the nasal bone were not significantly affected by age.

The morphology of the nasal bone was expressed by the ratio base/axis. This ratio was significantly increased in HR patients compared

Table 2. **Descriptive statistics (means and standard deviations) of cephalometric measurements in the fronto-nasal field of HR patients according to gender and compared with healthy controls**

	Males				Females				
	Control		HR		Control		HR		Adjusted comparison of HR and control
	N = 23		N = 12		N = 26		N = 24		
Variable name	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p-value
Frontal sinus									
Spo^-Sa^ (mm)	12.67	4.42	13.16	5.17	9.96	3.36	10.07	5.52	0.815
Sh-Sl^ (mm)	27.12	8.50	23.94	10.42	26.02	9.47	23.63	13.60	0.406
Sh-Sl (mm)	28.16	8.71	27.21	11.56	28.90	10.67	25.59	13.94	0.517
Spo-Sa (mm)	13.89	4.94	15.18	7.11	10.49	4.96	10.09	6.21	0.863
Nasal bone									
N_Na (mm)	27.12	3.97	24.37	4.90	25.24	4.14	24.15	3.39	0.122
NNa_NS (degree)	117.72	6.08	117.03	4.57	114.97	5.75	114.23	6.33	0.543
Base/axis (ratio)	0.45	0.07	0.58	0.12	0.45	0.09	0.52	0.12	0.010*
Nasal area (mm^2)	98.94	27.06	103.97	25.05	90.29	26.38	94.76	25.68	0.440

p-values are from the regression analysis after adjustment for the effect of gender, age, and clustering.
*p-value <0.05.

with controls (Table 2). In HR patients with severe skeletal impact, the percentage of 'high' ratio base/axis was almost twice that of the mildly affected group (Table 3).

Discussion

Detailed analyses of nasal bone morphology have not previously been extensively reported in the literature. In this study, we report abnormal nasal bone morphology (eaglebeak-like) in HR patients, primarily because of an increased proximal width of the nasal bone.

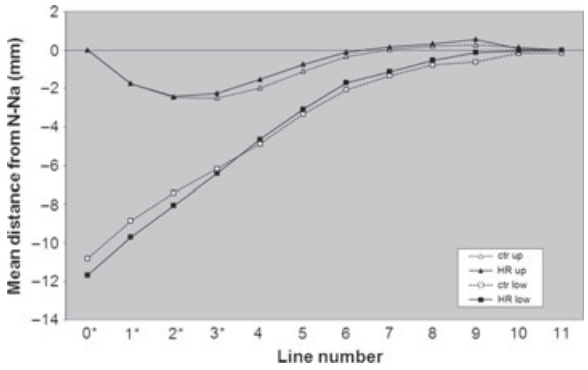
Despite the rarity of the HR disease, the number of patients was relatively high and the number equals or exceeds the number of patients included in previous cephalometric HR studies (4, 5, 7). Furthermore, the patients of our study have been uniformly diagnosed, and except for three cases, the diagnosis was genetically verified. In the group of patients with HR, the male:female ratio was 1:2, which was in accordance with the X-linked inheritance of the disease, but not significantly different from the apparently equal gender distribution in the control group (Table 1). In the analyses of the study, we adjusted for the potential effect of the gender. The analysis of 3-dimensional (3D) anatomical structures (the frontal sinus and the nasal bones) was performed on 2-dimensional (2D) radiographs, which to some extent limits the interpretation of the results. The advantage of 2D-methods is the comparability with previous studies where 2D methods traditionally have been used in cephalometric studies of craniofacial structures [e.g., Jensen and Kreiborg (23), Ruf and Pancherz (16), Lexner et al. (24), Al-Jundi et al. (7)].

The frontal sinus and bone resorption

In this study, the size of the frontal sinus varied considerably in both groups (i.e., HR patients and controls), but the differences between the groups were not statistically significant (Table 2). These findings of size variation are in accordance with a previous study regarding variations in sinus development in healthy children (15). In HR patients, the unaffected resorption during development of the frontal sinus indicates a normal osteoclast formation and function within the frontal bone. Only three of 36 HR patients

Females

Line[a]		0	1	2	3	4	5	6	7	8	9	10	11
N[b]	CTR	26	26	26	26	26	26	25	20	15	7	5	1
	HR	24	24	24	24	24	24	24	17	12	2	1	0



Males

Line[a]		0	1	2	3	4	5	6	7	8	9	10	11
N[b]	CTR	23	23	23	23	23	23	22	22	19	11	5	1
	HR	12	12	12	12	12	11	11	9	6	2	2	0

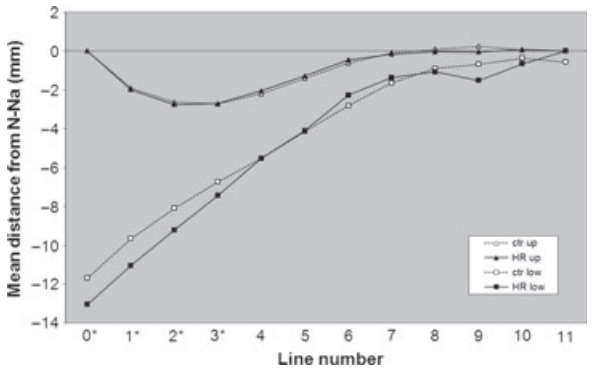


Fig. 4. Morphology of the nasal bone in HR patients and controls (ctr) according to gender. Mean distances from the line N-Na to the upper (up) and the lower (low) border of the nasal bone measured at perpendicular lines (No. 0–11) to the axis of the nasal bone. [a]Line number of perpendicular lines to the nasal axis. 0 = N-L0, 1 = U1-L1, 2 = U2-L2, etc. [b]N are numbers of assessable measurements for the variable. *Line numbers with significant difference in width of nasal bone, HR patients in comparison with controls adjusted for the effect of gender, age, and clustering.

did not have a frontal sinus at all. In contrast, patients with cleidocranial dysplasia (CCD, MIM 119600) generally have a missing or hypoplastic frontal sinus (23). This indicates an impaired osteoclast function in CCD although a runt-related transcription factor 2 gene (*RUNX2*, MIM 600211) association with osteoclast function has not yet been reported.

In adults in contrast to growing children, the effect of age upon the size of osseous structures, for example, the frontal sinus, was supposed to be the same in all age groups of this study. This might be in contradiction with the knowledge on post-menopausal osteoporosis in women and the age-related bone loss in both men and women which induce increasing bone loss with increasing age, especially in women. However, the post-menopausal and the age-related remodeling primarily impact the internal trabecular bone (25). Thus, it can be justified to include all age groups in this study of macroscopic dimensions of bony structures.

The nasal bone and bone formation

According to this study, the morphology of the nasal bone in HR patients was abnormal because of an extensive proximal width of the bone (Table 2, Figs 4 and 5). Further, the degree of abnormal morphology of the nasal bone seemed to be related to the severity of the general skeletal impact of HR (Table 3). The age had no or minimal impact on the size and the morphology of the nasal bone. This indicates that the changes in morphology occur primarily during early childhood or even earlier in fetal development. Prenatally, the nasal bone develops bilaterally in the mesenchyme in close relation to the chondral nasal capsule. The osseous structure develops directly from the mesenchymal cells using the chondral nasal capsule as a scaffold (26). Later in the post-natal development, the proximal part of the nasal bone remains surrounded by bony structures of cartilaginous origin (i.e., structures of the ethmoid bone), but the apical part of the nasal bone develops without the support from bony structures of cartilaginous origin (Fig. 1). In the adult HR patients, the mean nasal bone length was reduced in both genders in comparison with controls, although the difference did not reach the level of statistical significance (Table 2). In our former report, which included children (11), the nasal bone length was significantly reduced, and the same has been reported in an animal study (10). It remains unanswered, if the significant difference in the former report was caused by an inaccuracy in the statistical analysis not adjusting for the different dimensional effects of the age depending on the age group (e.g., growing children vs. mature adults). More likely, the

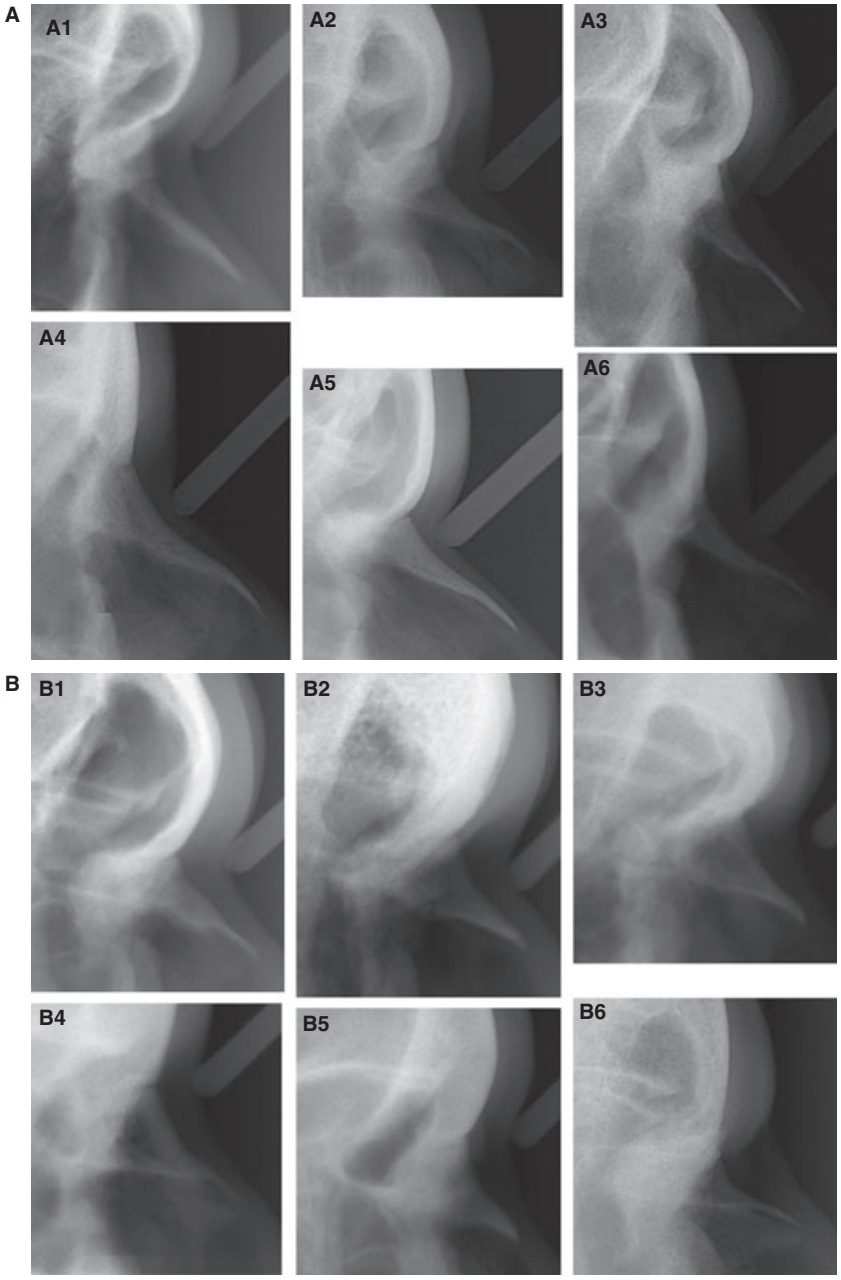


Fig. 5. Radiographic appearance of the nasal bone. A: Examples from healthy controls. B: Examples from HR patients. A1: male 21 years; A2: female 40 years; A3: male 53 years; A4: female 51 years; A5: female 39 years; A6: female 45 years; B1: female 40 years; B2: male 23 years; B3: male 33 years; B4: female 23 years; B5: female 49 years; B6: female 65 years.

non-significant difference in the nasal bone length was caused by the reduced sample size of the present report, which was indicated by the negative regression-coefficient for the effect of HR and the 95% confidence interval hardly exceeding zero. In other diseases, a reduced size of the nasal bone has been reported, for example, in 51 patients with achondroplasia in whom the reduced size has been related to abnormalities in the cartilaginous developed nasal septum (27). The reporting of a reduced length of the nasal bone in 20 patients with cleft lip indicates alternative, intrinsic, and non-cartilaginous related factors of importance in the development of the nasal bone (28). In HR patients, the eagle-beak-like appearance of the nasal bone reflected increased bone formation in the proximal part, which was supported by structures of cartilaginous origin, and the morphological results could be interpreted as disturbances in modeling with a net gain of bone in the proximal part. Alterations in some unknown signaling from the cartilaginous scaffold might explain the disturbances in bone modeling of the proximal part, which

Table 3. **Relation between the skeletal severity and the ratio nasal base/nasal axis (N-L0/Nmi-Na) in 36 HR patients. The number (%) in the low-ratio group compared with the high-ratio group according to the skeletal severity**

Nasal base/axis	N	Skeletal severity		
		Mild	Severe	*p*-value
Low	16	9 (56)	7 (44)	0.056
High	20	5 (25)	15 (75)	

Low: ratio base/axis <0.5; High: ratio base/axis >0.5.
p-value from chi-squared test.

develops supported by the scaffold. Apparently, the modeling of the apical part of the nasal bone, which is not supported by these structures, had another character. The mechanisms behind the increased width of the proximal part of the nasal bone might be identical with the mechanisms responsible for the increased thickness of the theca, which develops with the meninges as a scaffold. The knowledge of impaired osteoclastogenesis in FGF23–associated HR (13) supports the suggestions of disturbances in the modeling of bone, although the reason for the apparent differences according to the presence of a supporting scaffold remains unclear.

Conclusions

In comparison with healthy controls, the size of the frontal sinus was unaffected in HR patients, indicating normal ability of the osteoclasts to perform internal resorption of the frontal bone.

The morphology of the nasal bone was abnormal (eaglebeak-like appearance) which indicated an overall impact upon bone formation, and the increased width of the proximal part was an indication of impaired bone modeling in bony tissue supported by cartilage during growth. Furthermore, the degree of abnormal morphology of the nasal bone tended to correlate with the severity of the general skeletal impact of HR.

Clinical Relevance

In patients with hypophosphatemic rickets, the abnormal morphology of the nasal bone was a radiological sign of disturbances in bone formation. In the usage of profile cephalograms for orthodontic treatment planning, the clinician's awareness of the morphology of the nasal bone as well as other cranial structures is advocated, as the morphology of bony structures might reflect abnormalities in bone metabolism and indicate a general disease, for example, hypophosphatemic rickets.

Conflict of interest

The authors declare that they have no conflict of interest.

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