Sphenoid Bone Pneumatisation on Lateral Cephalograms of Patients With Neurofibromatosis Type 1

REINHARD E. FRIEDRICH^{1,2*}, HANNAH T. SCHEUER^{1,2*}, JAN F. KERSTEN³ and HANNA A. SCHEUER^{4,5}

¹Department of Oral and Craniomaxillofacial Surgery,
Eppendorf University Hospital, University of Hamburg, Hamburg, Germany;

²Neurofibromatosis Laboratory, Hamburg, Germany;

³Competence Centre for Epidemiology and Health Services Research for Healthcare Professionals (CVcare),
University Medical Centre Hamburg-Eppendorf, Hamburg, Germany;

⁴Orthodontic Practice, Hamburg-Lokstedt, Hamburg, Germany;

⁵Department of Orthodontics, Eppendorf University Hospital, University of Hamburg, Hamburg, Germany

Abstract. *Background/Aim: Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary disease that causes tumors and many developmental disorders, e.g., cranial dysplasia. The purpose of this retrospective study was to analyse the pneumatisation of the sphenoid bone in NF1. Patients and Methods: The anonymised lateral cephalograms of 166 NF1 patients and 166 age- and sex-matched controls were examined for anterior-posterior sphenoid pneumatisation. The patient group analysis considered whether the patients had been affected by a facial plexiform neurofibroma (FPNF). Results: Sphenoid pneumatisation was significantly lower in NF1 patients than in controls [odds ratio (OR)=0.184; 95%CI=0.11-0.32; p<0.001]. A FPNF statistically significantly reduced sinus formation in patients (OR=0.38; p=0.002). Conclusion: The condition 'NF1' has an effect on sphenoid pneumatisation. The findings are relevant for planning surgical procedures in this region and confirm current concepts to evaluate NF1 as a histogenesis control gene. The examination technique and basis of calculation presented here are easy-to-use and low-irradiation exposure instruments for screening for differences in sphenoid bone pneumatisation in defined populations.*

Neurofibromatosis type 1 (NF1) is a relatively common monogenic disorder with a plethora of findings and symptoms (1). While the disease has been known for a long time (2), there are many obvious and hidden skeletal alterations in NF1 (3) of which the public is not aware (4, 5). NF1 patients usually have a lower-than-normal body height (6), may show macrocranium (7), develop early osteoporosis (8), may develop scalloping and pseudarthrosis of bones (9, 10) and have skull defects (11). Particularly striking findings of the skull are calvarial defects (11, 12) and the diagnostically relevant sphenoid dysplasia (13). The anterior skull defects and dysplasias are often (13), but not always (14, 15), topographically related to a histologically proven nerve sheath tumour that is characteristic for NF1: plexiform neurofibroma (PNF) (16).

The NF1-associated pathognomonic bone dysplasia of the cranial base affects the sphenoid wings (17) and the sella turcica (18). A topographic correlation can be traced for both skeletal alterations to adjacent unilaterally developed PNF of the trigeminal nerve in the majority of patients (13, 19). The sphenoid wings and sella turcica develop during embryonic phases of coordinated cartilage and bone formation (20-22). PNF is assumed to develop during prenatal phases of life (23-26). Skeletal alterations in the area of the trigeminal nerve of NF1 patients are frequently congenitally present and are potentially caused or at least triggered by the adjacent nerve (27, 28).

The sphenoid sinus is a well-defined structure of the sphenoid bone that may show initial signs of development at the time of birth (29). However, the sinus originates prior to birth and is distinct to the region of the later osseous organ as a pouch-like protuberance at the distal border of the ethmoid mucosa. This primitive sinus lays anterior to the pre-sphenoid (29-32). The actual development of the sphenoid sinus occurs soon after birth (33-36), shows certain

This article is freely accessible online.

*These Authors contributed equally to this study.

Correspondence to: Reinhard E. Friedrich, MD, DMD, Ph.D., FEBOMFS, Department of Oral and Craniomaxillofacial Surgery, Eppendorf University Hospital, University of Hamburg, Martinist. 52, D-20246 Hamburg, Germany. Tel: +49 40741053259, e-mail: rfriedrich@uke.de

Key Words: Cephalometry, neurofibromatosis type 1, plexiform neurofibroma, sphenoid sinus.

Figure 1. Schematic representation of sphenoid sinus size classification in anteroposterior direction (from left to right: post-sellar, sellar, pre-sellar, and conchal; anterior is to the right).

growth spurt phases (37) and is highly variable in terms of final total volume and spatial orientation of pneumatization (38). Previous studies on NF1-associated skull alterations demonstrated dysplastic growth of hard tissue of the skull base adjacent to a cranial nerve sheath tumour or arachnoidal cyst (11, 13). Therefore, the question remains whether this correlation between bone alteration and adjacent neurofibroma in this region also applies to an intraosseous bone transformation that becomes apparent only after birth.

The aim of this study was to determine sphenoid bone pneumatization on plain radiographs from NF1 patients. We considered whether a potential influence on the sphenoid pneumatization can be defined as a general feature of the disease or a local neurogenic tumour impact on the measured item. We hypothesised that the disease influences pneumatization of the sphenoid sinus. Considering earlier works on skeletal morphology of the paranasal sinuses in neurofibromatosis (39, 40), we assumed that sphenoid pneumatization is less pronounced in NF1 patients, especially in individuals with trigeminal PNF (41).

Patients and Methods

Group characteristics. The anonymised lateral cephalograms of 332 individuals were examined for anterior-posterior pneumatization of the sphenoid sinus. The total study population consisted of 166 NF1 patients and 166 control individuals.

Patient group. This study was conducted from February 1, 2019 to January 31, 2020. NF1 patients were defined by updated diagnostic criteria (3) [age: 5.39-78.33 years; 182 females and 150 males (54.8%:45.2%); age group years (ys): 5 to <18: 92 (27.7%), 18 to <40: 144 (43.4%), 40 to <60: 79 (23.8%), 60 to 80: 17 (5.1%)] and are described elsewhere in detail (19, 41). The NF1 group was differentiated according to disease-specific facial phenotypes (41). NF1 patients who developed cutaneous neurofibromas of the integument, optionally including the face, were defined as a group termed ‘disseminated cutaneous neurofibroma’ patients (DCNF group). By this definition, none of these patients had a facial plexiform neurofibroma (FPNF). This diagnostic exclusion was examined on the basis of histological findings in cases with previous surgery in the facial area, supplemented by imaging of the head and neck region, *e.g.*, computed tomography and magnetic resonance tomography, if available (19). The second NF1 group was

characterised by a FPNF of a different size and extent (FPNF group). In the vast majority of these patients, a clinical PNF diagnosis was histologically confirmed in the context of tumour-reductive and plastic-reconstructive interventions.

Reference group. This group was defined by randomly selected cephalograms of individuals; one subject was matched to each NF1 patient by age and gender. Exclusion criteria for control radiographs were patient history of known facial trauma or dysplasia or known inherited disease. Furthermore, X-ray images with technical deficiencies that impaired or made impossible the exact assessment of the study region were excluded. The age of the selected controls differed from the age of the NF1 patients for a maximum of ± 6 months, except for the small group of NF1 patients older than 60 years who were selected with an age difference of ± 4 years on average. The X-ray controls were generated from the digital X-ray archive of a dental practice for orthodontics, Hamburg (Hanna A. Scheuer). These radiographs were archived after identification and assignment to the complementary patient with age and gender information, and personal data were replaced by sequential numbers addressing radiographs for the NF1 patient and associated control.

Registration of cephalometric data. Lateral cephalograms were performed according to a standard technique (42, 43). For digital cephalometric evaluation, the X-ray images were scanned and digitised as described elsewhere (41).

The X-rays were examined by the principle authors and an orthodontist. The first and the senior author have over 30 years’ experience in the evaluation of cranial radiographs. If the definition of a boundary of the sphenoidal sinus was ambiguous for the individual, this item was determined by a consensus re-evaluation of the X-ray image. The determination of the degree of pneumatization was repeated after four weeks with 20 cephalograms. The results were in all cases consistent with the assessment of the degree of pneumatization of the first examination.

Classification of the sphenoid sinus pneumatization in lateral cephalograms. The extent of sphenoid pneumatization is defined according to the relationship between cavity and sella turcica (29). The typing of sphenoid bone pneumatization used in this study is widely implemented in anatomical and radiological diagnostics (44-46) (Figures 1 and 2). In brief, staging of sphenoid bone pneumatization is related to the position of the cavity’s posterior wall to the anterior sella border. Only the rudimentary pneumatization of the bone, which is by definition confined to areas directly adjacent to the ethmoid, does not refer to the sella turcica; it has become known as “conchal”. This term characterises the

Figure 2. Sphenoid bone pneumatisation on lateral cephalograms (cropped images); A: post-sellar; B: sellar; C: pre-sellar; D: conchal; anterior is to the right.

Table I. Assignment of the pneumatisation stages to the respective diagnostic group (n=332).

Pneumatisation degree/group	Conchal		Presellar		Sellar		Postsellar		Total	
	N	%	N	%	N	%	N	%	N	%
FPNF	12	16.2	17	23	29	39.2	16	21.6	74	100
DCNF	3	3.3	10	10.9	37	40.2	42	45.7	92	100
Co-FPNF	4	5.4	5	6.8	26	35.1	39	52.7	74	100
Co-DCNF	4	4.3	5	5.4	19	20.7	64	69.6	92	100
Total	23	6.9	37	11.1	111	33.4	161	48.5	332	100

N: Number; FPNF: facial plexiform neurofibroma; DCNF: disseminated cutaneous neurofibroma; Co-FPNF: control group of FPNF group; Co-DCNF: control group of DCNF group.

relationship of a very small cavity to its origin from the ethmoid. A sinus that reaches beyond the conchal region but does not attach to the anterior sella's border is referred to as laying in front of the sella ("presellar"). A "sellar" pneumatisation is defined when the dorsal boundary of the sphenoid sinus expands at least beyond the anterior, with a slightly arched border towards the cup-like bottom of the sella, but it ends prior to a line defined by the longitudinal axis of the dorsum sellae and extends caudally into the body of the sphenoid. A "postsellar" pneumatisation occurs when the pneumatisation extends dorsally beyond this line.

The pneumatisation type was registered according to topographical correlations, followed by numerical transfer into four degrees in order of increasing dorsal pneumatisation: 1=conchal, 2=presellar, 3=sellar and 4=postsellar. A higher number represents a more posterior pneumatisation. The value 0 for aplasia was not assigned; even in the few cases with very low pneumatisation, there was at least rudimentary radiotranslucency in the sphenoid body. Radiological examination can detect the pneumatisation in only one plane due to the selected projection. Therefore, side differences in the pneumatisation of the bilaterally developed sphenoid bone were neither recorded nor considered potential extensions of the cavitation in other regions. The ordinal scaled values (see above) were assigned to the study groups, and the data were prepared for further statistical evaluations.

Age. Individual examinations were performed to determine the influence of age on pneumatisation. The age limits of the group definition included both the completed age of 14 (as the limit of completed puberty) and the completed age of 18 (as the limit of completed adolescence) in the calculations. Age limits were defined

by considering that pneumatisation is a developmental process that extends over a well-documented period of time (35-37, 47).

Ethics. All patients provided informed consent to the scientific study of X-ray images and evaluation of medical findings. The study protocol was approved by the local University authority (Eppendorf University Hospital, University of Hamburg, Hamburg, Germany, 17.05.2018) as a prerequisite to fulfil the requirement of a dissertation in dentistry (Hannah T. Scheuer). All procedures in this study involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Data were anonymised prior to analysis, and the investigators studying the radiographs were blinded to diagnosis, identity of individuals and assignment of the single case to a diagnostic group. The investigations of anonymised data were performed in accordance with Hamburg Health Care Act (Hamburgisches Gesundheitsdienstgesetz). According to the laws of this federal state, studies of this type do not need to be assessed by an ethics committee.

Statistical analysis. Chi-square test and Fisher's exact test were used to investigate differences in pneumatisation stages. Continuous data were expressed as mean and standard deviation [M (SD)] and compared with Student's *t*-test. The estimators are supplied with 95% confidence intervals (95%CI) and associated *p*-values. Finally, an ordinal logistic regression model was used to investigate the pneumatisation of the sphenoid bone, with group as a factor: control, FPNF and DCNF. Statistical significance level was set at $p < 0.05$.

Table II. Contribution of diagnostic groups to the total number of each pneumatization stage (N=332).

Pneumatization degree/group	FPNF		DCNF		Co-FPNF		Co-DCNF		Total	
	N	%	N	%	N	%	N	%	N	%
Conchal	12	52.2	3	13	4	17.4	4	17.4	23	100
Presellar	17	45.9	10	27	5	13.5	5	13.5	37	100
Sellar	29	26.1	37	33.3	26	23.4	19	17.1	111	100
Postsellar	16	9.9	42	26.1	39	24.2	64	39.8	161	100
Total	74	22.3	92	27.7	74	22.3	92	27.7	332	100

N: Number; FPNF: facial plexiform neurofibroma; DCNF: disseminated cutaneous neurofibroma; Co-FPNF: control group of FPNF group; Co-DCNF: control group of DCNF group.

Results

The radiographs of 332 individuals were examined and evaluated [182 females (54.8%) and 150 males (45.2%)]. The age of the entire study group was between 5.39 and 78.33 years (ys) [females: 7.17-70.14 ys, M=32.92 (SD=14.06) ys; males: 5.39-78.33 ys, M=27.64 (SD=17.76) ys].

Differences in pneumatization type frequencies were obvious between the control and NF1 groups (Table I). More than half of the conchal pneumatizations were diagnosed in the FPNF group (Table II). Furthermore, almost half of all presellar pneumatizations were also identified in this patient group. Sellar pneumatizations were relatively common in all groups. The number of cases with postellar pneumatization was low in FPNF patients (Table II).

General comparison of findings between diagnostic groups showed that the degree of sphenoid bone pneumatization in NF1 patients was lower compared to controls.

The mean pneumatization stage of the NF1 overall group [n=166; mean: 3.01 (SD=0.94, SEM=0.07)] was lower compared to the control group [n=166; mean: 4.46 (SD=0.8, SEM=0.06)]. The difference was statistically highly significant ($p<0.001$; 95%CI=-0.65; -0.27; difference in means: -0.45). The mean pneumatization stage of the FPNF group [n=74; mean: 2.66 (SD=0.1, SEM=0.12)] was lower than in the corresponding control group [n=74; mean: 3.35 (SD=0.84, SEM=0.1)]. The difference was statistically highly significant ($p<0.001$; 95%CI=-0.99; -0.39; difference in means: 0.69). The mean pneumatization stage of the DCNF group [n=92; mean: 3.28 (SD=0.79, SEM=0.08)] was lower than in the corresponding control group [n=92; mean: 3.55 (SD=0.79, SEM=0.08)]. The difference was statistically significant ($p=0.021$; 95%CI=-0.5; -0.04; difference in means: -0.27).

There was a statistically significant difference in staged sphenoid pneumatization between males and females when analysing the whole and the NF1 groups; this difference was the slightest in the control group.

The mean pneumatization stage of females in the entire study group [n=182; mean: 3.38 (SD=0.78, SEM=0.058)]

was more advanced than in males [n=150; mean: 3.05 (SD=1.02, SEM=0.083)]. This difference was statistically highly significant ($p<0.001$; 95%CI=-0.53; -0.14; difference in means: -0.331). The mean pneumatization stage of female NF1 patients [n=91; mean: 3.19 (SD=0.8, SEM=0.084)] was more advanced than in male NF1 patients [n=75; mean: 2.29 (SD=1.04, SEM=0.12)]. This difference was statistically significant ($p<0.006$; 95%CI=-0.68; -0.12; difference in means: -0.4). The mean pneumatization stage of the female individuals in the control group [n=91; mean: 3.58 (SD=0.7, SEM=0.073)] was more advanced than males of the control group [n=75; mean: 3.32 (SD=0.92, SEM=0.11)] This difference was statistically significant ($p=0.044$; 95%CI=-0.51; -0.014; difference in means: -0.262).

These comparisons did not consider age effects. Further investigation demonstrated that the influence of the factor 'gender' is possibly an 'age' effect (t -test: about 5 years age difference, $p=0.045$).

The age comparison of females [n=91: mean: 32.99 ys (SD=14.01, SEM=1.47)] and males [n=75; mean: 27.48 ys (SD=17.7, SEM=2.04)] of the NF1 group shows a statistically significant difference ($p=0.026$, 95%CI=-10.37; -0.65; difference in means: -5.51). The age comparison of females [n=91: mean 32.85 ys (SD=14.2, SEM=14.9)] and males [n=75; mean: 27.81 ys (SD=17.95, SEM=2.07)] of the control group shows a statistically significant difference ($p=0.045$, 95%CI=-9.97; -0.12; difference in means: -5.04).

Furthermore, the age difference between the FPNF group [n=74; age: 27.09 ys (SD=16.23, SEM=1.89)] and the DCNF group [n=92; age: 33.24 ys (SD=15.3, SEM=1.6)] was statistically significant (t -test, age difference: -6.15 ys; 95%CI=-11 to -1.3; $p=0.013$). The age difference between the NF1 groups was due to the much earlier need for treatment of FPNF patients. This phenomenon is due to the more frequent indication for X-ray diagnosis earlier in life in this patient group. To account for the age factor and the developmental phase of the sinus, all groups were subdivided according to the age criterion 'completed eighteenth year of life'. This analysis by individual groups revealed an increase

Table III. Impact of age (≥ 18 years versus < 18 years) on pneumatisation stage.

Group	Calculated mean pneumatisation degree		Statistical comparison (t-test)		
	Mean (SD)	SEM	Diff	95%CI	p-Value
FPNF < 18 years (N=29)	2.28 (0.92)	0.17	-0.64	-1.09; -0.18	0.007
FPNF ≥ 18 years (N=45)	2.91 (0.97)	0.15			
DCNF < 18 years (N=17)	2.59 (0.94)	0.23	-0.85	-1.24; -0.47	< 0.001
DCNF ≥ 18 years (N=75)	3.44 (0.66)	0.08			
Co-FPNF < 18 years (N=29)	2.97 (1.02)	0.19	-0.64	-1.01; -0.26	0.001
Co-FPNF ≥ 18 years (N=45)	3.60 (0.58)	0.09			
Co-DCNF < 18 years (N=17)	2.82 (1.13)	0.27	-0.9	-1.28; -0.52	< 0.001
Co-DCNF ≥ 18 years (N=75)	3.72 (0.58)	0.07			

N: Number; SD: standard deviation; SEM: standard error of the mean; CI: confidence interval; FPNF: facial plexiform neurofibroma; DCNF: disseminated cutaneous neurofibroma; Co-FPNF: control group of FPNF group; Co-DCNF: control group of DCNF group; Diff: difference in means.

in pneumatisation for all groups; that is, the growth of the cavity in the analysed projection was demonstrated for all groups (Table III). Indeed, the difference in the FPNF group between those over and under 18 years concerning the level of pneumatisation is significant. It shows the age dependent development of the sphenoid sinus. However, the degree of pneumatisation in the FPNF group is significantly lower even in young children and adolescents. The difference in pneumatisation stages when comparing the age groups within the FPNF group is smaller than in the DCNF group (Table III). If the inclusion criterion of the analysis was age over 18 years, then there was no statistically significant difference in the degree of sphenoid pneumatisation between the sexes in either the control or NF1 groups (Tables IV and V). We also identified interesting differences when comparing the groups using this age criterion (Table VI):

The degree of sphenoid sinus pneumatisation did not differ statistically significantly between the two control groups;

The pneumatisation stage was lower in both patient groups compared to controls;

Sphenoid pneumatisation was significantly lower in the FPNF group compared to the DCNF group.

Following these individual analyses, the measured values and parameters were summarised and calculated in an ordinal logistic regression model. The respective patient groups were compared against the control group and with each other. Prerequisite for the inclusion of a case in the calculation was the completion of the pneumatisation of the sphenoid. We decided to set the cut-off at 18 years to have safety margin to

the known range of terminal pneumatisation during puberty. FPNF group showed an OR of 0.184 (95%CI=0.11-0.32; $p < 0.001$) compared to control, that means: a FPNF patient had about one-fifth of the chance of a subject in the control group to reach one step higher in pneumatisation degree (DCNF group: OR=0.451; 95%CI=0.27-0.75; $p = 0.002$), *i.e.* 54.9% decreased chance to reach the next step in pneumatisation compared to the control group). It follows that the individual affected by NF1 is more likely to have a considerably lower level of pneumatisation than the representative of the age and gender-appropriate control group, and this effect is further increased in patients with FPNF. Adulthood, *i.e.*, an age over 18 years resulted in an OR of 4.8 (95%CI=0.34-7.9; $p < 0.001$). Gender had no statistically significant influence on the pneumatisation stage (OR=1.51; 95%CI=0.98-2.34; $p = 0.063$).

When comparing the patient groups (DCNF and FPNF) with one another, the OR was 0.38 ($p = 0.002$), that means FPNF patients have a decreased chance to achieve a higher degree of pneumatisation than the DCNF group by 62%.

Discussion

This study provides evidence for reduced sphenoid sinus pneumatisation in the anterior-posterior direction, as determined by lateral cephalograms of patients with the syndromic disease NF1 compared to age- and sex-matched controls. The difference in pneumatisation staging between NF1 patients and controls became even greater when the

Table IV. Impact of gender on pneumatisation stage in individuals aged ≥ 18 years.

Group	Age						Age comparison (Mann-Whitney)	Calculated mean sphenoid pneumatisation						Statistical comparison of pneumatisation grade (<i>t</i> -test)		
	Female			Male				Female			Male			Diff	95%CI	<i>p</i> -Value
	N	Mean (years)	Min; max (years)	N	Mean (years)	Min; max (years)		N	Mean (SD)	SEM	N	Mean (SD)	SEM			
FPNF (N=45)	23	35	18.6; 54.5	22	38	20.2; 78.3	0.716	23	3.04 (1.02)	0.21	22	2.77 (0.92)	0.2	-0.27	-0.86; 0.32	0.36
DCNF (N=75)	51	38.7	18.4; 63.5	24	37.5	19.3; 66.7	0.555	51	3.41 (0.7)	0.09	24	3.5 (0.66)	0.14	0.09	-0.24; 0.42	0.59
Co-FPNF (N=45)	23	35.2	18.7; 54.8	22	38	20.7; 74	0.733	23	3.57 (0.59)	0.12	22	3.64 (0.58)	0.12	0.07	-0.28; 0.42	0.69
Co-DCNF (N=75)	51	38.5	18.1; 70.1	24	38.7	20; 76.2	0.883	51	3.69 (0.65)	0.09	24	3.79 (0.42)	0.085	-0.07	-0.53; 0.39	0.75

N: Number; SD: standard deviation; SEM: standard error of the mean; CI: confidence interval; FPNF: facial plexiform neurofibroma, DCNF: disseminated cutaneous neurofibroma; Co-FPNF: control group of FPNF group; Co-DCNF: control group of DCNF group; Diff: difference in means.

Table V. Differences in gender frequency in individuals aged ≥ 18 years in diagnostic groups and controls.

Group	Age						<i>p</i> -Value ^a
	Females			Male			
	N	Mean (years)	Min; max (years)	N	Mean (years)	Min; max (years)	
FPNF	23	35.22	18.6; 54.5	22	38.13	20.2; 78.3	0.716
DCNF	51	38.74	18.3; 63.5	24	37.5	19.3; 66.7	0.555
Co-FPNF	23	35.24	18.7; 54.8	22	38	20.7; 74	0.733
Co-DCNF	51	38.46	18.1; 70.1	24	38.7	20; 76.2	0.883
pb	0.554			0.993			

^aMann-Whitney (independent samples), statistically significant at level $p < 0.05$; ^bKruskal-Wallis (independent samples), statistically significant at level $p < 0.05$. N: Number; FPNF: facial plexiform neurofibroma; DCNF: disseminated cutaneous neurofibroma; Co-FPNF: control group of FPNF group; Co-DCNF: control group of DCNF group.

influence of a tumour pathognomonic in NF1, namely FPNF, was considered. The pneumatisation grade of NF1 patients with and without FPNF differed significantly.

Anterior skull base in NF1. There has been a great deal of interest in the description of skull base dysplasia in NF1 (17, 48), in particular using imaging techniques (49, 50). While initial descriptions refer to the study of individual or a few cases [for review: (51)], there are several current studies published on the radiographic morphology of the orbit and the skull base in NF1 (52-55). However, the focus of studies on skull base dysplasia in NF1 is on the pathognomonic malformation of the sphenoid bone, especially the wings and the sella turcica (18). Individual studies also focus on the deformation of adjacent bones (11, 13, 54, 56), shortening of

the anterior skull base (57), and they discuss surgical procedures to correct orbital dysplasia (58-62). Some authors are concerned with whether the sphenoid bone changes are genuine skeletal malformations or the consequence of a tumour manifestation, but they do not address the pneumatisation of the bone (13, 63-65). Indeed, sphenoid pneumatisation in NF1 patients has not been studied in detail. Earlier radiological studies have already indicated that pneumatisation of paranasal sinuses may be altered in neurofibromatosis patients. However, this observation is only supported by a cursory indication (66).

Altered paranasal sinuses in NF1. Systematic studies on the radiological morphology of paranasal sinuses in the context of NF1 were performed for the maxillary sinus (40). The

Table VI. Comparison of pneumatisation stages for individuals ≥ 18 years old (NF1 versus control groups).

Group	Pneumatisation		Comparison (<i>t</i> -test)		
	Mean (SD)	SEM	Diff	95%CI	<i>p</i> -Value
FPNF (N=45)	2.91 (0.973)	0.145			
vs.	vs.	vs.			
Co-FPNF (N=45)	3.6 (3.6)	0.086	-0.69	-1.02; -0.4	<0.001
FPNF (N=45)	2.91 (0.973)	0.145			
vs.	vs.	vs.			
DCNF (N=75)	3.44 (0.663)	0.08	-0.53	-0.83; -0.23	0.001
DCNF (N=75)	3.44 (0.66)	0.08			
vs.	vs.	vs.			
Co-DCNF (N=75)	3.72 (0.58)	0.07	-0.28	-0.48; 0.08	0.007
Co-FPNF (N=45)	3.6 (0.58)	0.086			
vs.	vs.	vs.			
Co-DCNF (N=75)	3.72 (0.58)	0.067	-0.12	-0.34; 0.1	0.28

N: Number; NF1: neurofibromatosis type 1; SD: standard deviation; SEM: standard error of the mean; CI: confidence interval; FPNF: facial plexiform neurofibroma; DCNF: disseminated cutaneous neurofibroma; Co-FPNF: control group of FPNF group; Co-DCNF: control group of DCNF group; Diff: difference in means.

results suggest the relationship between unilateral hypoplastic maxillary sinus and orbital deformation of the same side. In these cases, the impact of a growing FPNF on the enlargement of the orbit at the expense of the maxillary sinus is discussed (39). Both the maxillary and sphenoid sinus almost completely develop postnatally (29). Therefore, comparison of impaired pneumatisation of these sinuses and certain facial phenotypes in NF1 is evident. However, a corresponding oval-like deformity of the increased orbit and latero-caudal extension of orbital rim is very common in the case of NF1-associated hypoplastic maxillary sinus (67). The orbit is regularly affected by the invasion of a diffuse PNF (13). These radiological signs indicate that the tumour may have grown beyond the orbit into the face. In general, the cheek is also largely infiltrated by the tumour, which typically grows in continuity with the orbital mass (39, 40, 67). From this established constellation of morphological findings, one can deduce that the hypoplastic maxillary sinus in NF1 is usually not an independent or 'spontaneous' event. It is much more likely the result of growth inhibition due to the enlarged orbit and extensive FPNF growth (56).

Altered sphenoid bone in NF1. A direct relationship between FPNF and skeletal dysplasia is described in detail for the sphenoid wing (13). However, an adjacent tumour has not been detected in all cases of surgically explored sphenoid bone dysplasia (14, 15, 68). Alternatively, arachnoid cysts may have the same inhibiting effects on bone formation or preservation as an orbitally extending FPNF (11). Indeed, a

growing arachnoid cyst can – analogous to PNF growth – contribute to the sometimes-progressive reduction of adjacent bones and protrusion of soft tissues (68). From these observations and studies on the malformation of the sphenoid bone in NF1, it follows that topographically closely related soft tissue alterations (FPNF and cyst) can usually be detected in this bone deformity as well as in maxillary sinus pathologies (deformity and hypoplasia). In contrast, the less pneumatized sphenoid sinus of NF1 patients is not adequately explained by an adjacent nerve sheath tumour because the effect is already conspicuous in patients of the DCNF group. In the FPNF group, this finding is slightly more pronounced. Thus, the pathogenesis of reduced sphenoid pneumatization differs from the unilateral hypoplasia of the maxillary sinus in NF1. The cause for the difference in pneumatization of sphenoid and maxilla in NF1 is unknown. Some authors suggest a possible association between conspicuous cephalometric findings, such as shortened anterior skull base, and bone haploinsufficiency in NF1 patients (57). Haploinsufficiency of the bone is an important factor for pseudarthrosis of long bones in NF1 (10, 69). On the other hand, the constitutive mutation of the *NF1* gene may exert an effect on cellular components of the mucous membrane of the sinus that results in impaired aeration of the bone (70). We have no experience with mucosal examination of the sphenoid sinus in NF1. Database research did not yield any results on this topic. In a single case, we observed a maxillary sinus cyst in a child with NF1 that was not a cyst but rather a diffuse neurofibroma of the mucosa of the maxillary sinus. However, the tumour had no effect on the symmetrical development of the sinus walls at the time of surgery. We suspect this finding to be a rare case of a limited neurofibroma arising in the maxillary sinus; it probably originated postnatally in an already developed sinus.

Development of the sphenoid sinus. The sphenoid sinus develops shortly after birth (29), although radiological proof of a cavity does not exist until around the second year of life in the majority of cases (36, 71, 72). In the formation of paranasal cavities, uniform involuting processes occur in preparation of the formation of the respective cavity (73). Bone marrow conversion occurs prior to development of intraosseous cavity formation. This process is visible in cross-sectional imaging (33). Further formation of the cavity occurs during childhood, and the definitive size of the sinus is reached around the time of puberty (71, 74). Thus, we assumed that determining the lower limit of 18 years of age in evaluating sinus pneumatization would ensure that no individuals were included for whom substantial growth spurts of the sinus would have been considered.

Some authors suggest that the paranasal sinus develops completely different compared to the ethmoid (32). Phylogenetic arguments for the separate development of the

respiratory and olfactory organs exist regarding this assessment (75). In particular, the occasional observable arrest of pneumatization of the paranasal sinus in healthy subjects who show normal ethmoid development indicates that the paranasal sinuses are not organs that merely develop as a postnatal extension of the ethmoid (30, 76). As far as can be assessed by the radiological projection of this study, ethmoid pneumatization was normal in both study groups.

Size and shape of the sphenoid sinus. The sphenoid sinus is considered the most variable of the paranasal sinus (29). There are variations in the sinus size range from aplasia to the aeration of adjacent skull base bones. All these variants are to be regarded as normal, unless further findings that are to be regarded as pathological occur simultaneously in an individual case. It follows that the size and shape of the intact sphenoid sinus has no diagnostic value as a single parameter. However, hypoplasia of the sinus that is reproducibly associated with a disease can be used as a diagnostic aid (see below). Agenesis of the sphenoid sinus is rare outside syndromes (77, 78). Hyperaeration of the sinus, for example, can cause functional and aesthetic impairments by broad connection of the paranasal sinus to each other and protrusion of the sinus walls beyond the natural borders of the skull (79). Such extreme hyperaeration and/or hypoplasia of the sinuses were absent in the study groups.

Nerve supply of sphenoid bone and sinus. The course of the terminal branches of the trigeminal nerve that supplies the sphenoid sinus reflects emergence of the sphenoid sinus from the dorsal boundary of ethmoid (29). In early embryonic phases, the branches of the trigeminal nerve and the precursors of the sphenoid develop close together. For example, the cartilaginous preformation of the trigeminal nerve's bony foramina rapidly follows the development of the nerve branches (20-22, 80-82). A sphenoidal nerve differentiates early in the foetal period as a communicating branch between the otic and pterygopalatine ganglia (83). In the course of both neural differentiation and cartilage development, the nerve is extended and displaced by the developing ala temporalis while remaining in close contact with the hard tissue (84).

The sensory innervation of the sphenoid sinus occurs *via* the trigeminal nerve (85). After leaving the Gasserian ganglion, the branches of the nerve are embedded into peripheral nerve sheath cells (86). The vessels of the trigeminal branches are also surrounded by a dense network of peripheral nerves (87). However, information on the neural anatomy is inconsistent, specifically as to which branch of the trigeminal nerve provides sensory supply to the sinus. Some authors describe the innervation of the sphenoid sinus as the property of terminal branches of the posterior ethmoidal nerve (88), a branch of the nasociliary nerve, which in turn

is a major branch of the ophthalmic nerve (85). Other authors agree that the innervation occurs *via* terminal branches of the first and second trigeminal nerve branch, in particular rami orbitales (89, 90). These differences in anatomical description may also be due to the fact that the posterior ethmoidal nerve is not regularly developed or detectable (90). Regardless of this assessment, the trigeminal nerve supplies the sphenoid sinus mucosa. However, there are numerous communications between the branches of the trigeminal nerve and the facial nerve, especially for the maxillary nerve (91, 92). The glandular secretion of the sphenoid sinus is controlled *via* terminal branches of the facial nerve (89). As a bone nerve ('Knochennerv'), the spinosus nerve is described; it branches off as the first branch of the mandibular nerve before or after the passage of the main branch through the oval foramen and innervates the sphenoid (93). The spinosus nerve also supplies the adjacent meninges (94). These cursory references to the neural anatomy of the sphenoid document the intimate intertwining of the main branches of the trigeminal nerve with the development of the sphenoid bone and adjacent soft tissue (11, 13).

Classification of sphenoid sinus pneumatization. The classifications of sphenoid pneumatization vary considerably (31, 46, 95-97). Therefore, comparisons of the frequency of pneumatization types must consider the age range and gender distribution of each study and also examine the definition of each label that addresses a pneumatization stage. For example, neither the term 'presellar' nor 'sellar' is unequivocally used in studies on sphenoid pneumatization (46, 96-99). Furthermore, reviews and individual studies have indicated that there are significant ethnic differences in sphenoid pneumatization (99, 100). Considering these limitations of data comparability, conchal pneumatizations in adults are usually below 5%, sellar pneumatizations constitute approximately half of the cases and postsellar pneumatizations are generally around 30% (46, 101-103). Larger variations exist in the published frequencies of presellar pneumatizations, for which ethnic differences must be considered (103). In comparison with frequency distributions of sphenoid pneumatization presented in the literature, data of the control groups correspond to these general assessments (46, 101, 102, 104). The proportion of conchal pneumatizations of the FPNF group is significantly higher than in other studies on sphenoid bone pneumatization of non-syndromal populations. The proportion of presellar pneumatizations is also very high in the FPNF group. While the number of presellar pneumatizations in the DCNF group is high, this proportion is also achieved in studies of non-NF1 patients from other countries (103). For the above reasons, analysis of patients with age- and sex-matched controls is advantageous in order to detect discrete differences in a defined population.

Altered pneumatization of the sphenoid sinus in various diseases. Sphenoid bone pneumatization is noticeably altered in some diseases. A small sphenoid sinus on lateral skull radiographs is characteristic in cystic fibrosis (CF). Sinus hypoplasia is so characteristic of this disease that it has been noted that CF diagnosis should be checked if the sphenoid's pneumatization is apparently of normal size (105). Interestingly, there is a genotype-phenotype correlation for the sphenoid pneumatization in CF (106, 107). By far the most common mutation in the gene responsible for CF (108) is associated with a significantly lower sphenoid pneumatization on lateral X-ray images of the skull compared to other pathogenic mutations in CF (106). The general hypoplasia of paranasal cavities is considered to be a direct result of primary growth hormone insensitivity of the bone in Laron syndrome (109). Hypoplasia of the sphenoid sinus is frequently observed in patients with trisomy 21. In these cases, the proportion of conchal sinus type and missing aeration is very high (110, 111). In contrast, hyperaeration of the sphenoid sinus is a common finding in patients with a different type of aneuploidy, namely Klinefelter syndrome (112), and a known finding in other complex syndromes (111, 113). These phenomena provide evidence of genetic influences on the development of paranasal sinuses. The frequently diagnosed arrest of sphenoid pneumatization in sickle cell disease suggests an impaired vascular component active in the fatty involution of the bone as a prerequisite of cavitation (114, 115).

Conclusion

Patients with NF1 show less pneumatized sphenoid bone than control individuals of the same age and sex. The initial hypothesis was accepted. The results may be useful for planning skull base surgery in NF1 patients (116). Lateral cephalometry is a low-exposure study technique, but it requires complementary cross-sectional imaging for special surgical applications (117). The results confirm accepted assessments of NF1 as a syndrome with an extremely wide range of skeletal findings (69). The presented study supports current concepts emphasising the *NF1* gene's histogenesis control functions (118), besides the well-known characterisation of NF1 as a tumour-predisposition syndrome (26, 119). The examination technique and basis of calculation presented here are easy-to-use and low-irradiation exposure instruments for screening for differences in sphenoid bone pneumatization in defined populations.

Conflicts of Interest

The Authors have no conflicts of interest with regard to the work presented. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All Authors contributed to the design of the study, evaluation of data, and writing the manuscript. All Authors have released the manuscript for publication.

Acknowledgements

The Authors thank Prof. (em.) Michail S. Davidoff, MD, anatomist, Hamburg Museum of Medical History, University Hospital Hamburg Eppendorf, for critically examining the manuscript.

References

- Friedman JM: Neurofibromatosis 1. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K and Amemiya A (eds.). GeneReviews®, Seattle, WA: University of Washington, Seattle; 1993-2019, 1998. PMID: 20301288.
- Adrian C: Über Neurofibromatose und ihre Komplikationen. Beitr Klin Chir 31: 1-98, 1901.
- Cimino PJ and Gutmann DH: Neurofibromatosis type 1. Handb Clin Neurol 148: 799-811, 2018. PMID: 29478615. DOI: 10.1016/B978-0-444-64076-5.00051-X
- Cohen Jr MM: Perspectives on craniofacial asymmetry. VI. The hamartoses. Int J Oral Maxillofac Surg 24: 195-200, 1995. PMID: 7594750. DOI: 10.1016/s0901-5027(06)80126-8
- Legendre CM, Charpentier-Côté C, Drouin R and Bouffard C: Neurofibromatosis type 1: persisting misidentification of the "elephant man" disease. J Am Board Fam Med 24: 112-114, 2011. PMID: 21209351. DOI: 10.3122/jabfm.2011.01.100219
- Clementi M, Milani S, Mammi I, Boni S, Monciotti C and Tenconi R: Neurofibromatosis type 1 growth charts. Am J Med Genet 87: 317-323, 1999. PMID: 10588837. DOI: 10.1002/(sici)1096-8628(19991203)87:4<317::aid-ajmg7>3.0.co;2-x
- Weichert KA, Dine MS, Benton C and Silverman FN: Macrocranium and neurofibromatosis. Radiology 107: 163-166, 1973. PMID: 4632000. DOI: 10.1148/107.1.163
- Heervä E, Leinonen P, Kuorilehto T, Peltonen S, Pöyhönen M, Väänänen K and Peltonen J: Neurofibromatosis 1-related osteopenia often progresses to osteoporosis in 12 years. Calcif Tissue Int 92: 23-27, 2013. PMID: 23108390. DOI: 10.1007/s00223-012-9661-y
- Crawford AH, Schumaier AP and Mangano FT: Management of cervical instability as a complication of neurofibromatosis type 1 in children: A historical perspective with a 40-year experience. Spine Deform 6: 719-729, 2018. PMID: 30348350. DOI: 10.1016/j.jspd.2018.04.002
- Brekelmans C, Hollants S, De Groote C, Sohler N, Maréchal M, Geris L, Luyten FP, Gincels L, Sciort R, de Ravel T, De Smet L, Lammens J, Legius E and Brems H: Neurofibromatosis type 1-related pseudarthrosis: Beyond the pseudarthrosis site. Hum Mutat 40: 1760-1767, 2019. PMID: 31066482. DOI: 10.1002/humu.23783
- Arrington DK, Danehy AR, Peleggi A, Proctor MR, Irons MB and Ullrich NJ: Calvarial defects and skeletal dysplasia in patients with neurofibromatosis Type 1. J Neurosurg Pediatr 11: 410-416, 2013. PMID: 23414129. DOI: 10.3171/2013.1.PEDS12409
- Friedrich RE, Emami P, Hagel C, Wikner J and Hanken H: Repair of occipital bone defects in neurofibromatosis type 1 by

- means of CAD/CAM prefabricated titanium plates. *Craniofacial Trauma Reconstr* 11: 324-330, 2018. PMID: 30574278. DOI: 10.1055/s-0037-1608699
- 13 Jacquemin C, Bosley TM and Svedberg H: Orbit deformities in craniofacial neurofibromatosis type 1. *AJNR Am J Neuroradiol* 24: 1678-1682, 2003. PMID: 13679291
- 14 Binet EF, Kieffer SA, Martin SH and Peterson HO: Orbital dysplasia in neurofibromatosis. *Radiology* 93: 829-833, 1969. PMID: 4980937. DOI: 10.1148/93.4.829
- 15 Friedrich RE, Heiland M, Kehler U and Schmelzle R: Reconstruction of sphenoid wing dysplasia with pulsating exophthalmos in a case of neurofibromatosis type 1 supported by intraoperative navigation using a new skull reference system. *Skull Base* 13: 211-217, 2003. PMID: 15912180. DOI: 10.1055/s-2004-817697
- 16 Scheithauer BW, Woodruff JM and Erlandson RA (eds.). *Tumors of the Peripheral Nervous System. Atlas of Tumor Pathology. Third Fascicles, Third Series, Fascicle 24.* Washington, DC: Armed Forces Institute of Pathology. pp. 105-218, 303-372, 385-404, 1999.
- 17 Tauber S: Haemangioma cavernosum venosum capitis. *Wien Klin Wschr* 19: 938-940, 1905.
- 18 DiMario FJ Jr, Bowers P, Jagjivan B, Burleson J, Langshur S and Greenstein RM: Analysis of skull anthropometric measurements in patients with neurofibromatosis type 1. *Invest Radiol* 28: 116-120, 1993. PMID: 8444567. DOI: 10.1097/00004424-199302000-00006
- 19 Friedrich RE, Lehmann JM, Rother J, Christ G, Zu Eulenburg C, Scheuer HT and Scheuer HA: A lateral cephalometry study of patients with neurofibromatosis type 1. *J Craniofac Surg* 45: 809-820, 2017. PMID: 28365079. DOI: 10.1016/j.jcms.2017.02.011
- 20 Shapiro R and Robinson E: *The Embryogenesis of the Human Skull. An Anatomic and Radiographic Atlas.* Cambridge: Harvard University Press, 1980.
- 21 Kjaer I: Ossification of the human fetal basicranium. *J Craniofac Genet Dev Biol* 10: 29-38, 1990. PMID: 2373754.
- 22 Kjaer I: Radiographic determination of prenatal basicranial ossification. *J Craniofac Genet Dev Biol* 10: 113-123, 1990. PMID: 2211961.
- 23 Upadhyaya M, Spurlock G, Monem B, Thomas N, Friedrich RE, Kluwe L and Mautner V: Germline and somatic NF1 gene mutations in plexiform neurofibromas. *Hum Mutat* 29: E103-E111, 2008. PMID: 18484666. DOI: 10.1002/humu.20793
- 24 Dadlani R, Sadanand V, Ghosal N and Hegde AS: Congenital giant plexiform neurofibroma with occipital calvarial dysplasia in association with meningoencephalocele in neurofibromatosis type 1 and segmental neurofibromatosis: report of 2 cases. *J Neurosurg Pediatr* 12: 458-464, 2013. PMID: 24032991. DOI: 10.3171/2013.8.PEDS12624
- 25 Joshi A, Lancelot M, Bhattacharjee NR, Polavarapu S, Beltaos E and Sobowale B: Extensive plexiform neurofibroma in a premature neonate. *Clin Med Res* 13: 36-40, 2015. PMID: 25380612. DOI: 10.3121/cmr.2014.1224
- 26 Pemov A, Li H, Patidar R, Hansen NF, Sindiri S, Hartley SW, Wei JS, Elkahoun A, Chandrasekharappa SC, NISC Comparative Sequencing Program, Boland JF, Bass S, NCI DCEG Cancer Genomics Research Laboratory, Mullikin JC, Khan J, Widemann BC, Wallace MR and Stewart DR: The primacy of NF1 loss as the driver of tumorigenesis in neurofibromatosis type 1-associated plexiform neurofibromas. *Oncogene* 36: 3168-3177, 2017. PMID: 28068329. DOI: 10.1038/ncr.2016.464
- 27 Podolsky ML and Fields WS: Plexiform neuroma of the trigeminal nerve. *J Pediatr* 45: 707-716, 1954. PMID: 13212616. DOI: 10.1016/s0022-3476(54)80267-8
- 28 Greig AV, Kirkpatrick NA, Joshi N, Kelly M and Waterhouse N: Giant hemifacial plexiform neurofibroma arising from trigeminal ganglion. *J Craniofac Surg* 20: 833-836, 2009. PMID: 19480042. DOI: 10.1097/scs.0b013e3181a28a19
- 29 Lang J: *Klinische Anatomie des Kopfes. Neurokranium – Orbita – Kraniozervikaler Übergang.* Springer-Verlag, Berlin-Heidelberg, pp. 148-150, 1981.
- 30 Zuckerkandl E: *Normale und pathologische Anatomie der Nasenhöhle und ihrer pneumatischen Anhängen.* W. Braumüller, Wien, 1893.
- 31 van Gilse PHG: The development of the sphenoidal sinus in man and its homology in mammals. *J Anat* 61: 13-166, 1927.
- 32 Witmer L: The phylogenetic history of paranasal air sinuses. In: Koppe HNT, Alt KW (eds.). *The Paranasal Sinuses of Higher Primates – Development, Function, and Evolution.* Quintessence Publishing, Chicago, 1999.
- 33 Aoki S, Dillon WP, Barkovich AJ and Norman D: Marrow conversion before pneumatization of the sphenoid sinus: Assessment with MR imaging. *Radiology* 172: 373-375, 1989. PMID: 2748818. DOI: 10.1148/radiology.172.2.2748818
- 34 Szolar D, Preidler K, Ranner G, Braun H, Kern R, Wolf G, Stammberger H and Ebner F: Magnetic resonance assessment of age-related development of the sphenoid sinus. *Br J Radiol* 67: 431-435, 1994. PMID: 8193887. DOI: 10.1259/0007-1285-67-797-431
- 35 Schmid F, Du Bala U and Ewald R: Die Entwicklung der Keilbeinhöhle. *Monatsschr Kinderheilkd* 114: 309-311, 1966. PMID: 5988148.
- 36 Zeitler P, Pahnke J and Braiteringer S: MR-tomographische Untersuchung zur Entwicklung der Keilbeinhöhle. *Laryngorhinootologie* 79: 526-531, 2000. PMID: 11050979. DOI: 10.1055/s-2000-6939
- 37 Adibelli ZH, Songu M and Adibelli H: Paranasal sinus development in children: a magnetic resonance imaging analysis. *Am J Rhinol Allergy* 25: 30-35, 2011. PMID: 21711972. DOI: 10.2500/ajra.2011.25.3552
- 38 Gibelli D, Cellina M, Gibelli S, Oliva AG, Codari M, Termine G and Sforza C: Volumetric assessment of sphenoid sinuses through segmentation on CT scan. *Surg Radiol Anat* 40: 193-198, 2018. PMID: 29270712. DOI: 10.1007/s00276-017-1949-1
- 39 Holt GR: E.N.T. manifestations of Von Recklinghausen's disease. *Laryngoscope* 88: 1617-1632, 1978. PMID: 100661. DOI: 10.1288/00005537-197810000-00008
- 40 Friedrich RE, Giese M, Mautner VF, Schmelzle R and Scheuer HA: Fehlbildungen der Kieferhöhle bei Neurofibromatose Typ 1. *Mund Kiefer Gesichtschir* 6: 363-367, 2002. PMID: 12448243. DOI: 10.1007/s10006-002-0417-0
- 41 Friedrich RE, Baumann J, Suling A, Scheuer HT and Scheuer HA: Sella turcica measurements on lateral cephalograms of patients with neurofibromatosis type 1. *GMS Interdiscip Plast Reconstr Surg DGPW* 6: Doc05, 2017. PMID: 28401031. DOI: 10.3205/iprs000107
- 42 Hofrath H: Die Bedeutung der Röntgenfern- und Abstandsaufnahme für die Diagnostik der Kieferanomalien. *Fortschr Kieferorthop* 1: 232-258, 1931.

- 43 Broadbent BH: A new x-ray technique and its application to orthodontia. *Angle Orthod* 1: 45-66, 1931.
- 44 Yonetsu K, Watanabe M and Nakamura T: Age-related expansion and reduction in aeration of the sphenoid sinus: volume assessment by helical CT scanning. *AJNR Am J Neuroradiol* 21: 179-182, 2000. PMID: 10669247.
- 45 Tomovic S, Esmaceli A, Chan NJ, Shukla PA, Choudhry OJ, Liu JK and Eloy JA: High-resolution computed tomography analysis of variations of the sphenoid sinus. *J Neurol Surg B Skull Base* 74: 82-90, 2013. PMID: 24436893. DOI: 10.1055/s-0033-1333619
- 46 Štoković N, Trkulja V, Dumić-Čule I, Čuković-Bagić I, Lauc T, Vukičević S and Grgurević L: Sphenoid sinus types, dimensions and relationship with surrounding structures. *Ann Anat* 203: 69-76, 2016. PMID: 25843780. DOI: 10.1016/j.aanat.2015.02.013
- 47 Spaeth J, Krügelstein U and Schlöndorff G: The paranasal sinuses in CT-imaging: development from birth to age 25. *Int J Pediatr Otorhinolaryngol* 39: 25-40, 1997. PMID: 9051437. DOI: 10.1016/S0165-5876(96)01458-9
- 48 Davidson KC: Cranial and intracranial lesions in neurofibromatosis. *Am J Roentgenol* 98: 550-556, 1966. PMID: 4958624. DOI: 10.2214/ajr.98.3.550
- 49 Winkelbauer A: Die Veränderungen am Schädel skelet bei der Neurofibromatosis. *Dtsch Z Chir* 205: 230-257, 1927.
- 50 Holt JF and Wright EM: The radiologic features of neurofibromatosis. *Radiology* 51: 647-664, 1948. PMID: 18891292. DOI: 10.1148/51.5.647
- 51 Giese M: Die Veränderungen der Kiefer und der Zahnstellung bei Neurofibromatose Typ 1 (Dissertation). Eppendorf University Hospital (Hamburg), University of Hamburg; 1995.
- 52 D'Ambrosio JA, Langlais R and Young RS: Jaw and skull changes in neurofibromatosis. *Oral Surg Oral Med Oral Pathol* 66: 391-396, 1988. PMID: 3140162. DOI: 10.1016/0030-4220(88)90252-6
- 53 van Es S, North KN, McHugh K and De Silva M: MRI findings in children with neurofibromatosis type 1: a prospective study. *Pediatr Radiol* 26: 478-487, 1996. PMID: 8662066. DOI: 10.1007/BF01377205
- 54 Kaste SC and Pivnick EK: Bony orbital morphology in neurofibromatosis type 1 (NF1). *J Med Genet* 35: 628-631, 1998. PMID: 9719366. DOI: 10.1136/jmg.35.8.628
- 55 Heervä E, Peltonen S, Pirttiniemi P, Happonen RP, Visnapuu and Peltonen J: Short mandible, maxilla and cranial base are common in patients with neurofibromatosis 1. *Eur J Oral Sci* 119: 121-127, 2011. PMID: 21410551. DOI: 10.1111/j.1600-0722.2011.00811.x
- 56 Friedrich RE, Stelljes C, Hagel C, Giese M and Scheuer HA: Dysplasia of the orbit and adjacent bone associated with plexiform neurofibroma and ocular disease in 42 NF-1 patients. *Anticancer Res* 30: 1751-1764, 2010. PMID: 20592374.
- 57 Cung W, Freedman LA, Khan NE, Romberg E, Gardner PJ, Bassim CW, Baldwin AM, Widemann BC and Stewart DR: Cephalometry in adults and children with neurofibromatosis type 1: implications for the pathogenesis of sphenoid wing dysplasia and the "NF1 facies". *Eur J Med Genet* 58: 584-590, 2015. PMID: 26360873. DOI: 10.1016/j.ejmg.2015.09.001
- 58 Jackson IT: Neurofibromatosis of the skull base. *Clin Plast Surg* 22: 513-530, 1995. PMID: 7554720.
- 59 Snyder BJ, Hanieh A, Trott JA and David DJ: Transcranial correction of orbital neurofibromatosis. *Plast Reconstr Surg* 102: 633-642, 1998. PMID: 9727426. DOI: 10.1097/00006534-199809030-00005
- 60 Pessis R, Lantieri L, Britto JA, Leguerinel C, Wolkenstein P and Hivelin M: Surgical care burden in orbito-temporal neurofibromatosis: Multiple procedures and surgical care duration analysis in 47 consecutive adult patients. *J Craniomaxillofac Surg* 43: 1684-1693, 2015. PMID: 26210305. DOI: 10.1016/j.jcms.2015.06.023
- 61 Naran S, Swanson JW, Ligh CA, Shubinets V, Taylor JA and Bartlett S: Sphenoid dysplasia in neurofibromatosis: patterns of presentation and outcomes of treatment. *Plast Reconstr Surg* 142: 518e-526e, 2018. PMID: 30020238. DOI: 10.1097/PRS.00000000000004779
- 62 Niu J, Wang J, Wang D, He X, Li Z, Li X, Su F and Jia W: Clinical, radiological features and surgical strategies for 23 NF1 patients with intraorbital meningoencephalocele. *Neurol Sci* 40: 1217-1225, 2019. PMID: 30868483. DOI: 10.1007/s10072-019-03826-2
- 63 Macfarlane R, Levin AV, Weksberg R, Blaser S and Rutka JT: Absence of the greater sphenoid wing in neurofibromatosis type I: congenital or acquired: case report. *Neurosurgery* 37: 129-133, 1995. PMID: 8587673. DOI: 10.1227/00006123-199507000-00020
- 64 Havlik RJ and Boaz J: Cranio-orbital-temporal neurofibromatosis: are we treating the whole problem? *J Craniofac Surg* 9: 529-535, 1998. PMID: 10029765. DOI: 10.1097/00001665-199811000-00007
- 65 Alwan S, Tredwell SJ and Friedman JM: Is osseous dysplasia a primary feature of neurofibromatosis 1 (NF1)? *Clin Genet* 67: 378-390, 2005. PMID: 15811002. DOI: 10.1111/j.1399-0004.2005.00410.x
- 66 Kleinsasser O and Brandt P: Die Knochenveränderungen am Schädel bei Neurofibromatose und ihre Pathogenese. *Acta Neurochir* 7: 364-376, 1959. PMID: 14409744. DOI: 10.1007/BF01407977
- 67 Friedrich RE, Rother J, Christ G, Lehmann M, Eulenburg CG, Giese M and Scheuer HA: Analysis of orbital plain radiographs for orbital deformities in neurofibromatosis type 1 patients, with special reference to alterations of the orbital rim as indicators of adjacent plexiform neurofibroma. *Anticancer Res* 33: 1081-1090, 2013. PMID: 23482785.
- 68 Chapman PH, Curtin HD and Cunningham MJ: An unusual pterygopalatine meningocele associated with neurofibromatosis type 1. Case report. *J Neurosurg* 93: 480-483, 2000. PMID: 10969948. DOI: 10.3171/jns.2000.93.3.0480
- 69 Schindeler A and Little DG: Recent insights into bone development, homeostasis, and repair in type 1 neurofibromatosis (NF1). *Bone* 42: 616-622, 2008. PMID: 18248783. DOI: 10.1016/j.bone.2007.11.006
- 70 Yang FC, Staser K and Clapp DW: The plexiform neurofibroma microenvironment. *Cancer Microenviron* 5: 307-310, 2012. PMID: 22821631. DOI: 10.1007/s12307-012-0115-x
- 71 Fujioka M and Young LW: The sphenoidal sinuses: radiographic patterns of normal development and abnormal findings in infants and children. *Radiology* 129: 133, 1978. PMID: 693864. DOI: 10.1148/129.1.133
- 72 Jang YJ, Kim SC: Pneumatization of the sphenoid sinus in children evaluated by magnetic resonance imaging. *Am J Rhinol* 14: 181-185, 2000. PMID: 10887625. DOI: 10.2500/105065800782102771

- 73 Simonson TM and Kao SC: Normal childhood developmental patterns in skull bone marrow by MR imaging. *Pediatr Radiol* 22: 556-559, 1992. PMID: 1491927. DOI: 10.1007/BF02015347
- 74 Maranon G and Armengaud FG: Chronology of the sphenoidal sinus and its value in diagnosis. *Br Med J* 1(4865): 778-779, 1954. PMID: 13140859. DOI: 10.1136/bmj.1.4865.778
- 75 Jankowski R: The Evo-Devo Origin of the Nose, Anterior Skull Base and Midface. Springer-Verlag, Paris, 2013.
- 76 Kuntzler S and Jankowski R: Arrested pneumatization: witness of paranasal sinuses development? *Eur Ann Otorhinolaryngol Head Neck Dis* 131: 167-170, 2014. PMID: 24709406. DOI: 10.1016/j.anorl.2013.01.008
- 77 Anik I, Anik Y, Koc K and Ceylan S: Agenesis of sphenoid sinuses. *Clin Anat* 18: 217-219, 2005. PMID: 15768410. DOI: 10.1002/ca.20096
- 78 Köse TE, İşler C, Şenel ŞN, Şitilci T, Özcan İ and Aksakallı N: Frank-ter Haar syndrome - additional findings? *Dentomaxillofac Radiol* 45: 20150119, 2016. PMID: 26582053. DOI: 10.1259/dmfr.20150119
- 79 Morton ME: Excessive pneumatization of the sphenoid sinus: a case report. *J Maxillofac Surg* 11: 236-238, 1983. PMID: 6579159. DOI: 10.1016/s0301-0503(83)80055-1
- 80 Müller F and O'Rahilly R: The human chondrocranium at the end of the embryonic period, proper, with particular reference to the nervous system. *Am J Anat* 159: 33-58, 1980. PMID: 7446441. DOI: 10.1002/aja.1001590105
- 81 Nemzek WR, Brodie HA, Hecht ST, Chong BW, Babcook CJ and Seibert JA: MR, CT, and plain film imaging of the developing skull base in fetal specimens. *AJNR Am J Neuroradiol* 21: 1699-1706, 2000. PMID: 11039353.
- 82 Chow MSM, Wu SL, Hui V, Chow TCH and Yew DT: Revisit the cavernous sinus from fetus to adult - New and old data. *Anat Rec (Hoboken)* 301: 819-824, 2018. PMID: 29193866. DOI: 10.1002/ar.23734
- 83 Domenech Mateu JM and Pueyo Mur FJ: Development and arrangement of the tympanic plexus and the nerve of the pterygoid canal during the human embryonic and fetal periods. *Acta Morphol Neerl Scand* 18: 253-272, 1980. PMID: 7415880.
- 84 Yamamoto M, Ho Cho K, Murakami G, Abe S and Rodríguez-Vázquez JF: Early fetal development of the otic and pterygopalatine ganglia with special reference to the topographical relationship with the developing sphenoid bone. *Anat Rec (Hoboken)* 301: 1442-1453, 2018. PMID: 29669195. DOI: 10.1002/ar.23833
- 85 Lang J and Reiter W: Über die dem Orbitadach und -rand angelagerten Strecken des N. ophthalmicus und seiner Äste. *Neurochirurgia (Stuttg)* 30: 129-134, 1987. PMID: 3683698. DOI: 10.1055/s-2008-1054080
- 86 Kehrli P, Maillot C and Wolff MJ: Anatomy and embryology of the trigeminal nerve and its branches in the parasellar area. *Neurol Res* 19: 57-65, 1997. PMID: 9090638.
- 87 Smoliar E, Smoliar A and Belkin VS: Innervation of human trigeminal nerve blood vessels. *Cells Tissues Organs* 165: 40-44, 1999. PMID: 10460972. DOI: 10.1159/000016672
- 88 McGregor Buchanan A: Manual of Anatomy, Systematic and Practical, Including Embryology, Volume 3. St. Louis: CV Mosby, pp. 1080, 1914.
- 89 Schiebler TH, Schmidt W: Anatomie: Zytologie, Histologie, Entwicklungsgeschichte, makroskopische und mikroskopische Anatomie des Menschen, 5th edition. Springer-Verlag, Berlin-Heidelberg, pp. 440, 2013.
- 90 Parks ET: Cone beam computed tomography for the nasal cavity and paranasal sinuses. *Dent Clin North Am* 58: 627-651, 2014. PMID: 24993926. DOI: 10.1016/j.cden.2014.04.003
- 91 deSantis M, Anderson KJ, King DW and Nielsen J: Variability in relationships of arteries and nerves in the human orbit. *Anat Anz* 157: 227-231, 1984. PMID: 6507890.
- 92 Hwang K, Yang SC and Song JS: Communications between the trigeminal nerve and the facial nerve in the face: a systematic review. *J Craniofac Surg* 26: 1643-1646, 2015. PMID: 26114519. DOI: 10.1097/SCS.0000000000001810
- 93 von Luschka H: Der Nervus spinosus. *Arch Anat Physiol Wiss Med* 445-448, 1853.
- 94 Lee SH, Hwang SJ, Koh KS, Song WC and Han SD: Macroscopic innervation of the dura mater covering the middle cranial fossa in humans correlated to neurovascular headache. *Front Neuroanat* 11: 127, 2017. PMID: 29311855. DOI: 10.3389/fnana.2017.00127
- 95 Cope VZ: Internal structure of the sphenoid sinus. *J Anat Physiol* 51: 127-136, 1917.
- 96 Hammer G and Rådberg C: The sphenoidal sinus. An anatomical and roentgenologic study with reference to transsphenoid hypophysectomy. *Acta Radiol* 56: 401-422, 1961. PMID: 13904157.
- 97 Hardy J: Surgery of the pituitary gland, using the open trans-sphenoidal approach. Comparative study of 2 technical methods. *Ann Chir* 21: 1011-1022, 1967. PMID: 5629961.
- 98 Elwany S, Yacout YM, Talaat M, El-Nahass M, Gunied A and Talaat M: Surgical anatomy of the sphenoid sinus. *J Laryngol Otol* 97: 227-241, 1983. PMID: 6833847. DOI: 10.1017/s0022215100094056
- 99 Lu Y, Pan J, Qi S, Shi J, Zhang X and Wu K: Pneumatization of the sphenoid sinus in Chinese: The differences from Caucasian and its application in the extended transsphenoidal approach. *J Anat* 219: 132-142, 2011. PMID: 21517841. DOI: 10.1111/j.1469-7580.2011.01380.x
- 100 Anusha B, Baharudin A, Philip R, Harvinder S and Shaffie BM: Anatomical variations of the sphenoid sinus and its adjacent structures: a review of existing literature. *Surg Radiol Anat* 36: 419-427, 2014. PMID: 24146215. DOI: 10.1007/s00276-013-1214-1
- 101 Batra PS, Citardi MJ, Gallivan RP, Roh HJ and Lanza DC: Software-enabled computed tomography analysis of the carotid artery and sphenoid sinus pneumatization patterns. *Am J Rhinol* 18: 203-208, 2004. PMID: 15490566.
- 102 Kayalioglu G, Erturk M and Varol T: Variations in sphenoid sinus anatomy with special emphasis on pneumatization and endoscopic anatomic distances. *Neurosciences (Riyadh)* 10: 79-84, 2005. PMID: 22473192.
- 103 Hamid O, El Fiky L, Hassan O, Kotb A and El Fiky S: Anatomic variations of the sphenoid sinus and their impact on trans-sphenoid pituitary surgery. *Skull Base* 18: 9-15, 2008. PMID: 18592020. DOI: 10.1055/s-2007-992764
- 104 Idowu OE, Balogun BO and Okoli CA: Dimensions, septation, and pattern of pneumatization of the sphenoidal sinus. *Folia Morphol (Warsz)* 68: 228-232, 2009. PMID: 19950072.
- 105 Eggesbø HB, Eken T, Eiklid K and Kolmannskog F: Hypoplasia of the sphenoid sinuses as a diagnostic tool in cystic fibrosis. *Acta Radiol* 40: 479-485, 1999. PMID: 10485235. DOI: 10.3109/02841859909175571

- 106 Woodworth BA, Ahn C, Flume PA and Schlosser RJ: The delta F508 mutation in cystic fibrosis and impact on sinus development. *Am J Rhinol* 21: 122-127, 2007. PMID: 17283574. DOI: 10.2500/ajr.2007.21.2905
- 107 Halderman AA, Lee S, London NR, Day A, Jain R, Moore JA and Lin SY: Impact of high- *versus* low-risk genotype on sinonasal radiographic disease in cystic fibrosis. *Laryngoscope* 129: 788-793, 2019. PMID: 30549259. DOI: 10.1002/lary.27595
- 108 Schaaf CP and Zschocke J: *Basiswissen Humangenetik*. Springer, Berlin-Heidelberg, pp. 220-224, 2013.
- 109 Kornreich L, Horev G, Schwarz M, Karmazyn B and Laron Z: Craniofacial and brain abnormalities in Laron syndrome (primary growth hormone insensitivity). *Eur J Endocrinol* 146: 499-503, 2002. PMID: 11916617. DOI: 10.1530/eje.0.1460499
- 110 Fischer-Brandies H, Schmid RG and Fischer-Brandies E: Craniofacial development in patients with Down's syndrome from birth to 14 years of age. *Eur J Orthod* 8: 35-42, 1986. PMID: 2937647. DOI: 10.1093/ejo/8.1.35
- 111 Miller JD, Capusten BM and Lampard R: Changes at the base of skull and cervical spine in Down syndrome. *Can Assoc Radiol J* 37: 85-89, 1986. PMID: 2941438.
- 112 Kosowicz J and Rzymiski K: Radiological features of the skull in Klinefelter's syndrome and male hypogonadism. *Clin Radiol* 26: 371-378, 1975. PMID: 1201634.
- 113 Gökçe E, Beyhan M and Sade R: Radiological imaging findings of Dyke-Davidoff-Masson syndrome. *Acta Neurol Belg* 117: 885-893, 2017. PMID: 28374239. DOI: 10.1007/s13760-017-0778-7
- 114 Prabhu AV and Branstetter 4th BF: The CT prevalence of arrested pneumatization of the sphenoid sinus in patients with sickle cell disease. *AJNR Am J Neuroradiol* 37: 1916-1919, 2016. PMID: 27151749. DOI: 10.3174/ajnr.A4801
- 115 Arpaci T. Arrested pneumatization of the sphenoid sinus mimicking skull base tumours: MRI prevalence in children with haematologic diseases. *Int J Neurosci* 128: 1040-1043, 2018. PMID: 29724144. DOI: 10.1080/00207454.2018.1473397
- 116 Kosty J, Staarman B, Zimmer LA and Zuccarello M: Infundibular hemangioblastoma in a patient with neurofibromatosis type 1: Case report and review of the literature. *World Neurosurg* 88: 693.e7-693.e12, 2016. PMID: 26724614. DOI: 10.1016/j.wneu.2015.12.030
- 117 Onerci M, Ariyürek M, Tacal T and Aydingöz U: Shortcomings of lateral sinus radiograph in the preoperative determination of the extent of endonasal endoscopic sinus surgery. *Laryngoscope* 105: 843-846, 1995. PMID: 7630297. DOI: 10.1288/00005537-199508000-00014
- 118 Riccardi VM: Neurofibromatosis type 1 is a disorder of dysplasia: The importance of distinguishing features, consequences, and complications. *Birth Defects Res A Clin Mol Teratol* 88: 9-14, 2010. PMID: 19691086. DOI: 10.1002/bdra.20616
- 119 Legius E, Marchuk DA, Collins FS and Glover TW: Somatic deletion of the neurofibromatosis type 1 gene in a neurofibrosarcoma supports a tumour suppressor gene hypothesis. *Nat Genet* 3: 122-126, 1993. PMID: 8499945. DOI: 10.1038/ng0293-122

Received September 7, 2020

Revised November 17, 2020

Accepted November 18, 2020