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A Posterior-Anterior Cephalometric Study of Skull Symmetry in Patients With Neurofibromatosis Type 1

REINHARD E. FRIEDRICH[1*], GEORG CHRIST[1*], HANNAH T. SCHEUER[2] and HANNA A. SCHEUER[2,3]

[1]*Department of Oral and Craniomaxillofacial Surgery, Eppendorf University Hospital, University of Hamburg, Hamburg, Germany;*
[2]*Private Praxis for Orthodontics, Hamburg-Lokstedt, Hamburg, Germany;*
[3]*Department of Orthodontics, Eppendorf University Hospital, University of Hamburg, Hamburg, Germany*

Abstract. *Background/Aim: Neurofibromatosis type 1 (NF1) is a tumor predisposition syndrome. Bone findings make a significant contribution to the clinical diagnosis of NF1. It has been suggested that there are characteristic skeletal features of the NF1 patients' skull that cause a specific 'NF1 facies'. To test this thesis, skull examinations were carried out on NF1 patients. Patients and Methods: The posteroanterior (PA) cephalograms of 76 patients with NF1 were analyzed using defined measuring points. Patients with confirmed facial plexiform neurofibromas (PNF) were excluded from the study. A special interest of the investigation was the symmetry of the measuring points defined as the distance to the median sagittal plane. Results: NF1 patients have a slightly larger distance to the Z-plane than controls at the zygomatic arch and mastoid measurement points (p=0.027 and 0.028, respectively). In contrast, the distances of the juga and antegonion measurement points from the horizontal reference plane are larger in the control group (p=0.002 and 0.480, respectively). The transverse development of the midface at the level of the zygomatic arch showed no differences from the control group (p=0.841). The transverse diameter of the skull at the mastoid and juga measurement points is smaller in the NF1 group compared to the control group (p=0.010 and 0.002, respectively). There is a statistically significant left-right (LR) asymmetry of the distances to the median sagittal plane in favor of the left side in the patient group (p=0.002 to 0.037). However, the numerical deviations from the control group are small overall. Conclusion: Considering the natural, biological deviations of cephalometric measurements of the individual from idealized geometric norms, the facial skeleton of NF1 patients is symmetrically developed. It is unlikely that the calculated LR asymmetry of the patients has a visible effect. In comparison to cephalometric values of a normal population, no characteristic facial skeleton of the NF1 patient in the PA projection of the skull can be derived from these findings. Clear asymmetries of the facial skeleton should give rise to further diagnosis to clarify the suspicion of facial PNF.*

*These Authors contributed equally to this study.

Correspondence to: Prof. Reinhard E. Friedrich, MD, DMD, Ph.D., FEBOMFS, Department of Oral and Craniomaxillofacial Surgery, Eppendorf University Hospital, University of Hamburg, Martinistr. 22, D-22046 Hamburg, Germany. Tel: +49 741053259, e-mail: rfriedrich@uke.de

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Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary disease diagnosed in approximately 1: 2,500 to 1: 3,000 live births. The disease's penetrance is almost complete, and the variability of findings and symptoms is very high (1). NF1 is a tumor predisposition syndrome. Individuals affected with NF1 are predestined to develop peripheral nerve sheath tumors called neurofibromas (2). It is assumed the tumor cells are derived from Schwann cells or their precursors, *i.e.*, derivatives of the neural crest (3). In fact, many NF1-related tumors are derived from derivatives of the neural crest. NF1 has been suggested to represent the paradigm of 'neurocristopathies' (4). NF1 is also a disease of the bone (5). The craniofacial skeleton arises from the neural crest (6, 7). Typical and often tumor-associated malformations have been reported for the craniofacial area, such as sphenoid bone dysplasia (8, 9) or jaw deformities (10, 11). However, there are also general changes in the skull rated as characteristic findings of NF1, *e.g.*, macrocranium (12) and increased interorbital distance (13, 14). In fact, it has been concluded from skull studies that NF1 patients present a distinctive facial phenotype (15). On the other hand, recent cephalometric studies revealed that abnormal changes in the facial skeleton of NF1 patients can be reliably traced back to the topography of a tumor characteristic of NF1 patients, the facial plexiform neurofibroma (PNF) (16).

PNF is a precancerous lesion and PNF of the facial region frequently causes severe disfigurement. The skeletal aspect in the region of facial PNF is often characterized by bone distortion or destruction causing facial asymmetries. The skeletal lesions are assigned to the area in which the tumor spreads. The diagnosis of the skeletal proportions of the NF1 patient is an essential factor in assessing the local tumor burden from a tumor with significant local destructive power. However, it is still open to discussion whether asymmetries of the skull are a constitutive feature of NF1 patients or are necessarily associated with PNF or other pathologies that can cause local transformations of the bone [*e.g.*, local effects such as vascular malformations or haploinsufficiency of osteogenic cells in defined body sites (9)]. Therefore, the aim of this study was the cephalometric analysis of NF1 patients with a particular interest in measuring the symmetry of the skull in a suitable radiological projection.

Patients and Methods

Patients. Seventy-six adult patients (age >18 years) with NF1 were examined, for whom a posteroanterior (PA) cephalogram could be evaluated (31 men and 45 women). All patients had NF1 according to the currently valid diagnostic criteria (1). Only patients who had not developed a facial plexiform neurofibroma (PNF) were included in the study group. The exclusion of facial PNF was based on the clinical examination of the patient (REF), magnetic resonance imaging (MRI) or computed tomography (CT) findings, surgical reports in cases with facial soft tissue tumor treatment and histological examinations of surgical specimen. Patients with a skeletal procedure of the skull were excluded from the evaluation, except for those who stated that teeth had been extracted.

The main interest of the investigation was the symmetry analysis of bilateral measuring points to reference planes. Symmetry of the bilaterians relative to their long axis is a constitutive characteristic of the taxon (17). Therefore, intra-individual comparisons of bilaterally registered measurement values were carried out on the radiographs. Measurement points were excluded from the evaluation that could not be clearly identified in an individual.

The cephalometric measurement results were compared with the data of a control group (n=21, male=15, female=6; mean=23.5 years, minimum=18.5 years, maximum=30.67 years). The group characteristics are described in detail elsewhere (16, 17).

The angle of the connecting line between bilateral measuring points and the Z-plane was determined to identify deviations from the horizontal plane. Since growth-dependent influences on the measurement results are irrelevant in this comparison, measurements from patients and test subjects who were younger than 18 years of age at the time of the X-ray examination were also considered in these calculations. For angle calculations, the group size is increased (controls: 23, patients: up to 94).

Radiology. The X-ray examinations were carried out using a Lumex® cephalostat (B. F. Wehmer Co., Inc., Franklin Park, IL, USA, and Siemens, Erlangen, Germany). Equipment and performance of the radiological investigation met the required technical standards in cephalometry (18) and have been described in detail elsewhere (16, 17).

Data registration and measurement. All radiographs were scanned and processed using the Dental Vision® software (Computerforum, Elmshorn, Germany). Anonymized personal data were registered in Ortho Express® (Computerforum). The process of digitizing X-ray images and the digital measurement and evaluation of the data have been described in detail elsewhere (16, 17).

Most measuring points were bilateral. During the measurements, mean values were calculated derived from the distances between the respective measuring points and the reference planes. In the case of statements about the mean value of bilateral routes without specifying the side of the body, the judgements are based on the double data set, *i.e.*, in the analysis of measurement values with reference to the Z-plane. Calculations of total horizontal distances (crossing M-plane) are based on the addition of the distance of both bilateral measurement points to the median sagittal plane.

Definition of landmarks and calculation of measurement values. All lines and angles are defined by reference points. Line segments are designated by the acronyms of their radiologically defined endpoints. Angles are defined and designated by the acronyms of constitutive line segments (Table I). Definition of cephalometric landmarks is detailed elsewhere (17).

Reliability of measurements. The examination of the differences in the accuracy of the measured value determination both in the intra- and inter-observer comparison (19, 20) are listed in detail elsewhere (17).

Determination of the main planes (Z-plane, M-plane). The essential orientation of PA cephalometry is the definition of the Z-plane. Both radiological reference points (Z-points) are defined as the medial demarcation of the orbital margin in the zygomaticofrontal suture on each side (ZR, ZL). The connection of the reference points defines with empirical accuracy a plane parallel to the horizontal plane and is termed Z-plane. The median sagittal reference plane (M-plane) of the skull was constructed as a perpendicular to the Z-plane. M-plane is defined as a rectangular line connecting the center of crista galli and the Z-plane. Distances of skeletal reference points to the median sagittal plane are measured as distances meeting the lines from these points at right angles.

Lines between bilateral measuring points define horizontal lines on PA-cephalogram. Ideally, these horizontal lines run parallel to the Z-plane. Deviations of related bilateral measuring points in the vertical dimension define lines that cross the extended Z-plane at one body side at an acute angle. The smaller the angle, the better the parallel alignment of the planes relative to the Z-plane in norma frontalis. The angle between the Z-plane and the extended connecting lines of bilateral measuring points was evenly located on both sides of the body.

The analysis focuses on the assessment of the skeletal measuring points of the midface, the middle cranial base and the mandible.

Ethics. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. This study was conducted in compliance with the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Data were anonymized prior to analysis, and the investigators studying the radiographs were blinded for diagnosis and the identity of individuals. The investigations of anonymized data were performed in accordance with Hamburgisches Gesundheitsdienstgesetz (Hamburg Healthcare

Table I. *Reference points of posterior-anterior cephalograms. Distances are defined by the acronym of the measuring point and the respective reference plane (-M or -Z).*

Reference point	Abbreviation	Definition
Antegonion right	AGR	Point located at the greatest concavity of the right antegonial notch of the mandible
Antegonion left	AGL	Point located at the greatest concavity of the left antegonial notch of the mandible
Menton	Me	The most caudal point of the bony chin
Juga right	JR	Point located most medial and cranial at the outside of the maxillary tuberosity/zygomatic buttress on the right side
Juga left	JL	Point located most medial and cranial at the outside of the maxillary tuberosity/zygomatic buttress on the left side
Mastoid process right	MaPR	Caudal tip of right mastoid process
Mastoid process left	MaPL	Caudal tip of left mastoid process
Zygomatic arch right	ZAR	Point located most lateral on the right zygomatic arch
Zygomatic arch left	ZAL	Point located most lateral on the left zygomatic arch
Spina nasalis anterior	Sp	Frontal projection of the tip of the anterior nasal spine, located in the middle of the skull, below the nasal concavity
Crista galli	Cg	A cockscomb-like protrusion of the upper edge of the perpendicular plate of the ethmoid bone
Z right	ZR	Point on the inner side (towards the orbital) of the right zygomatico-frontal suture
Z left	ZL	Point on the inner side (towards the orbital) of the left zygomatico-frontal suture

Act). This type of investigation did not require the approval of the local ethics committee.

Statistics. The statistical tests used were the arithmetic mean, standard deviation, paired and unpaired *t*-test. The significance level was set at $p<0.05$. All calculations were carried out with SPSS (Statistical Package for the Social Sciences, IBM Corp., Armonk, VA, USA).

Results

Within the control group, the intra-individual side-by-side comparisons of the distances between the measuring points and the reference plane are not significantly different. The intra-individual comparison of the distances between the measuring points and the reference plane proves the symmetrical development of the facial skull in the control group (Table II).

Within the NF1 patient group, the intra-individual comparison of the distances to the reference planes shows no statistically significant differences between the sides of the body for the values of the Z-plane: in relation to the horizontal plane, the measuring points are located symmetrically to one another. In contrast, in the patient group, the distances between the measuring points and the M-plane are slightly larger on the left than on the right. These differences are statistically significant ($p=0.002$ to 0.037). However, none of the mean differences reaches a value of more than about 2 mm (Table III).

The comparison of the measured values of the two study groups reveals several statistically significant differences (Table IV). The distance between the measuring points "zygomatic arch" and "mastoid process" to the Z-plane of NF1 patients is slightly larger than that of the control group ($p=0.027$ and 0.028). The reverse relationship applies to the juga measuring point ($p=0.002$). The small differences between the measuring points in relation to the horizontal plane of the skull are indicated by the very small angles that result from the intersection of the straight lines. Indeed, the differences between the angles of these measuring points and the horizontal plane (Z-plane) are statistically significant only for the measuring point "juga" ($p=0.025$). This finding is verified for measuring points "zygomatic arch" ($p=0.870$) and "antegonion" ($p=0.066$) and proves the symmetry of the facial skull in both groups on PA cephalographs in relation to the Z-plane.

The distances between the measuring points and the median plane do not differ between the two groups regarding the lateral extension of the zygomatic bone. This measuring point has no statistically significant differences in the side comparison of the distances between the two groups (p=0.838). In contrast, the distance between the mastoid process and the median plane is smaller in NF1 patients than in the control group ($p=0.007$). The overall distance (MaPR-MaPL) is also lower in the patient group compared to the control group ($p=0.010$). These relationships also apply to the "juga" and "antegonion" measuring points.

The distances between the two unilateral measuring points are on average somewhat larger in the NF1 group. However, the differences in the mean values are small. As expected, the deviations from the median level are greater for the point "menton" compared to the point "ANS".

In summary, there is no significant LR difference in the measured values in relation to the horizontal plane (Z-plane). In contrast, there is a significant LR difference of the

Table II. *Side comparison of the measured values (L/R=right/left) in controls (t-test).*

Measurement	N	Mean value (mm)	Mean differences (mm)	Minimum (mm)	Maximum (mm)	SD	*p*-Value
Zygomatic arch							
ZA – Z-plane	21	L: 28.62	0.682	22.97	37.74	4.08	0.395
		R: 28.13		20.66	34.16	3.66	
ZA – M-plane	21	L: 68.02	–0.721	57.84	72.19	2.52	0.396
		R: 68.74		63.24	74.83	3.46	
Mastoid process							
MaP - Z-plane	21	L: 52.90	0.636	40.56	69.41	7.33	0.278
		R: 52.17		41.39	66.91	7.10	
MaP - M-plane	21	L: 56.23	–1.32	50.08	63.38	3.29	0.293
		R: 57.56		51.85	66.81	4.40	
Juga							
J - Z-plane	21	L: 57.14	0.95	50.08	64.17	3.93	0.764
		R: 57.04		51.17	62.44	3.42	
J - M-plane	21	L: 34.37	0.777	31.20	37.53	1.87	0.104
		R: 35.15		31.92	39.14	1.75	
Antegonion							
AG - Z-plane	21	L: 98.31	–0.167	84.20	107.00	6.19	0.749
		R: 98.47		85.81	107.54	5.55	
AG - M-plane	21	L: 46.00	–0.049	37.68	57.19	4.11	0.960
		R: 46.05		41.94	53.96	3.20	

measured values in relation to the median-sagittal plane (M-plane). The distances are larger on the left side. However, the differences are quantitatively small. Table II, Table III and Table IV summarize the results.

Discussion

This study analyses skull symmetry in patients with type 1 neurofibromatosis who have not developed a PNF of the face. As a result, the examination provides evidence of a largely symmetrically developed face in the patient group. Within the framework of physiological variability of the biological structures' shape (21), facial cutaneous neurofibromas, irrespective of number, do not affect the symmetry of the facial skeleton. However, the facial skull measurements show statistically significant differences for some typical cephalometric measurements in NF1 patients. The interaction of discrete skeletal changes results in a somewhat closer position of the lower midface/skull base and the outer limitation of the jaw angle (relative to the M-plane), showing a narrowing of the skull in these regions. Furthermore, the findings reveal a slight tendency towards a long face (measured relative to the Z-plane). Left-right (LR) comparison of the distances between horizontal measuring points and the median sagittal plane in the NF1 group proved a quantitatively small but statistically significant greater distance on the left side. However, the differences in the measured values are small and in no way contradict the assumption that the patient's face appears essentially symmetrical.

NF facies. One reason for this investigation was the repeated claim that a typical shape of the face of NF1 patients can be described (15, 22-24). This view was contradicted early on (25), but further studies pointed out that there are well-documented findings at least for some patients with a defined mutation status of the NF1 gene, suggesting a characteristic facial phenotype (26, 27). However, the facial findings of subgroups of NF1 patients with noticeable facial features are not specific to the disease as such, but rather a well-known phenomenon for numerous genetic diseases, lately mainly discussed in connection with so-called RASopathies (28-30). The facial findings in genetically defined subgroups such as RASopathies (27) are very likely to have a skeletal basis; examples include the enlarged glabella and the prominent forehead (31). It was therefore obvious to use radiological examinations to record measurable abnormalities in the skull of NF1 patients. More recent lateral cephalometry analyzes have shown a shortening of the skull base region resulting in a sagittal shortened midface (15). This finding was emphasized as an essential constitutive factor for the development of the 'NF1 facies' (15). The results of the referred study were obtained from NF1 patients who had not developed facial PNF (15). Another investigation, using the same radiological technique, has shown that the proportions of the face of NF1

Table III. *Side comparison of the measured values (L/R=right/left) in NF1 patients without facial plexiform neurofibroma (DNF group) (t-test).*

Measurement	No. of individuals	Side	Mean value (mm)	Difference of the means	Minimum (mm)	Maximum (mm)	SD	*p*-Value
Zygomatic arch								
ZA – Z-plane	94	L	29.45	–0.434	9.31	42.14	4.83	0.112
		R	29.89		10.73	39.48	4.45	
ZA – M-plane	94	L	68.03	1.88	56.18	81.40	5.08	0.002**
		R	66.14		54.11	78.20	4.81	
Mastoid process								
MaP – Z-plane	94	L	55.18	0.227	37.53	75.84	8.36	0.508
		R	54.95		32.88	75.31	7.99	
MaP – M-plane	94	L	55.31	1.91	44.59	69.31	4.70	0.012*
		R	53.39		43.89	65.96	4.79	
Juga								
Juga – Z-plane	92	L	52.56	–0.091	38.90	65.49	5.24	0.659
		R	52.65		38.84	67.14	5.40	
Juga – M-plane	92	L	33.39	0.782	25.30	40.51	3.01	0.037*
		R	32.61		22.23	40.51	3.19	
Antegonion								
AG – Z-plane	94	L	95.19	0.326	72.60	118.30	8.79	0.327
		R	94.86		73.79	118.15	9.05	
AG – M-plane	94	L	43.98	1.73	33.56	57.66	4.99	0.003**
		R	42.26		29.95	51.44	3.73	

*$p<0.05$, **$p<0.01$.

patients do not differ from those of a group with harmonious skeletal configuration and ideal occlusion (16). In this second study, angles between cephalometric measuring points were calculated and compared with normal values. Angular norms can be used in cephalometric calculations for both males and females (32). When using angular dimensions, no changes in the skull proportions of NF1 patients were detected (16). However, on lateral cephalometry, deviations of the skull were recorded once the patients with facial PNF were analyzed (16). Among the patients with facial PNF, tumors of the third trigeminal branch with associated mandibular deformation were particularly noticeable (11). These changes always occurred on the same side as the facial PNF. The unaffected side of the skull showed measurements (angles) that did not differ from those of the patients without facial PNF and the control group (16). In both cephalometric examinations reported and in the one presented, no findings of any genetic examination were known or reported, so a preselection of patients according to mutation status is excluded or at least very unlikely. The present study is based on an entire group of NF1 patients without considering the potential effects of certain mutations. It therefore seems to be logical to check the symmetry of the face of the NF1 patient not affected by a facial PNF on PA radiographs to get a general assessment of the relationships between skull measurement points and to assess the symmetry of the skull.

Natural asymmetry of the skull. Some studies suggest that the right side of the skull is larger than the left, while others hold the opposite opinion (33). The various causes for the LR asymmetry or laterality of the skull (and the face) have been discussed for a long time (34-48), ranging from local effects of asymmetrical brain growth on the development of the facial skeleton (36, 37), to cellular spatial orientation concerning electrical voltage differences on cell membranes (42). Some concepts attribute LR asymmetry to embryonic levels of organization (42). Factors such as handiness may be associated with facial asymmetry (43). On the other hand, the preferred left-sided development of cleft lip and palate is a well-known example of preferential lateralization in embryonic developmental disorders. This facial developmental disorder is more common in males. However, current studies on the laterality of the normal, healthy face rule out a significant influence of gender (33, 43). Facial asymmetry is independent of dentition (39). In general, minor asymmetries between the left and right sides of the face are considered clinically insignificant (45). The intra-individual distances between the main measuring points and the center line are statistically significantly increased in favor of the left side in the NF1 group. However, none of the average side differences reached the limit of 2 mm, which is assumed to be relevant for an asymmetry to become visible (33).

Table IV. *Comparison of the measurement results between the DNF and the control groups. Statistically conspicuous comparisons are marked with an asterisk (*p<0.05; **p<0.01, ***p<0.001) (t-test).*

Measurement	N	Mean value (mm/°)	Mean difference (mm/°)	Minimum (mm/°)	Maximum (mm/°)	SD	*p*-Value (two tailed)
Zygomatic arch to Z-plane	21	28.37	2.16	22.62	35.95	3.65	0.027*
	76	30.53		20.80	40.07	3.96	
Zygomatic arch to M-plane	21	68.37	–0.161	63.73	72.02	2.35	0.838
	76	68.21		60.85	76.42	3.37	
ZAR-ZAL	21	136.77	–0.316	127.44	144.16	4.73	0.841
	76	136.45		121.67	152.89	6.75	
Angle: ZAR-ZAL to Z-Plane	23	0.851	0.026	0.01	2.17	0.59	0.870
	92	0.877		0.02	3.82	0.73	
Mastoid process to Z-Plane	21	52.53	4.06	40.98	68.16	7.01	0.028*
	76	56.58		37.24	75.56	7.48	
Mastoid process to M-plane	21	56.89	–2.00	52.96	61.96	2.67	0.007**
	76	54.89		48.64	61.44	2.98	
MaPR-MaPL	21	111.35	–3.70	103.77	121.85	5.23	0.010**
	76	107.64		95.69	119.40	5.78	
Juga to Z-Plane	21	57.09	–3.81	50.70	63.31	3.61	0.002**
	75	53.27		42.75	65.90	5.05	
Juga to M-plane	21	34.75	–1.87	32.34	38.16	1.54	0.002**
	75	32.88		27.02	39.00	2.53	
J-J	21	69.54	–3.75	64.67	76.35	3.08	0.002**
	75	65.79		54.15	78.12	5.06	
Angle: Juga-plane to Z-plane	23	0.88	0.518	0.06	2.48	0.71	0.025*
	92	1.40		0.03	4.21	1.03	
Antegonion to Z-plane	21	98.39	–1.26	85.03	107.25	5.75	0.480
	76	97.12		81.08	118.24	7.61	
Antegonion to M-plane	21	46.02	–2.16	42.11	53.93	2.94	0.005**
	76	43.85		38.44	54.55	3.06	
AR-AL	21	92.08	–4.30	84.23	107.87	5.86	0.005**
	76	87.77		77.27	109.27	6.11	
Angle: AR-AL to Z-plane	23	1.09	0.57	0.14	3.55	0.93	0.066
	94	1.66		0.3	5.79	1.39	
Unilateral measurement points							
Anterior nasal spine to M-Plane	21	0.703	0.426	0.0	1.6	0.49	0.017*
	76	1.12		0.0	3.3	0.76	
Menton to M-plane	21	2.07	0.894	0.3	6.3	1.93	0.099
	74	2.96		0.0	8.9	2.22	

Distances are given in millimeters (mm), angles in degrees (°).

Alternative referencing for horizontal plane: sphenoid bones. Earlier work has demonstrated the symmetry of the sphenoid bone (in relation to the median sagittal plane). Some evaluation methods of PA cephalograms are based on referring to this horizontal plane (38). However, the sphenoid bone by no means develops strictly symmetrically (49). Furthermore, sphenoid bone alteration is a characteristic feature in NF1 patients (50). Sphenoid bone dysplasia is so characteristic of NF1 that it is recognized as one of the main criteria in the clinical diagnosis of the disease (1). The prevalence of sphenoid bone dysplasia in NF1 is unknown and likely less than 5% (51). Major asymmetry of sphenoid is also recognized in individuals not affected by NF1 (46). Sphenoid bone dysplasia in NF1 often develops associated with other local changes that are characteristic of the entity, especially the orbital/periorbital PNF and / or local malformations of the meninges (52). However, association of sphenoid bone dysplasia with other typical pathologies in NF1 has not been demonstrated in every case of the bone deformity (53). The present investigation referred to the orbital edges as the horizontal referencing points of measurements to exclude the influence of potential malformations of the sphenoid on the measurement results. PNF-associated orbital changes are almost always unilateral (8). It is known from previous studies that PNF-associated changes in the orbital edge mainly affect the lower and lateral quadrant (8). An undetected orbital PNF with a skeletal alteration in the anterior orbital border could lead to a noticeable displacement of the suture and thus influence the angle between the Z-plane and the bilateral horizontal measuring point distances.

Table V. *Selected studies with cephalometric data on bilateral reference points of the skull (M/F=Males/Females).*

Author(s)/year	Country/ Population	Group characteristics	Measurement points and distances (mm). Mean values and standard deviation (SD).			
			Z	ZA	Juga	AG
Peck *et al*., 1991 (47)*	USA	N=52, 15-46 years, (M/F=3/49)	Total distance: 104.2 (4.8), right 52.2 (2.6), left: 52.0 (2.4)	139.5 (6.3), Right: 70.1 (SD 3.4) left: 69.4 (SD 3.6)	-	-
Cortella *et al*., 1997 (44)**	USA	N=22, 18 years (M/F=no data)	-	-	Total distance: 64.7 (SD 2.7) [59.1 (2.4)***]	Total distance: 86.4 (SD 4.5) [79.1 (SD 41)***]
Snodell *et al*., 1993 (72)	USA	N=50, 18 years, (M/F=1/1)	-	Males: 134.06 (4.80); females: 126.03 (5.68)	Males: 66.24 (3.12), females: 61.8 (2.97)	-
Huertas and Ghafari, 2001 (32)	USA	N=30; 18 years (M/F=14/16)	-	-	Total distance: males=61.50 (2.49); females=59.05 (2.65)	Total distance: males=79.10 (4.04), females=76.75 (2.82)
Al-Sehaibany *et al*., 2002 (71)	USA	N=30, adolescents (M/F=no data)	-	-	Right: 30.43 (2.36), left: 32.38 (2.02) p=0.0002	-
Hesby *et al*., 2006 (73)	USA	N=36, 26.4 years (M/F=1/1)	n.d.	n.d.	Total distance: 61.57 (3.92)	Total distance: 83.04 (SD 4.42)
Cheung *et al*., 2011 (66)****	China	N=100, 16-40 years (M/F=1/1)	Right: 48.11 (2.65), left: 47.78 (2.87)	Right: 65.56 (3.80); left: 65.12 (3.70)	Right: 32.03 (2.36), left: 32.23 (2.28)	-
Reddy *et al*., 2016 (33)	India	N=100, 18-25 years (M/F=1/1)	Right: 47.257 (SD 2.25), left: 47.129 (SD 2.166), *p*=0.676	Right: 66.78 (SD 3.3), left: 66.74 (SD 3.9), *p*=0.7	Right: 32.98 (SD 1.81), left: 33.01 (1.96), *p*=0.897	Right: 44.05 (SD 2.8), left: 43.64 (SD 31.1), *p*=0.34

*Peck *et al*.: Measurement point of lateral orbit defined as intersection of latero-medial orbital rim and sphenoid; **Cortella *et al*.: mean for both sexes, ***Value corrected for magnification; ****Cheung *et al*.: CBCT study.

Plain PA radiographs of the skull are a suitable radiographic measure to screen for sphenoid asymmetry in NF1 (25) and to assess symmetry of orbital entrance (8). A skeletal impact of unrecognized PNF could neither be proven in the comparison of the estimated area of the orbital openings nor in the measured values (angles) (8). As mentioned, the exclusion of facial PNF was a constitutive criterion for the study group, revealed by careful analysis of further findings. The parallel alignment of the horizontal lines defined from bilateral skull measuring points to the reference planes on PA cephalograms, *e.g*., Z-plane, has been confirmed by other studies (33).

Landmark determination and measurement errors. The use of scanned X-rays from exposed film and their digital processing does not cause any changes in the skeletal reference points on cephalograms that limit their diagnostic evaluation (54). However, any scientific analysis of X-rays requires information on the measurement accuracy of the study (55-58). Identifying landmarks is a critical step in cephalometric analysis and is prone to error. Inter-individual differences in measurements are more common than intra-individual (59, 60). Error analysis of landmark determination of the study has been presented in detail elsewhere (17). The measurement accuracy of this study is above the required indices.

Limitations of the study. The investigation has obvious limitations that limit the generalization of the findings. On the one hand, the size of the control group is significantly smaller than the study group. Physiological deviations in the development of the skull can escape observation in small control groups and thus falsify the comparisons with the study group. In fact, investigations with this collective have

Table VI. *Standard values for horizontal distances between bilateral cephalometric measuring points on PA cephalograms of a radiological longitudinal skull growth study in children and adolescents (48). The measurement results for the final age (18 years of age) of the serial examinations are reproduced. Measured values are in mm (t-test).*

Distance	Males					Females					*t*-value
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	
Lo - Lo	14	95.8	4.5	87.0	103.2	17	92.8	3.3	86.3	98.0	–2.1*
ZAR-ZAL	14	133.9	6.5	124.2	144.3	17	127.6	5.8	118.0	140.0	–2.8
Mx - Mx	14	76.1	4.1	69.5	82.2	17	71.8	4.7	63.6	80.0	–2.6*

LO: Latero-orbitale, Z-point; Mx: bimaxillary width (deepest point of concavity formed by the lateral wall of the maxilla and inferior border of maxillary zygomatic process. The measuring point largely corresponds to the measuring point "juga"); *p<0.05.

Table VII. *Standard values for distances of cephalometric measuring points from the median sagittal plane on PA cephalograms of a radiological longitudinal study of skull growth in children and adolescents (48). The measurement results for the final age (18 years old) of the serial examinations are reproduced. Measured values are in mm (t-test).*

Distance	Gender	N	Right side				Left side				*t*-value
			Mean	SD	Min	Max	Mean	SD	Min	Max	
Lo – M-plane	Male	14	47.9	2.2	43.5	51.2	47.8	2.4	43.5	52.0	–0.8
	Female	17	46.4	1.7	43.0	49.0	46.4	1.6	43.3	49.0	0.0
ZA – M-plane	Male	14	67.7	3.5	62.6	74.0	66.1	3.3	61.0	70.2	–2.9*
	Female	17	64.1	3.1	58.0	70.0	63.5	2.9	59.0	70.0	–1.5
Mx – M-Plane	Male	14	38.0	1.8	34.0	40.8	38.0	2.5	34.0	41.3	0.0
	Female	17	35.9	2.4	31.8	40.0	35.9	2.5	31.8	40.0	0.0

LO: Latero-orbitale, Z-point; Mx: bimaxillary width (deepest point of concavity formed by the lateral wall of the maxilla and inferior border of maxillary zygomatic process. The measuring point largely corresponds to the measuring point "juga"); *p<0.05.

been questioned with reference to the size of the control group (61). The ethical justification for recourse to a historical collective of cephalometries has already been pointed out (vide supra). On the other hand, the selection of the control group is in no way due to a lack of evaluable cephalograms. Rather, this control group ideally meets the requirements for a harmonic skull, as used in a widespread cephalometric analysis (62, 63). The norms used in this cephalometric analysis are undoubtedly limited to the referred population, *e.g.*, Caucasian. However, the study group also derives from the so-called Caucasian population, so the comparison is justified in this regard. On the other hand, the measuring points, which are almost symmetrically positioned in NF1 patients according to this study, in the case of a globally proven, autosomal dominant disease are, with a high probability, also distributed in other races in such a way that similar cephalometric results can be expected outside the population examined here, provided that the disease-specific inclusion criteria are met.

Another limitation of the statements about the cranial structure of NF1 patients is the use of two-dimensional X-ray images for the analysis. In the last decades, the development of radiological techniques and their application to skull measurement has focused on three-dimensional data. However, the problem of measurement accuracy and error analysis must be considered in every study, regardless of the radiological imaging technology (64). For example, positioning errors may occur both with X-ray techniques that are based on three-dimensional recording of the object (55, 56, 58); this is well-known in standard cephalometry (64). Nevertheless, two-dimensional cephalometry is still a standard tool in orthodontic and maxillofacial surgery treatment planning, for which the skull assessment in the lateral cephalogram is essential (63). The study is an extension of a well-recognized cephalometric analysis (63) for evaluating cephalometric radiographs registered in PA projection (17). Plain radiography is expressly recommended for screening cranial findings in NF1 patients (25) and the scientific analyzes carried out here prove the usefulness of this projection for identifying subtle skeletal alterations in the study groups.

Evaluation of the measurement results with reference to the literature. Investigations on the asymmetry on PA cephalograms with reference to the median sagittal plane show a cranio-caudal increase of asymmetry of reference points (47). Evidence of symmetry in the upper midface confirms this general cephalometric experience and larger differences in the ‘menton’ distance to the M-plane are also to be expected. Ethnic differences must be considered when evaluating the measurement results (65, 66).

The results of the present examination show symmetrical development of the NF1 patients’ midface in the transverse extent at the level of the zygomatic arch (67). It is therefore unlikely that the zygomatic region, which is prominent in both groups, can be used as a distinguishing feature for the so-called ‘NF facies’. The result is also valuable as a reference for the assessment of NF1 patients with facial PNF and orbital/periorbital tumor extension, because in the latter cases, the zygomatico-fronto-temporal complex frequently is deformed and the zygomatic arch on the affected side can be significantly displaced (8). The results of this study suggest that such skeletal deformation will not be registered without identifying topographical reference to a PNF (16), a very likely congenital tumor. Compared to data in the literature, lateral differences of the midface are known based on measurements of the distance of the zygomatic arch to the median plane (48). However, the lateral differences are quantitatively very small, so that it remains doubtful whether these measurement results correspond to a visible asymmetry. Only the mean distance of the mastoid measuring point to the Z-plane shows a remarkable mean difference between the two groups (4.06 mm). However, it is unlikely that this difference is significant for the facial phenotype. Another factor for the critical evaluation of the measurement results are differences in the respective recording technology, which can have an influence on symmetry perception. These differences can escape registration, especially in the case of very small differences in the measurement values (48, 68, 69). Table V, Table VI and Table VII provide some data on cephalometric measurement results from the literature. The studies have used the measurement points of this study. The sample research results show that normal cephalometric values are in a variable range and that ethnic differences should be considered in the assessment.

Furthermore, any shortening - within narrow quantitative limits – on one side of the facial skeleton can be compensated for by lengthening of the bone at the nearby measuring points in the respective plane. In other words, discrete skeletal asymmetries can probably be compensated intra-individually and thus influence the overall impression of a symmetrical face less strongly than can be assumed from the comparison of the side-related individual measurement values (70). For example, it was reported that in adolescents in an orthodontic study group (n=30), the right antegonial notch was statistically significantly larger than the left (71). Another finding of the study was that the distance between the juga point and the median sagittal plane being greater on the left than on the right in this group. The differences were small in absolute terms and are probably an expression of the physiological variation in the spatial configuration of biological systems falling below the limit of the visible facial asymmetry (33). Of note, the compensation for skeletal asymmetries can also be achieved through functional adaptation of the soft tissue.

Conclusion

This investigation shows almost symmetrical distances between the cephalometric measuring points and the respective horizontal or median-sagittal reference plane. The data support the assumption that NF1 patients have a slight tendency to develop a long face. Intraindividual LR differences are statistically conspicuous. However, the differences between the sides are quantitatively very small and probably without any influence on the facial appearance. Larger asymmetries of the facial skeleton revealed on radiographs or being visible to the investigator without instrumental support require clarification, especially regarding the identification of a facial PNF.

Conflicts of Interest

The Authors have no conflicts of interest regarding the work presented.

Authors’ Contributions

Conceptualization of the study: REF, GC, HAS; diagnosis of patients: REF; adaptation of the cephalometric software for radiological analysis, primary data collection and analysis: GC; data review: REF, HAS, HTS; drafting of manuscript: REF, GC, HAS; final approval of the study: all Authors.

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