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A lateral cephalometry study of patients with neurofibromatosis type 1

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ABSTRACT

Purpose: Neurofibromatosis type 1 (NF1) is an autosomal dominant transmitted tumour suppressor syndrome and also a bone disease. Osseous dysplasia affecting the craniofacial region is characteristic of NF1. The aim of this study was to analyse the lateral cephalograms of NF1 patients in comparison to individuals who were not affected by this condition in order to describe the skeletal phenotype of NF1 in more detail.

Materials and methods: The study comprises the lateral cephalograms of 172 patients with established NF1 diagnoses (female = 85, male = 87). NF1 patients were distinguished by radiological and/or histological findings of the facial region suggestive of plexiform neurofibroma (PNF) or disseminated cutaneous NF (DNF). The analysed radiographs of a collection of 29 healthy volunteers with ideal occlusion served as controls. The focus of this analysis was cephalometrically defined angles.

Results: Cephalometric analyses of patients with DNF did not differ from those of controls for the vast majority of parameters. However, the measurement results of patients with PNF differed significantly from those of healthy volunteers and patients with DNF. The number of trigeminal nerve branches affected in PNF patients had an effect on the measurement results.

Conclusion: Lateral cephalograms revealed no significant alteration of the facial skeleton in NF1 patients as compared to controls. Indeed, the stigma of a so-called 'NF1 facies' cannot be derived from the cephalometric findings presented. Notably, a wide range of deviating readings were recorded for individuals with facial PNF. Clinicians who treat patients with NF1 should be aware of deviations from cephalometric standards on lateral cephalograms in NF1 patients, especially when craniofacial surgical procedures are planned. Some of these findings, particularly asymmetries of the facial skeleton, could be indicators of an associated PNF.

1. Introduction

Neurofibromatosis type 1 (NF1) is a relatively common human autosomal dominant inherited disease affecting a multitude of organs and systems (Riccardi, 1992). About 1:2500 children living at birth are affected by this condition (Lammert et al., 2005a; Ferner et al., 2007). Predecessors with established NF1 diagnosis are known in about every second affected individual (Riccardi, 1992). Diagnosis is made in most cases with the aid of repeatedly revised clinical diagnostic criteria proposed by the US National Institutes of Health (National Institutes of Health, 1987, 1988; Gutmann et al., 1997; Ferner and Gutmann, 2013). The identification of a relevant gene coding for a protein that was later denominated neurofibromin represented a great step forward in our understanding of the pathogenesis of NF1 (Daston and Ratner, 1992). Mutations of this gene located on chromosome 17q11.2 are causal for NF1

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(Viskochil et al., 1990; Seizinger et al., 1987). The most recognized findings in NF1 is neurofibroma, i.e. benign nerve sheath tumours most likely originating from Schwann cells or their precursors (von Recklinghausen, 1882; Verocay, 1910). However, it was early after establishing neurofibromatosis as a morphologically defined entity that skeletal lesions were identified as a distinct facet of what is now called the NF1 phenotype (Adrian, 1901). The disease is now accepted a genetic skeletal disorder (Lammert et al., 2005b; Stevenson et al., 2007; Elefteriou et al., 2009; Seitz et al., 2010; Adrian, 1901). In several locations – including the craniofacial bones – a close association of plexiform neurofibroma (PNF) and osseous dysplasia was noted (Friedrich et al., 1994, 2003 & 2013), but this association may not necessarily be provided in every case (Binet et al., 1969; Friedrich, 2011). In the facial region, various locations of PNF show the underlying pattern of a more or less close topographical association with the terminal branches of the trigeminal nerve (Riccardi, 1992). These tumours can cause extensive facial soft tissue damage leading to severe disfigurement and are almost always confined to one side of the face (Friedrich, 2010). In the facial region, the PNF may also cause severe osseous alterations (Heine, 1927; D'Ambrosio et al., 1988). In contrast to these well-known local facial affections characteristic for a morphologically defined tumour type in NF1, some authors have suggested a distinctive facial appearance of NF1-affected individuals which is not caused by tumour growth (Grabb et al., 1980; Kaplan and Rosenblatt, 1985; Lin et al., 1989; Norman, 1972). Cephalometric analyses of NF1 patients led to the conclusion that sagittal projections of mandible, maxilla and cranial base are reduced compared to those in matched controls. Thus, these distinct skeletal findings may have a reproducible effect on the physiognomy of the individual NF1 patient. Indeed, it was concluded from these findings that skeletal variations of the viscerocranium may contribute to form the NF1-phenotype (Heervä et al., 2011). However, these differences proved to be significant only in adults. Furthermore, the study group included only a small number of patients affected with trigeminal PNF. Recently, these metric sagittal findings on cephalograms of NF1 patients were confirmed in another study (Cung et al., 2015). On the other hand, Riccardi has recalled the distinctive facial appearance of NF1 patients as caused by pigmentation disorders, macrocephaly, and neurofibroma. He emphasizes that NF1 patients appear to share facial characteristics of their family members (Riccardi, 1992, 1999). In another report, Friedman and Riccardi (1999) stressed their assessment that not a single set of facial characteristics defines patients with NF1 as a group. Taking into consideration the importance of cephalometric findings for the evaluation of facial proportions, the relationship of certain skull parts is of particular importance. This topographical relationship can be measured in angles (Hasund, 1974). Determining these relationships could provide more insights into the skeletal basis of NF1 affected individuals and contribute to clarify contradictory assumptions for a characteristic facial expression that could stigmatize. Furthermore, a cephalometric analysis of NF1 patients should be a prerequisite for planning craniofacial surgical procedures in these individuals (Heiland et al., 2004). Therefore, this study intended to describe the cephalometrically defined relationship of the jaws to the skull base with special reference to the impact of PNF on the observations.

2. Materials and methods

Standardized lateral cephalograms used for cephalometric analysis were investigated for 172 white patients with NF1 (male: 87 (50.58%), female: 85 (49.42%)). These patients were radiologically investigated for skeletal anomalies in the department of oral and craniomaxillofacial surgery, Eppendorf University Hospital, University of Hamburg, between 1980 and 2010. The age of patients at the time of radiography ranged from 4 to 78 years (mean for males, 27.6 years) and from 7 to 62 years (mean for females, 33.1 years). All patients fulfilled the updated diagnostic criteria of NF1 (Gutmann et al., 1997) and were citizens of Germany. Patients with a history of surgical skeletal procedures or trauma of the facial skeleton were excluded from evaluation. All patients gave informed consent to the scientific study of X-ray images and evaluation of medical findings. This study was approved by the local University authority as a prerequisite to fulfil the requirement of a dissertation in dentistry (J.M.L.). All procedures performed in this study involving human participants were 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 anonymized prior to analysis, and the investigators studying the cephalograms were blinded for diagnosis, identity of individuals, and assignment of the single case to a diagnostic group (J.M.L.; H.A.S.). The investigations of anonymized data were performed in accordance with Hamburgisches Gesundheitsdienstgesetz.

Out of this collective, 96 patients showed disseminated cutaneous neurofibroma (DNF) but no facial plexiform neurofibroma (PNF) as revealed by complementary imaging (computed tomography [CT], magnetic resonance imaging [MRI], B-scan ultrasound) and histology in the course of surgical treatment (REF) for neurogenic tumours (DNF group). A further 72 patients were evaluable who showed histologically verified facial PNF (PNF group). A patient was considered as having a PNF and categorized in this group if any facial region was affected by this type of tumour irrespective whether further DNF occurred in this region. The PNF were assigned to the facial cutaneous territories of the trigeminal nerve's three branches by means of MRI and/or CT, by analysis of facial photographs and with respect to surgical reports including remarks on findings of tumour extension (REF). Subgroups of PNF patients were identified according to the nerve branch or branches affected by this tumour. Patients with hemifacial PNF, i.e. PNF affecting all trigeminal nerve branches, constituted a separate group. All facial PNF showed a unilaterally restricted growth pattern. Patients were included only in the total group of patients with facial PNF, but not in the subgroups, if the assignment of the PNF to the trigeminal branches was ambiguous. This is the reason why the total group of PNF patients is larger than the sum of the PNF subgroups.

The reference group consisted of 29 individuals (males 18 (62.1%), females 11 (37.2%)). The age of these individuals was 17–26 years (females, mean 23.2 years) and 16–35 years (males, mean 25.7 years). This reference group comprised a collection of well-defined lateral cephalograms of individuals who had voluntarily contributed their radiographs to a former study (Ibe, 1993, 1995). These subjects all exhibited ideal dental occlusion, without ever having been treated by orthodontics or any history of trauma or craniofacial malformation. We chose this archival group for comparison in order to define potential alterations of cephalometric parameters in the study groups with those of individuals who fulfilled ideal orthodontic relationships as one requisite defining a harmonious face (Segner and Hasund, 1991). Definition of cephalometric landmarks and principles of analysis are detailed elsewhere (Hasund, 1974).

2.1. Data registration and measurement

The cephalometric procedure did not change during the recruitment time and is described elsewhere in detail (Scheuer et al., 2001; Scheuer, 2008). Anonymized personal data were registered in Ortho Express® (Computerforum, Elmshorn, Germany). All radiographs were scanned and processed in Dental