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Cephalometrics in Stickler syndrome: Objectification of the typical facial appearance

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ABSTRACT

Introduction: Stickler syndrome is a connective tissue disorder characterized by orofacial, ocular, skeletal and auditory symptoms. The orofacial phenotype mainly consists of midfacial hypoplasia, micrognathia and cleft palate. Large phenotypic variability is evident though. Few studies have tried to substantiate the typical facial appearance in Stickler syndrome patients.

Methods: Molecularly confirmed Stickler patients were invited to undergo cephalometric analysis based on a lateral radiograph in standardized conditions. Angular and linear measurements were performed according to Steiner's and Sassouni's analysis and compared with age- and gender-matched reference values.

Results: Thirteen patients aged 10–62y were included, twelve of whom had type 1 Stickler syndrome (*COL2A1* mutation) and one type 2 Stickler syndrome (*COL11A1* mutation). The position of maxilla and mandible relative to the cranial base was not significantly different from the reference population (S-N-A: $p = 0.73$, S-N-B: $p = 0.43$). The mandibular plane and y-axis showed an elevated angle with the cranial base in most patients, although not significant for the total group (S-N to Go-Me: $p = 0.20$, S-N to S-Gn: $p = 0.18$). Dental analysis was normal, except for a higher overjet value ($p = 0.006$) and a higher angle between occlusal plane and Frankfort plane ($p = 0.022$).

Conclusion: Cephalometric analysis was not able to thoroughly prove the abnormal facial appearance in Stickler syndrome. The majority of patients had normal dentofacial proportions. The most frequently observed anomaly in our series is a rather short and posteriorly rotated mandible, but clinical variability is high.

1. Introduction

Stickler syndrome or hereditary arthro-ophthalmopathy is a group of connective tissue disorders characterized by ocular, skeletal, orofacial and auditory symptoms. Patients might exhibit high myopia, retinal detachment, joint hypermobility, early osteoarthritis, midfacial hypoplasia, micrognathia, cleft palate and sensorineural hearing loss (Rose et al., 2005). Large phenotypical heterogeneity is apparent, partly explained by the underlying genotype. The syndrome is predominantly caused by heterozygous mutations in the *COL2A1*, *COL11A1* and *COL11A2* genes, leading to type 1, type 2 and type 3 Stickler syndrome, respectively. Clinical distinction is based on the vitreous appearance, which is usually membranous in type 1, beaded in type 2 and normal in type 3 Stickler syndrome (Snead et al., 1999). Moreover, hearing loss is more prevalent, more severe and symptomatic at a younger age in type 2 and type 3 Stickler syndrome compared with type 1 (Acke et al., 2012).

The facial appearance was not described in the index family of Stickler syndrome, but became delineated in subsequent reports (Opitz et al., 1972; Stickler et al., 1965). Typical signs include midfacial hypoplasia, micrognathia, prominent eyes, low nasal bridge,

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short upturned nose with anteverted nares and long philtrum. These signs are more pronounced in childhood and tend to improve with age (Temple, 1989). Facial asymmetry might be present, as well as epicanthic folds and hypertelorism (Herrmann et al., 1975).

Oral symptoms include midline defects, ranging from overt cleft palate to a high-arched palate or bifid uvula. Pierre Robin sequence (PRS) might be diagnosed in young Stickler patients based on the facial appearance and especially in presence of overt cleft palate. PRS is a clinical entity characterized by the triad of micrognathia, glossoptosis and airway obstruction, whereas palatal clefting is frequently present in PRS patients. Estimates suggest that about 20% of all PRS patients are patients with Stickler syndrome, being the most prevalent disease in syndromic PRS (Evans et al., 2006).

The presence of orofacial manifestations in Stickler patients can be explained by the fact that type II and the associated type XI collagens are important in skeletal growth, given their contribution to the development of the embryonic cartilaginous skeleton. Type II collagen is supposed to act in a dual way in craniofacial development and growth: on the one hand it is transiently expressed during early development suggesting an inductive or instructive role, on the other hand it is involved in the growth of the cartilaginous skeleton (Rintala et al., 1997; Wood et al., 1991). During the postnatal period, type II and type XI collagen are present in growth plates, enabling endochondral ossification. Consequently, alterations of these types of collagen might result in skeletal abnormalities including abnormal craniofacial development. Mice with a mutated *Col2a1*, *Col11a1* or *Col11a2* gene have a smaller head, short mandible, upward directed snout, cleft palate, protruding tongue, depressed nasal bone and reduced antero-posterior craniofacial growth in general (Li et al., 1995, 2001; Rintala et al., 1997). Moreover, the short mandible, formed by Meckel's cartilage, seems to be related to the presence of cleft palate as micrognathia leads to decreased oral volume and less space for the tongue to displace from between the palatal shelves. As a result, there is a delay in approximation of the palatal shelves, which renders contact and fusion of these shelves more difficult (Lavrin et al., 2001; Ricks et al., 2002; Tan et al., 2013).

Although the facial appearance of human Stickler patients is one of the most characteristic manifestations of the syndrome, it is probably the most difficult to objectify. Few studies have tried to objectively demonstrate the facial signs, and comparison of their results showed conflicting conclusions (Nowak, 1998). We therefore aimed to objectify the facial manifestations specific for Stickler syndrome and to clarify the role of cephalometrics in the diagnostic evaluation of Stickler patients.

2. Material and methods

2.1. Patients

Patients were recruited from the Center for Medical Genetics Ghent and the department of Otorhinolaryngology at Ghent University Hospital, Belgium. All patients had molecularly confirmed Stickler syndrome and completed a questionnaire including medical history and subjective evaluation of their own face. They underwent a clinical examination with palatal evaluation. Participants gave consent to review medical reports concerning previous orofacial treatments. The local Ethics Committee approved the study (EC 2011/509) and all patients signed informed consent prior to participation.

2.2. Imaging

A lateral cephalometric X-ray was taken using Orthoceph® OC200D (Instrumentarium Dental, Tuusala, Finland). The patients' heads were positioned in a cephalostat and oriented to the Frankforter plane with teeth in maximal occlusion (Broadbent et al., 1975). The cephalograms were digitized with an Agfa CR 30-X digitizer (Agfa Healthcare NV, Mortsel, Belgium) and processed with the software program MediaDent (ImageLevel, Kruibeke, Belgium).

2.3. Interpretation

The cephalograms were interpreted using angular and linear measurements of Steiner's and Sassouni's analysis (Sassouni, 1955; Steiner, 1953). Landmark tracing was performed by GDP, an experienced orthodontist. The used landmarks are provided in Table S1, whereas the performed measurements are shown in Fig. 1. Sagittal evaluation of the face included the position of the maxilla compared with the cranial base (angle sella-nasion-A point, normal value for adults 82°), the position of the mandible relative to the cranial base (angle sella-nasion-B point, normal value for adults 80°) and the maxillomandibular relation (angle A point-nasion-B point, normal value for adults 2–4°). Additional measurements were performed in order to better evaluate the mandibular and dental position, and the facial height.

Individual measurements were compared with reference values for adults, or age- and gender-matched control samples for minors (Argyropoulos et al., 1989; Broadbent et al., 1975; Riolo et al., 1974), taking into account differences in enlargement for the linear measurements (Dibbets et al., 2002). Statistical analysis included the calculation of Z values for each variable ([measured value in Stickler patient minus age- and gender-matched reference value]/standard deviation of reference value). Individual Z values outside of the (−1.96*SD to 1.96*SD) reference interval were considered significantly different from the reference population ($p < 0.05$). Additionally, a one-sample t-test could detect significant deviations from the reference population for the total Stickler group, taking into account all Z values of Stickler patients for a specific measurement ($p < 0.05$). We also performed this analysis separately for children and adults (only significant results are provided), as it has been shown that the facial phenotype is more pronounced in childhood (Temple, 1989), as well as for patients with and without cleft palate.

3. Results

3.1. Patients

Thirteen patients from eight families were included (Table 1), all of Caucasian descent. Mean age was 31.2 ± 17 years (range 10.2–62.0y). Gender distribution was four women versus nine men. Twelve patients had a *COL2A1* mutation compatible with type 1 Stickler syndrome, whereas one patient had a *COL11A1* mutation leading to type 2 Stickler syndrome. In seven patients (53.8%) the perception of their own face was normal, whereas it was abnormal in six patients (46.2%). Abnormalities included a short nose (3 patients), a retruded chin (2) and asymmetry of the face (1). Four patients were born with overt cleft palate (30.8%), one of whom was diagnosed with a Pierre Robin sequence (7.7%). Clinical examination revealed one patient with a high-arched palate and one patient with a bifid uvula, in addition to the four cleft palate patients. None had a submucous cleft. Previous orofacial surgery included repair of the cleft palate in four patients, adenotonsillectomy in one patient and third molar extraction in one patient.

3.2. S-N-A/S-N-B/A-N-B

Observed values for the principal angles of Steiner's analysis are provided in Table 2. Four patients had a significantly different S-N-A