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ORIGINAL ARTICLE

Dental Maturation in Children With the Syndrome of Crouzon and Apert

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Purpose: **Developing teeth are used to assess maturity and estimate age in a number of disciplines. The purpose of this investigation was to study the dental maturation in children with Crouzon or Apert syndrome compared with nonsyndromic controls.**

Patients and Methods: **Records of 40 children with Crouzon syndrome (18 boys and 22 girls, aged 4.0 to 17.9 years) and 28 children with Apert syndrome (10 boys and 18 girls, aged 3.9 to 15.1 years) were referred to the Department of Orthodontics, Cleft Palate Team and Craniofacial Team, Erasmus MC–Sophia. Data from syndromic children were compared with data from 451 nonsyndromic children (225 boys and 226 girls, aged 2.9 to 16.9 years). From panoramic radiographs, dental maturation was determined for patients with Crouzon and Apert syndromes and compared with data collected from control children. Logistic functions were constructed for dental maturation over time for syndromes and gender.**

Results: **Statistically significant gender differences in dental maturation scores were found for girls with Crouzon ($P < .05$) and Apert syndrome ($P < .05$). Patients with Apert syndrome demonstrated a significantly delayed dental maturation ($P < .05$), while patients with Crouzon syndrome showed a nonsignificant delay.**

Conclusions: **Dental maturation in patients with Apert syndrome was more delayed than in patients with Crouzon syndrome. The delay of tooth formation in patients with Crouzon or Apert syndrome suggests a possible common genetic association.**

KEY WORDS: *Apert, craniosynostosis, Crouzon, Demirjian's scoring system*

Dental maturity or dental age is a method for biological age determination (Demirjian et al., 1973). Clinicians have studied dental development in relation to chronological age and regard this to be superior to the use of other biological age determinations as indicators for chronological age (Moorrees et al., 1963; Anderson et al., 1976; Nik-Hussein et al., 2011). Developing tooth calcification has been shown to be less susceptible to environmental influences than skeletal development (Prahl-Andersen and Van der Linden, 1972; Prahl-Andersen et al., 1979; Mörnstad et al., 1995; Liversidge, 1999). Identification of key genes for tooth formation may show that disrupted dental development is caused by several independent defective genes, acting alone or in combination with other genes. Exploring these genes involved in different interacting molecular pathways may explain the wide variety in dental development patterns but can also explain their possible association with additional craniofacial anomalies (Wilke et al., 1997; De Moerlooze et al., 2000; Bachler and Neubüser, 2001; De Coster et al., 2007). This may clarify tooth anomalies seen in patients with craniosynostosis as the genes involved in odontogenesis are also partly involved in craniosynostosis syndromes (De Coster et al., 2007; Nieminen et al., 2011). Mutations in the gene encoding of the fibroblast growth factor receptor (FGFR) were found in most syndromes with craniosynostosis (Wilke et al., 1997). The list of genes that are involved in craniosynostosis includes those coding for FGFR1, FGFR2, and FGFR3 but also genes encoding transcription factors, such as MSX2 and TWIST (Wilke et al., 1997; Bachler and Neubüser, 2005; Nieminen et al., 2011).

The fibroblast growth factors (FGFs) are a family of intercellular signaling molecules that are important factors controlling bone development, growth, remodeling, and repair (De Coster et al., 2007). The FGF and the FGFR also have been shown to play an important role in tooth formation and regeneration (Kettunen and Thesleff, 1988; Kettunen et al., 2000; Nieminen et al., 2011). The FGFs

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Fgf-4, *-8*, and *-9* have been implicated as epithelial signals regulating mesenchymal gene expression and cell proliferation during tooth initiation and later during epithelial folding morphogenesis and the establishment of tooth shape. *Fgf-10* expression is observed in the presumptive dental epithelium and mesenchyme during tooth initiation, whereas *Fgf-3* expression appeared in the dental mesenchyme at the bud stage. During the cap and bell stage, both *Fgf-3* and *Fgf-10* were intensely expressed in the dental papilla mesenchymal cells both in incisors and molars. *Fgf-3* participates in signaling functions of primary enamel knot. The dynamic expression patterns of different *Fgfs* in dental epithelium and mesenchyme and their interactions suggest existence of regulatory signaling cascades between epithelial and mesenchymal *FGFs* during tooth development (Kettunen and Thesleff, 1988; Miletich and Sharpe, 2003; Lin et al., 2009; Nieminen et al., 2011).

Mutations of FGFR2 or FGFR3 are causal to retarded craniofacial growth and development in Crouzon and Apert syndromes (Wilke et al., 1997; Bachler and Neubüser, 2005). The involvement of FGFR2 in dentogenesis in animal studies may suggest that mutated FGFR2 genes may influence dental development seen in these syndromes (Wilke et al., 1997). Determining dental maturation of patients with Crouzon and Apert syndromes yields information not only about the general development of the dentition but also about the general development of the individual, thus giving an indication for the involvement of the mutated FGFR2 or FGFR3 in the unique growth pattern seen in these syndromes. The aim of this study is to compare dental maturation of patients with Crouzon and Apert syndromes with nonsyndromic Dutch children and to develop new standards for these syndromes.

Materials and Methods

A retrospective longitudinal design was conducted with data of 96 panoramic radiographs from 28 patients (10 boys and 18 girls) with Apert syndrome and 135 panoramic radiographs from 40 patients (18 boys and 22 girls) with Crouzon syndrome from Erasmus MC Craniofacial Center, Sophia Children's Hospital, in Rotterdam, The Netherlands. The median age at which the panoramic radiographs were taken was 9.2 years for patients with Crouzon syndrome, with a range from 4.0 to 17.9 years. The median age at which the panoramic radiographs were taken was 9.5 years for patients with Apert syndrome, with a range from 3.9 to 15.1 years. The use of data from human subjects followed an approved protocol and satisfied the requirement of the institutional review board (approval MEC-2010-304).

The control group consisted of 451 normal Dutch children (225 boys and 226 girls) included in a previously published study (Leurs et al., 2005). The median age of the controls at which the panoramic radiographs were taken was 7.7 years, with a range from 2.9 to 16.9 years.

The clinical diagnosis of Crouzon or Apert syndrome was confirmed with genetic testing to detect a mutation in the FGFR2 or FGFR3 gene.

The subjects for this study had panoramic radiographs taken according to the protocol for treatment planning and treatment of Caucasian patients with Crouzon or Apert syndrome between 1980 and 2011. When one left mandibular tooth was missing, the contralateral right mandibular tooth was used. When mandibular teeth were missing bilaterally, the panoramic radiographs were excluded because no dental maturity score can be determined in these cases. Dental agenesis, identified on radiographs, was verified by analysis of dental records, to exclude premature extractions. Panoramic radiographs with a maturity score of 100 were excluded because the dentition has matured.

Statistical Analysis of Dental Maturity Scores

The dental development scores for patients with Crouzon and Apert syndromes were compared with the scores of control children using a logistic curve-fitting procedure (Leurs et al., 2005). The function used for the 50th percentile curve of the data was $Y = 100*\{1/(1 + e^{-v\ (x-m)})\}$, in which v stands for velocity of the mean dental maturation over time and m for mean age at the 50th dental maturation percentile. Several logistic functions were estimated and graphed:

1. For control children (boys and girls), $Y = 100*\{1/(1 + e^{-0.559(x-5.586)})\}$ (Leurs et al., 2005)
2. For patients with Crouzon syndrome (boys and girls)
3. For patients with Apert syndrome (boys and girls)

For dental development to be determined over time, at least two consecutive panoramic radiographs are needed. For logistic curve fitting, at least three measurements are necessary. The patients with one or two radiographic measurements were used to improve the earlier-established logistic curves for estimating the logistic population mean. The data derived from one or two panoramic radiographs do not directly contribute to the calculation of velocity but are substantial to the level of the curve at a certain age. To calculate the 5th and 95th percentiles for the norm logistic curve, the SD was added and subtracted 1.96 times.

Dental Development Scores

The developmental stages of the seven left permanent mandibular teeth were assessed according to the method proposed by Demirjian et al. (1973). Each tooth of the mandible was given a score from A to H. These scores were converted into numbers and summed, referred to as the maturity score (Demirjian et al., 1973). Two examiners were trained by means of a tutorial program, available on CD-ROM (Demirjian, 1993–1994).

TABLE 1 Mean Difference for the Logistic Fits for Crouzon and Apert Syndromes for Gender*

	n	*Mean Difference*	*SD*	*SE*	*P Value*
Crouzon					
Boys	81	0.467	1.347	0.1497	NS
Girls	64	−1.082	1.611	0.2014	<.05
Total	145	−0.216	1.655	0.1374	NS
Apert					
Boys	85	−0.347	1.112	0.1206	NS
Girls	26	−1.617	0.829	0.1628	<.05
Total	111	−0.645	1.393	0.1120	<.05

* n is the number of panoramic radiographs; mean difference is mean maturity score difference; SD is the standard deviation for the mean difference; SE is the standard error for the mean difference; *P* value for mean difference compared with the Dutch control children.

Measurement Error

Intra- and interexaminer reliability is expressed by the intraclass correlation coefficient (ICC) for the dental maturity score. To assess intra- and interexaminer reliability, two examiners randomly rescored 35 panoramic radiographs. The ICC is comparable to the kappa coefficient. ICC values range from 0 to 1. An ICC of .61 to .80 is interpreted as substantial agreement and an ICC of .81 to 1.00 as an almost perfect agreement. Calculations were performed with the statistical software package SPSS version 11.5 (SPSS Inc., Chicago, IL).

Results

Measurement Error

The ICC for intraexaminer reliability was .96 (95% confidence interval [CI], .94 to .99). The ICC for interexaminer reliability was .97 (95% CI, .96 to .99). Both scores indicate high reliability.

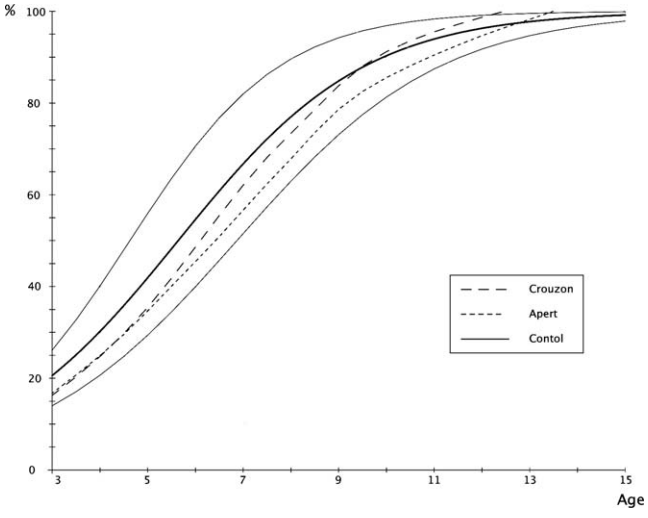

FIGURE 1 Dental maturation for male controls and male patients with Crouzon and Apert syndromes. The 5th, 50th, and 95th percentile lines for controls are indicated.

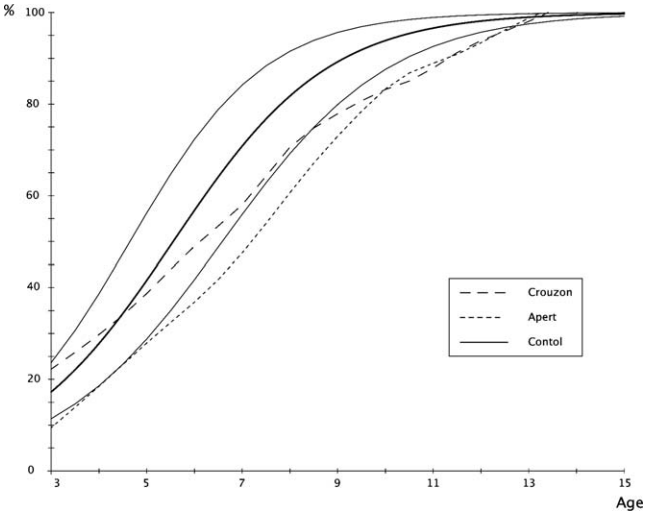

FIGURE 2 Dental maturation for Dutch female controls and female patients with Crouzon and Apert syndromes. The 5th, 50th, and 95th percentile lines for controls are indicated.

Dental Development Scores

Differences in dental development between patients with craniosynostosis and Dutch controls were found. The dental maturation of patients with Apert syndrome is significantly delayed (Table 1). Also, patients with Crouzon syndrome had delayed dental maturation scores compared with controls; these differences were not statistically significant (Fig. 1; Table 1). Compared with the Dutch norm, gender differences were also found. Female patients with Crouzon and Apert syndromes were statistically significantly delayed compared with controls (Figs. 1 and 2). Dental maturation of male patients with Crouzon and Apert syndromes was less mature than that of control subjects. A slight acceleration occurred between 9 and 12 years of age for male patients with Crouzon syndrome compared with controls.

Female patients with Crouzon syndrome at all ages were less matured than boys, although these differences were not statistically significant (Fig. 3). In patients with Crouzon syndrome, male patients showed delayed dental development before 6 to 7 years of age compared with female patients with Crouzon syndrome (Fig. 4). From this age on, female patients with Crouzon syndrome were less matured dentally compared with boys.

Discussion

The dental maturation in Dutch patients with Crouzon and Apert syndromes was compared with the dental

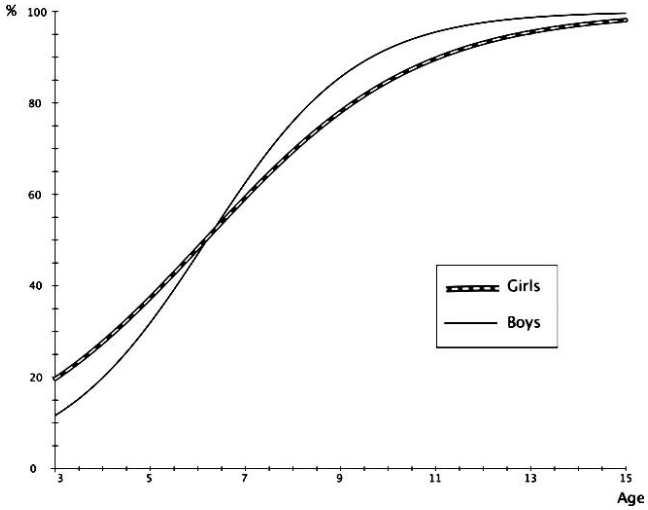

FIGURE 3 Dental maturation for male and female patients with Crouzon syndrome.

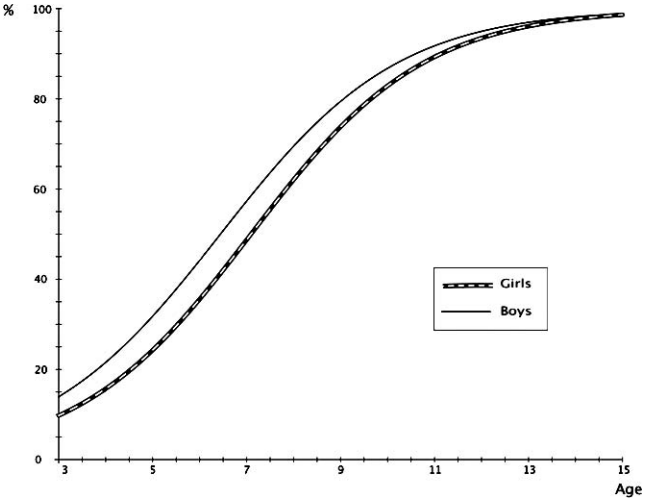

FIGURE 4 Dental maturation for male and female patients with Apert syndrome.

maturation in a nonsyndromic control group of the same ethnicity. In both syndromes, disturbances in the gene expression show abnormal skeletal growth and probably could also have influence on dental development (Wilke et al., 1997; De Coster et al., 2007). The correction of facial deformities in patients with craniosynososis syndromes is complex because of the esthetic and functional difficulties associated with these disorders. Management of these patients requires knowledge and understanding of craniofacial growth and development (Renier et al., 2000). An important role is determining the type and timing of orofacial interventions in which gender- and syndrome-specific data for dental maturation may attribute.

This study showed that the early dental maturation in syndromic patients is severely delayed (Table 1). Also, dental maturation in patients with Crouzon and Apert syndromes is abnormally distributed when compared with the nonsyndromic Dutch control group. The development over time at the 50th percentile was delayed compared with normal values (Figs. 1 and 2). One study in the literature investigated the relationship between dental maturity and Apert syndrome (Kaloust et al., 1997). This study showed a delayed dental maturity in patients with Apert syndrome, with a trend of increasing delay with increased age compared with a control group. The authors suggested a positive correlation between increased age and increased delay, extending equally the general growth of Apert children (Kaloust et al., 1997). However, gender differences were not accounted for.

Remarkable gender differences in dental maturation were found in patients with Crouzon and Apert syndromes. Girls with Crouzon and Apert syndromes showed statistically significant delayed dental maturation compared with boys. A large study of a normal sample ($n = 1031$) showed independent gender scores of dental maturity, which were always more advanced for girls (Chaillet et al., 2005). Girls were advanced already at 2 years of age until 12 years of age. Acceleration of dental maturation in boys started at 12 to 13 years, at the beginning of their puberty, and continued strongly until 18 years of age (Chaillet et al., 2005). Control Dutch boys and girls in the present study confirmed these findings. Gender differences in dental maturation for patients with craniosynostosis and control subjects (Field et al., 1991; Cohen and Kreiborg, 1993b; Chaillet et al., 2005) might be related to variability due to the limited sample size of syndromic patients.

There is evidence to suggest that tooth agenesis is related to dental maturation in patients with Crouzon and Apert syndromes (Kaloust et al., 1997; Lin et al., 2009). Dental maturation of permanent teeth in nonsyndromic children ($n = 108$) is delayed with dental agenesis (Ruiz-Mealin et al., 2012), and the severity of dental agenesis affects the magnitude of the delay (Ruiz-Mealin et al., 2012). The prevalence of tooth agenesis in patients with Crouzon and Apert syndromes is much higher than reported for the general population (Polder et al., 2004; Stavropoulos et al., 2011; Stavropoulos et al., 2012). High prevalence of tooth agenesis in patients with Crouzon and Apert syndromes might negatively influence delayed maturation in the present study, although the literature contains no consensus concerning delayed tooth development in patients with dental agenesis (Ruiz-Mealin et al., 2012).

The ability to determine dental maturity is important to those involved in treatment of patients with Crouzon or Apert syndrome (Kaloust et al., 1997). The oral surgeon plays an important role in determining the type and timing of orofacial interventions partly determined by the dental development (Cohen and Kreiborg, 1993; Kaloust et al., 1997). Dental development is particularly useful to the orthodontist when planning the treatment of different types of malocclusions in relation to surgical intervention. Dental maturation may also be of interest to molecular biologists,

because genetic mutations may alter dental morphogenesis (Kaloust et al., 1997).

Dental maturity assessed by the Demirjian method (Demirjian et al., 1973) is considered to be the most precise and accurate method (Hägg and Matsson, 1985). Most methods determine dental maturation according to the degree of dental calcification observed in x-rays of the jaws (Schour and Massler, 1941; Garn et al., 1959; Haavikko, 1970; Moorrees et al., 1963; Prahl-Andersen and Van der Linden, 1972; Gustafson and Koch, 1974; Anderson et al., 1976). This is in contrast to Demirjian's method of estimating dental maturity by the development stage of seven teeth in the left side of the mandible.

Further, the method developed by Demirjian et al. (1973) avoids magnification considerations and the need for direct measurements. Therefore, it is one of the simplest, practical, and widely used methods (Garamendi et al., 2005).

After the age of 15 years, the accuracy of Demirjian's age prediction decreases because most subjects reach dental maturity scores of 100. Adding the third molar might increase the possibility of prediction until 18 years of age. However, the high variability of third molar development (Mesotten et al., 2002; Gunst et al., 2003; Chaillet et al., 2005), a 20% chance of third molar agenesis (Polder et al., 2004), and small sample sizes make accuracy of dental maturation at an older age low.

Conclusion

To calculate the dental maturation for patients with Crouzon and Apert syndromes, scoring can be carried out according to the system of Demirjian et al. (1973). Girls and boys with Crouzon and Apert syndromes were delayed compared with dental maturation in normal Dutch children (Leurs et al., 2005). Gender differences between the syndromes showed that girls with Crouzon and Apert syndromes had a statistically significant less mature dental maturity compared with controls. Dental maturation in patients with Apert syndrome was more delayed than in patients with Crouzon syndrome. The delay of tooth formation in patients with Crouzon and Apert syndromes suggest a possible common genetic association.

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