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Dental development and tooth agenesis in children with velocardiofacial syndrome

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Background. Variations in dental development and tooth agenesis have been reported in children with velocardiofacial syndrome (VCFS).

Aim. The aim was to evaluate the dental development and missing permanent teeth in children with VCFS.

Design. Forty-five children (23 girls) with VCFS who had visited the cleft palate and craniofacial centre were studied retrospectively from orthopantomograms taken at the mean age of 7.9 years (range 5.8–12.9). Thirteen of the children with VCFS had palatal clefts. The deletion of 22q11 was verified by FISH techniques. The dental stages were assessed by the method of Demirjian, and the dental age was calculated according to the Finnish dental maturity reference values. A paired Student's *t*-test was used in the statistical analysis.

Results. Eight children (17%), four with palatal clefts, had tooth agenesis. Four children (9%) had agenesis of mandibular incisors. The missing teeth (n = 19) were mainly mandibular incisors (n = 6), maxillary lateral incisors (n = 2), and maxillary second premolars (n = 4). The dental age of the children with VCFS was not different from their chronological age, but there was great individual variation.

Conclusions. A high prevalence of missing permanent teeth, especially mandibular incisors, was observed. The need for thorough clinical and radiological dental examination in children with VCFS is emphasized.

Introduction

Velocardiofacial syndrome (VCFS) is one of the most common multiple anomaly syndromes. The labels DiGeorge sequence, 22q11 deletion syndrome, conotruncal anomalies face syndrome, CATCH 22, and Sedlackova syndrome have all been attached to the same disorder.[1] The estimates of the incidence have varied from 1 in 4000–5000 live births[2,3] to 1 : 2000.[1] VCFS is caused by an interstitial deletion of 22q1121-q23. Nevertheless, in a minority of patients, a mutation in TBX1 can be detected.[4] The deletion of 22q11 can be diagnosed with high accuracy by fluorescence *in situ* hybridization (FISH) techniques.

A wide variety of clinical features with variable expression have been described for the syndrome. The acronym CATCH-22 has been proposed to describe the phenotype (cardiac abnormality, abnormal faces, thymic hypoplasia, cleft palate, and hypocalcaemia).[5] Ryan *et al.*[6] presented clinical data of 558 patients collected from European centres with deletions within the DiGeorge syndrome critical region of chromosome 22q11. Nine per cent of the patients had a cleft palate and 32% had velopharyngeal insufficiency, 60% of the patients were hypocalcaemic, 75% of the patients had cardiac problems, and 36% of the patients who had an abdominal ultrasound had renal abnormality. Learning disabilities are seen in almost all the individuals with 22q11 deletions.[7] Speech and language deficits and behaviour and personality problems are also typical.[1] Clinical management is age-dependent focusing on acute medical problems and developmental disorders in infancy and the preschool years. The management shifts to cognitive, behavioural, and learning disorders during the school years, and then to the potential for psychiatric disorders, including

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psychosis, in late adolescence and the adult years.[1]

Facial dysmorphism is pronounced in VCFS with vertical excess, malar flatness, mandibular retrusion, and a prominent nose.[8,9] Cephalometrically, the faces are long, both maxillae and mandibles are retrognathic, and the lower jaws are posteriorly divergated.[10] The ears are low set,[6] and the mouth is often held open. Oral findings in children with 22q11 deletion include anomalies in dental enamel and tooth shape.[11,12] In addition, delayed dental development has been reported both in the primary and in the permanent dentition.[11,13] Klingberg *et al.*[11] studied 53 patients with 22q11 deletion syndrome whose mean age was 11 years. They found nine patients whose tooth development was delayed by more than two standard deviations. Agenesis of permanent teeth was found in six patients (11.3%). In another study[12] with 26 patients with VCFS whose age range was between 7 and 48.3 years, the occurrence of tooth agenesis (23.8%) was similar in both the study and control groups (15.4%). Interestingly, in both studies[11,12] three patients with missing mandibular permanent incisors were observed. Previous literature on single maxillary central incisor syndrome reported one individual with VCF.[14] Oberoi and Vargervik[15] studied three siblings with VCF. Two of the three had a single central incisor: one maxillary and one mandibular.

As variations in dental development and agenesis of permanent teeth have been reported in patients with VCFS, the purpose of this study was to evaluate in detail the dental development and the number and type of missing permanent teeth (excluding third molars) in Finnish children with VCFS. Finnish dental maturity values were used as dental maturation varies in children with different ethnic backgrounds.[16]

Material and methods

The patients comprised 45 Finnish children with VCFS who had visited the Cleft Palate and Craniofacial Center, Department of Plastic Surgery, Helsinki University Central Hospital, between the years 1980 and 2009 because of clefts or problems in language development. In all the patients, the deletion of 22q11 was verified by FISH techniques. The mean age of the children was 7.9 years (range 5.8–12.9). Half of the children (23) were girls. Thirteen of the children (29%) had palatal clefts, seven had isolated cleft palates (CP), and six submucous cleft palates (SMCP). Submucous cleft palates were verified in the cleft palate and craniofacial centre either clinically or by nasopharyngoscopy.

Dental development and the number and type of congenitally missing teeth (excluding third molars) were assessed using standardized dental panoramic radiographs (OPT) taken at the cleft palate and craniofacial centre. The developmental stages of seven left mandibular teeth were rated on an eight-stage scale, as described by Demirjian and Goldstein.[17] For each stage of the seven teeth, a biologically weighted score for girls and boys specific to Finnish children was used.[18] The method of calculating the weighed scores was the same as that presented by Demirjian and Goldstein.[17] The sum of the scores of the seven teeth was the dental maturity score of the child. The maturity score of the child was then converted to dental age using the Finnish reference values.[18] The dental stages were assessed by one senior orthodontist. The intraexaminer reliability in dental age assessment was determined by reassessing 20 randomly selected panoramic radiographs. Agreement was assessed by the Kappa coefficient of agreement, which was calculated for each tooth. The mean intraexaminer reliability was 0.89 Kappa (range 0.86–0.92).

A Student's paired *t*-test was used to compare the dental ages of children with VCFS with their chronological ages. The research protocol was approved by the Helsinki University Central Hospital.

Results

Eight children (17%), three boys and five girls, had tooth agenesis. Four of the children with missing teeth had clefts (three CP and one SMCP). The children with clefts had more severe tooth agenesis (1–6 missing

teeth) than the children without clefts (1–2 missing teeth). Four children (9%) – two without clefts, one with CP, and one with SMCP – had agenesis of mandibular incisors.

The number and the distribution of the missing teeth are given in Table 1.

Altogether, 19 missing permanent teeth were found. The missing teeth were mainly mandibular central incisors ($n = 5$), mandibular lateral incisors ($n = 1$), maxillary lateral incisors ($n = 2$), and maxillary second premolars ($n = 4$). Tooth agenesis in the maxilla was observed in three children, tooth agenesis in the mandible in three, and tooth agenesis in both jaws in two children. Supernumerary teeth were not observed.

The dental age of the children with VCFS was not different from their chronological age, but there was great individual variation.

The dental age of the children with VCFS was delayed by 0.4 years (range −1.2 to 1.7 years) when compared with their chronological age $P < 0.014$, ns. The dental age of the children with VCFS and agenesis of permanent teeth ($n = 8$) was delayed by 0.7 years (range −0.1 to −1 years), $P < 0.081$, ns. There were no significant differences in the dental maturation between the children with ($n = 13$) and without ($n = 32$) clefts $P < 0.108$, ns.

Discussion

According to this study, the prevalence of tooth agenesis in the children with VCFS was 17%. Half of these children had palatal clefts. The observed prevalence of tooth agenesis in the children with VCFS is higher than that of the general population, 2.2–10%,[19–22] about the same as in children with SMCP, 16%,[23] but lower than in children with isolated cleft palate, 33%.[24] In the general population, most of those with tooth agenesis lack 1–2 permanent teeth (hypodontia), whereas agenesis of more than two teeth is noticed in about 1%, and agenesis of six or more teeth (oligodontia) in 0.1–0.3%.[22] In the present study, most of the children with VCFS showed a mild tooth agenesis phenotype (hypodontia) with the absence of 1–2 permanent teeth, but two children with cleft palate had a more severe phenotype: one patient was missing three, the other six permanent teeth.

Most of the missing teeth in the children with VCFS were mandibular incisors ($n = 6$), followed by upper lateral incisors, upper and lower second premolars, second molars, and in one case an upper canine. The differentiation between the mandibular central and lateral incisors can be difficult. The agenesis of lower incisors (one-third of the missing teeth) was remarkably more frequent than in the general Caucasian population, 0.25–0.36%.[21,22] Nevertheless, the agenesis of lower incisors is more common in Asian populations.[22] The most common missing teeth in Finnish children without clefts of the palate[20] or with SMCP[23] and CP[24] are mandibular second premolars followed by maxillary lateral incisors.

Table 1. Type and number of missing permanent teeth in eight children with velocardiofacial syndrome.

			Maxillary arch						Mandibular arch						
			Right			Left			Right		Left				
Gender	Cleft	Age (years)	M2	P2	I2	I2	C	P2	P2	I1	I1	I2	P2	M2	Total
Girl		5.8								1	1				2
		6.1	1												1
	CP	7.8			1	1								1	3
	CP	8.2		1			1	1	1	1			1		6
		12.9								1	1				2
Boy		5.8			1	1									2
	CP	6		1				1							2
	SMCP	8										1			1
Total			1	2	2	2	1	2	1	3	2	1	1	1	19

I1, central incisor; I2, lateral incisor; C, canine; P2, second premolar; M2, second molar. CP, cleft palate; SMCP, submucous cleft palate.

Previously, da Silva Dalben *et al.*[12] observed tooth agenesis in 23% of patients with VCFS. They found no significant difference in the occurrence of tooth agenesis in patients with VCFS and controls. In a Swedish study,[11] agenesis of permanent teeth was found in 6/53 (11%) patients with 22q11 deletion syndrome. Missing mandibular permanent incisors have been reported in earlier studies with 22q11 deletion syndromes.[11,12,15] In addition, previous literature has reported two individuals with VCFS with missing maxillary central incisors.[14,15] In our material, no missing maxillary central incisors were observed. It should be noted that the material of the present study may be biased as all the children with VCFS had been sent to the cleft palate and craniofacial centre either because of the clefts of the palate or because of the problems in language development. Even if almost one-third of the children of this study had clefts, the high incidence of missing lower incisors both in the children with and without clefts is an important finding. Tooth agenesis is common in oral clefts and malformation syndromes, although the frequency and typical patterns of tooth agenesis vary. Typical syndromes with missing lower permanent incisors include Down syndrome (trisomy 21). In a study[25] with 98 subjects with Down syndrome, the majority (63%) had tooth agenesis. The most frequently missing teeth were lower lateral incisors (23.3%). Other syndromes with missing lower incisors include Kallmann syndrome and Axenfeld-Rieger syndrome.[26,27]

Another important finding of the present study is that the dental maturity of the children with VCFS was not delayed. Nevertheless, there was individual variation. In 251 Finnish children with isolated cleft palate without syndromes, the mean delay in dental age was 0.7 years.[28] The delay was found to increase with an increasing number of missing permanent teeth.[28] In submucous clefts of the palate, no significant delay in dental age has been observed.[29] Delayed dental development was reported in earlier studies of 22q11 deletion syndromes, although the mean dental ages of all patients were not calculated.[11,13] The dental stages in the present study were assessed as described by Demirjian and Goldstein,[17] but the dental age was estimated using the dental maturity reference values for Finnish children.[18] The maturity standards of Demirjian are based on French-Canadian children, and in Finland, the dental ages are advanced when compared with the French-Canadian children.[16]

A shortcoming of our study is that the children with VCFS were of different ages (mean age 7.9 years, range 5.8–12.9), and in some children, late developing premolars may appear. Nevertheless, if a tooth is not present at the age of 6 years, it is a sign of delayed dental maturation. The diagnosis of missing premolars in the Scandinavian population without clefts can be made with 97% certainty at about 8 years of age.[30] As lower teeth were used to evaluate the dental age, the development of the dentition was not influenced by surgical trauma or other local factors related to the cleft.

In conclusion, the dental age of the children with VCFS was not different from their chronological age. The prevalence of tooth agenesis (17%) was higher than in the general Finnish population. A high prevalence (9%) of missing lower incisors both in children with and without clefts with VCFS was found. There is a clear need for thorough clinical and radiological dental examination in children with VCFS.

What this study adds?

- Children with VCFS with or without clefts have a high prevalence of tooth agenesis (17%) and an especially high prevalence (9%) of missing lower incisors.

Why is this study important to paediatric dentists?

- It is important to thoroughly clinically and radiologically examine the dentition when treating children with VCFS.

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