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Severe hypodontia: identifying patterns of human tooth agenesis

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SUMMARY Tooth agenesis is the most common dental anomaly. The aim of this retrospective study was to identify common patterns of tooth agenesis in a sample of 92 patients (55 females and 37 males; mean age 27.7 years) with non-syndromic severe hypodontia. The Tooth Agenesis Code (TAC) procedure was used for that purpose. The patients in this study were missing between 6 and 22 permanent teeth (mean 11.6; median 10.0; SD 4.35). In the maxilla, 47.9 (left side) and 50.0 (right side) per cent can be described using only five different patterns. The most common patterns involved agenesis of the maxillary lateral incisor and both premolars. In the mandible, 35.8 (lower left) or 43.5 (lower right) per cent can be described by five patterns, the most common of which was agenesis of all mandibular premolars. When comparing patients with and without symmetric agenesis patterns (symmetry in the upper or lower arch versus no symmetry), a Student's *t*-test revealed no difference in the total number of missing teeth.

Common patterns of tooth agenesis were successfully identified in patients with non-syndromic severe hypodontia. The present findings may be used to develop interdisciplinary treatment protocols for the most common patterns to increase the quality of interdisciplinary treatment for patients with severe hypodontia.

Introduction

Agenesis of one or more permanent teeth is the most common dental anomaly in man (Vastardis, 2000; Nunn *et al.*, 2003). Hypodontia, agenesis of one or a few permanent teeth, without any systemic disorders is the mildest and most common phenotype. The prevalence of hypodontia is reported to vary between 2.3 and 10.1 per cent (Schalk van der Weide, 1992). The term 'severe hypodontia' (or oligodontia) is defined as agenesis of six or more permanent teeth, excluding the third molar (Schalk van der Weide, 1992). Severe hypodontia is a rare condition that can occur in association with genetic syndromes, as a non-syndromic isolated familial trait, or as a sporadic finding (Gorlin *et al.*, 2001). The prevalence of non-syndromic isolated severe hypodontia is reported to be 0.08 per cent in a Dutch population (Schalk van der Weide, 1992) and 0.16 per cent in a Danish population (Rølling and Poulsen, 2001). An extensive review on hypodontia was published by Arte (2001). Severe hypodontia has serious implications for the patient in terms of masticatory function, malocclusion, speech impairment, and psychological impact. As such, severe hypodontia can have a dramatic effect on a patient's (oral health-related) quality of life.

Evidence supporting a genetic aetiology for tooth agenesis has been presented (Vastardis, 2000; Kolenc-Fusé, 2004). To increase the understanding of severe hypodontia and facilitate the selection of patients for future genetic studies, a precise description of the phenotypes specifying which teeth are missing has become fundamental (Vieira, 2003). The recently introduced Tooth Agenesis Code (TAC) procedure can be used for that purpose, as it efficiently and unequivocally expresses the human dentition with respect to the number of missing teeth as well as the location (van Wijk and Tan, 2006).

The mandibular second premolar is, in most studies, the most frequently missing tooth (excluding third molars), followed by the maxillary lateral incisor or second premolar (Arte, 2001). However, it is not clear if common patterns of tooth agenesis can be found in a population of severe hypodontia patients. Therefore, the present study aimed to explore whether common patterns of tooth agenesis can be identified in subjects with non-syndromic severe hypodontia in the permanent dentition. Bearing in mind that specific teeth (e.g. second premolars and upper lateral incisors) are missing most frequently, it was hypothesized that common patterns of tooth agenesis can be identified in severe hypodontia patients.

Subjects and methods

Subjects

The sample consisted of 92 Caucasians (55 females and 37 males) who were diagnosed with non-syndromic severe hypodontia (agenesis of six or more permanent teeth, excluding the third molars). The patients were between 12 and 48 years of age (mean 27.7 years). When syndromic status was suspected, the patients were referred to a clinical

geneticist. Patients with syndromes or craniofacial anomalies were excluded from the sample. All subjects had been referred for treatment to the Department of Orthodontics, Academic Centre for Dentistry Amsterdam, and the Department of Orthodontics, Erasmus University Medical Centre, Sophia Children's Hospital, Rotterdam, The Netherlands. This study was performed according to the ethical principles described in the Declaration of Helsinki (World Medical Association, 1996).

Procedure

The diagnosis of severe hypodontia (including the exact location of dental agenesis) was confirmed by one author (BP-A) based on clinical examination and after studying the panoramic radiographs, plaster casts, and intra-oral photographs. The third molars were not taken into account because it was not possible to determine third molar agenesis accurately for all cases. All diagnoses were confirmed twice by one author (SPKT) by retrospectively studying the patients' dental charts, panoramic radiographs, plaster casts, and intra-oral photographs with an interval between the first and second assessment of at least 1 week ($\kappa = 0.891$). In 10 cases, discrepancies between the two investigators were identified and discussed until consensus was achieved.

To identify the most common agenesis patterns, the TAC procedure (van Wijk and Tan, 2006) was used. In short, binary arithmetic is used to represent the absence or presence of teeth by either '1' or '0'. The binary numbers are translated into corresponding unique values for each dental quadrant. The teeth are numbered 1–8, according to the Federation Dentaire International system (Peck and Peck, 1996). Each missing tooth is associated with a 'tooth value'. The tooth value can be determined by calculating $2^{(n-1)}$, in which n = tooth number. For example, the tooth value for the first premolar (tooth 4) is $2^{(3)} = 8$. The TAC is the sum of the tooth values. For example, a patient with agenesis of a lateral incisor and a first premolar has a TAC value of 2 + 8 = 10. Each dental quadrant is analysed separately. Thus, the TAC consists of the values assigned to each of the quadrants (q1, q2, q3, and q4) in the dentition and corresponds to a unique tooth agenesis pattern (van Wijk and Tan, 2006).

Statistical analysis

The Statistical Package for the Social Sciences (version 12.0; SPSS Inc., Chicago, Illinois, USA) was used for data analysis. A Student's *t*-test was used to determine differences in the total number of missing teeth in patients with symmetric and asymmetric dental agenesis patterns.

Results

The patients in this study were missing between 6 and 22 permanent teeth (mean 11.6; median 10.0; SD 4.35). Table 1 shows TAC values for all 92 patients. Frequency analyses revealed the most common tooth agenesis patterns in the maxilla and the mandible (Figure 1).

Table 1 Tooth Agenesis Code values in each quadrant for the 92 patients (55 females and 37 males) with severe hypodontia.

Case no.	q1	q2	q3	q4	Case no.	q1	q2	q3	q4
1	26	26	25	27	47	94	94	71	71
2	92	0	19	17	48	30	6	95	95
3	22	6	22	20	49	26	26	19	25
4	0	0	79	79	50	20	20	88	24
5	30	26	31	25	51	2	82	24	24
6	2	2	3	3	52	94	94	82	94
7	18	2	3	3	53	2	2	99	83
8	94	94	31	31	54	54	18	65	17
9	66	82	87	87	55	2	66	66	64
10	24	26	24	16	56	2	2	82	81
11	38	86	53	55	57	24	24	81	80
12	2	2	19	17	58	26	26	24	24
13	30	30	24	24	59	24	24	80	16
14	18	18	17	16	60	88	88	80	80
15	6	6	5	7	61	94	94	95	95
16	22	18	20	16	62	6	22	19	23
17	24	24	81	81	63	76	78	87	79
18	26	26	24	24	64	28	12	0	8
19	26	18	0	32	65	30	94	95	95
20	66	94	95	87	66	80	88	88	81
21	2	2	3	3	67	28	28	1	81
22	24	24	24	8	68	30	94	71	71
23	24	16	24	24	69	102	102	67	83
24	84	68	65	81	70	6	6	95	95
25	80	80	48	80	71	30	30	26	24
26	30	30	31	95	72	31	31	27	31
27	14	30	16	16	73	90	16	16	80
28	18	2	1	19	74	26	0	80	80
29	30	30	88	89	75	82	90	80	64
30	90	90	27	27	76	24	24	19	18
31	26	2	17	19	77	18	18	16	8
32	24	26	16	16	78	88	90	83	8
33	30	30	16	80	79	94	90	125	123
34	86	86	87	87	80	26	18	31	19
35	82	80	81	81	81	98	98	65	65
36	122	122	115	115	82	96	112	64	64
37	90	90	91	95	83	16	24	24	24
38	22	12	88	88	84	94	92	95	95
39	2	2	3	3	85	10	10	26	26
40	86	70	80	80	86	18	30	24	24
41	26	26	24	24	87	30	30	28	24
42	26	2	11	27	88	26	30	90	89
43	2	2	80	81	89	38	38	85	87
44	10	30	16	9	90	18	16	123	83
45	86	86	91	95	91	98	106	81	81
46	26	26	3	19	92	26	26	17	27

In each dental quadrant, $2^7 = 128$ different possible patterns may be found because in each quadrant seven teeth can be either present or missing. In the upper right dental quadrant (q1), a total of 30 different agenesis patterns were found. The most common pattern in q1 involving agenesis of the upper lateral incisor and both maxillary premolars (TAC value = 26) was seen in 14.1 per cent of the patients. In the upper left quadrant (q2), 31 different patterns were found. The most common pattern in q2, agenesis of the upper lateral incisor (TAC value = 2), was found in 12.0 per cent of the patients (Figure 1). Interestingly, the top six most

(a)

Maxilla

Upper right (q1)				Upper left (q2)			
TAC	Missing Teeth	Illustration	Percentage	TAC	Missing teeth	Illustration	Percentage
26	12, 14, 15		14.1	2	22		12.0
30	12, 13, 14, 15		10.9	26	22, 24, 25		10.9
2	12		9.8	30	22, 23, 24, 25		10.9
24	14, 15		8.7	94	22, 23, 24, 25, 27		7.6
18	12, 15		6.5	18	22, 25		6.5
Remaining patterns			50.0	Remaining patterns			52.1

(b)

Mandible

Lower right (q4)				Lower left (q3)			
TAC	Missing Teeth	Illustration	Percentage	TAC	Missing Teeth	Illustration	Percentage
24	44, 45		12.0	24	34, 35		10.9
81	41, 45, 47		8.7	16	35		6.5
95	41, 42, 43, 44, 45, 47		8.7	80	35, 37		6.5
80	45, 47		7.6	95	31, 32, 33, 34, 35, 37		6.5
16	45		6.5	3	31, 32		5.4
Remaining patterns			56.5	Remaining patterns			64.2

Figure 1 Most common patterns of tooth agenesis in each quadrant in (a) the maxilla and (b) the mandible with corresponding Tooth Agenesis Code (TAC) values, missing teeth, illustrations, and percentages within the sample. The teeth marked grey are missing. The third molars were not taken into account.

common patterns were identical in both q1 and q2, but the descending order was different. For example, agenesis of the upper lateral incisor (TAC value = 2) was the most common pattern in q2 and the second most common in q1 (Figure 1). In the lower dental quadrants (lower right = q4; lower left = q3), the total numbers of different patterns were 38 and 31, respectively. Both in q4 (12.0 per cent) and q3 (10.9 per cent), the most common pattern was agenesis of the mandibular first and second premolar (TAC value = 24). In the upper right dental arch, 50.0 per cent of the patients had a pattern that was in the top five most common patterns (Figure 1). For all other quadrants (q2, q3, and q4), the percentage of patients who had patterns within the top five most common patterns were 47.9, 35.8, and 43.5 per cent, respectively.

By comparing the TAC values, symmetry of agenesis patterns was assessed within the upper and lower dental arch (Table 2). Symmetry of agenesis patterns in the lower arch was found in 40.2 per cent and in the upper arch in 52.2 per cent of the patients. In 27.8 per cent of all cases, symmetry was found in both the upper (q1 = q2) and lower (q3 = q4) arch. When comparing patients with and without symmetric agenesis patterns (symmetry in the upper or lower arch versus no symmetry), no difference in the total number of missing teeth was found ($P > 0.05$). However, no patient showed overall symmetry (q1 = q2 = q3= q4). Table 3 shows all symmetric tooth agenesis patterns (TAC) in the maxilla and mandible. For example, in seven patients, both lateral incisors in the maxilla were absent (TAC value = 2).

Discussion

The present study identified the most common patterns of tooth agenesis in patients with severe hypodontia by means of the TAC procedure (van Wijk and Tan, 2006). The three most common patterns in the upper arch involved agenesis of the lateral incisor, canine, and both premolars. The most common pattern in the lower arch involved agenesis of all mandibular premolars. Other common patterns in the lower arch involved agenesis of the incisors, canine, both premolars, and the second molar (Figure 1). Agenesis of both the upper and the lower first molars was rare in the present sample. The six most common patterns in both the upper and the lower arches describe approximately half of all possible patterns. This clearly shows that common patterns of tooth agenesis are present in patients with non-syndromic, isolated severe hypodontia. The present findings may be used to develop interdisciplinary treatment protocols for the most common patterns. The use of treatment protocols may increase the quality of interdisciplinary treatment of severe hypodontia patients.

Inclusion or exclusion of third molars does not undermine the TAC procedure. When the third molars are excluded, the TAC values will range from 0 to 127 (128 TAC values). As third molar agenesis could not be determined accurately in the present study, these teeth were excluded. Data that do include the third molar can be easily transformed to exclude the third molar so that it can be compared across samples. This can be done by subtracting 128 from any TAC value in those patients with missing third molars. For example, a

Table 2 Symmetry of tooth agenesis patterns and corresponding percentages of symmetry within the sample.

Pattern symmetry	Comparison	Symmetry (%)
Upper arch	Right side versus left side	52.5
Lower arch	Right side versus left side	40.2
Left side	Upper left versus lower left	5.4
Right side	Upper right versus lower right	4.3
q1 versus q3	Upper right versus lower left	4.3
q2 versus q4	Upper left versus lower right	4.3

Table 3 Frequency of symmetric Tooth Agenesis Code (TAC) values in the maxilla and mandible.

Maxilla		Mandible	
TAC	*N*	TAC	*N*
26	7	94	4
2	7	26	4
30	6	2	4
24	5	30	4
94	4	24	3
86	2	18	2
90	2	86	2
18	2	98	2
6	2	6	1
31	1	16	1
98	1	88	1
10	1	10	1
38	1	96	1
102	1	90	1
88	1	14	1
80	1	66	1
0	1	0	1
122	1	82	1
20	1	122	1
28	1	22	1
Total	48	Total	37

patient without an upper lateral incisor and third molar has TAC = 130. If 128 is deducted, then TAC = 2 remains, which corresponds with agenesis of the lateral incisor. This results in data that do not include the third molar.

A recent study (Kim *et al.*, 2006) showed that tooth agenesis may be a symmetrical phenomenon. In this study, symmetry (left versus right) of tooth agenesis patterns was found in 40.2 per cent in the lower arch and in 52.2 per cent in the upper arch (Table 2). The relatively high degree of left versus right side symmetry of the patterns may indicate a possible common genetic cause. The relatively low symmetry of upper versus lower arch tooth agenesis (Table 2) may suggest that different mechanisms are responsible for tooth agenesis in the upper and lower arches.

Human tooth agenesis may be caused by several independent defective genes, acting alone or in combination with other genes, leading to a specific phenotypic pattern. Recently, genetic defects responsible for tooth agenesis are being identified. Mice lacking *Msx1* function manifest a cleft palate, deficient mandibular and maxillary alveolar bones, and failure of tooth development (Satokata and Maas, 1994). *Pax9* homozygous null mice fail to form teeth beyond the bud stage (Peters *et al.*, 1998). Mutations in *MSX1* and *PAX9* have been associated with tooth agenesis in humans but those mutations may have caused hypodontia in only a few cases (Vieira, 2003). The literature suggests that *MSX1* mutations account mainly for premolar agenesis and that *PAX9* mutations account mainly for molar agenesis. However, previous studies have shown that cleft patients with *MSX1* mutation may present with agenesis of the first, second, and third molars (De Muynck *et al.*, 2004; van den Boogaard *et al.*, 2000). In non-cleft patients, *MSX1* mutation is associated with third molar agenesis (Lidral and Reising, 2002). Agenesis of only one or two teeth cannot be explained by *MSX1* mutations (Lidral and Reising, 2002). Until now, it has been unclear exactly how genetic mutations are related to specific tooth agenesis patterns. The TAC analysis of clinical data combined with future genetic studies (with larger samples) may help clarify which specific tooth agenesis patterns are related to genetic mutations and which are not. A twin study showed that 55 per cent of monozygotic twins are discordant for hypodontia (Boruchov and Green, 1971). This may be indicative of epigenetic factors.

A study design taking into account the unique characteristics of both the sample and the phenotypes studied has been suggested as a way to improve the quality of future investigations (Vieira, 2003). The present research has shown that the TAC procedure may be useful for this purpose, as it has an advantage over existing methods in that it allows for easier data analysis. The frequently used graphical notation (Jumlongras *et al.*, 2001) can describe the exact location of missing teeth per case. However, the question whether specific patterns of tooth agenesis are more predominant than others can only be answered using the recently introduced TAC procedure (van Wijk and Tan, 2006). The TAC unequivocally expresses the phenotypes of the subjects with respect to the number of missing teeth as well as the location. Future research on hypodontia can efficiently report all phenotypes using the TAC procedure.

It is important to replicate the present study in different populations in other countries because this can significantly increase our knowledge about severe hypodontia. Further research is necessary to investigate whether specific tooth agenesis patterns are associated with different syndromes or craniofacial anomalies, as this may provide more insight into the genetic aetiology.

Conclusions

The most common patterns among patients with severe hypodontia were successfully identified using the TAC procedure. In the maxilla, about half of the agenesis patterns can be described using only five different patterns. The most

common patterns involved agenesis of the maxillary lateral incisor and both premolars. In the mandible, 35.8 (lower left) or 43.5 (lower right) per cent of the patterns can be described by five patterns. The most common pattern was agenesis of all mandibular premolars. Patients with and without symmetric agenesis patterns (symmetry in the upper or lower arch versus no symmetry) showed no difference in the total number of missing teeth.

The present findings may be used to develop treatment protocols for the most common patterns to increase the quality of interdisciplinary treatment for patients with severe hypodontia.

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