Patterns of tooth agenesis in patients with Down syndrome in relation to hypothyroidism and congenital heart disease: An aid for treatment planning

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Introduction: The purposes of this study were to investigate the patterns of tooth agenesis (oligodontia and nonoligodontia), maxillary canine impaction, and tooth transposition in subjects with Down syndrome and to determine whether congenital heart disease and hypothyroidism are parameters in tooth agenesis. Methods: The study included 114 patients with Down syndrome. The data were quantified by using standardized records, clinical examinations, panoramic radiographs, and solo roentgenograms. The subjects were differentiated into oligodontia (6 or more teeth missing) and nonoligodontia (5 or fewer teeth missing). Results: In these patients with Down syndrome, 59.6% had missing teeth. Those in the nonoligodontia group showed a tendency toward a negative correlation between congenital heart disease and agenesis ($P = 0.093$; odds ratio $= 0.49$) but a slight positive correlation between hypothyroidism and agenesis ($P = 0.060$; odds ratio $= 3.71$). In the oligodontia group, there was a quantitatively and qualitatively different pattern, indicating another phenotype. When both mandibular central incisors were missing, there was a remarkable chance for oligodontia ($P = 0.001$; odds ratio $= 38.8$). In the mandible, symmetrical agenesis of the canines and lateral incisors was more frequent in the nonoligodontia group. Conclusions: The oligodontia (with a different phenotype) and nonoligodontia groups had different patterns of agenesis. Maxillary canine impaction was not related to absence of the lateral incisors. Absence of both mandibular central incisors was a high predictor for oligodontia. Congenital heart disease and hypothyroidism are parameters involved in tooth agenesis. (Am J Orthod Dentofacial Orthop 2010;137:584.e1-584.e9)
thinner enamel and dentin,11 taurodontism,12 and tooth transpositions.8 None of these dental features is unique to people with DS. They occur also in the normal population, but the frequency in people with DS is higher.4,13 Maxillary canine impaction is considered an associated phenomenon8 and is supposed to coincide with the absence of, or peg-shaped, maxillary lateral incisors,14 a condition often seen in patients with DS.5

In addition to functional and esthetic problems, a disadvantage of congenital hypodontia is that there is less development of alveolar bone, resulting in decreased maxillary length and bone height.15 The latter factor makes patients with DS more vulnerable to loss of teeth from periodontal disease.16 Regular roentgen screening at 6, 9, 12, and 15 years of age is recommended.17 This provides information about hypodontia, impaction of teeth, stage of eruption, and development of the typically growing jaws.18 Guiding impacted teeth to the right positions might prevent malocclusion and lead to optimal bone height. Important for orthodontic treatment is that stature growth is retarded during childhood in patients with DS; the adolescent period is shorter,4 and maturation of the bones takes place around 15 to 17 years of age.19,20

The goals of this study were (1) to investigate the patterns of dental agenesis in oligodontia and nonoligodontia, maxillary canine impaction and tooth transposition; (2) to determine whether congenital heart diseases and hypothyroidism are parameters involved in tooth agenesis; and (3) to raise awareness of the consequences of these aspects of the developing dentitions in patients with DS.

MATERIAL AND METHODS

The sample involved 126 subjects with DS, all referred to the Centre for Special Care Dentistry, CBT Rijnmond, in Rotterdam, The Netherlands, by general practitioners. About 50% of the patients had roentgenograms taken under general anesthesia. Twelve patients were eliminated because taking roentgenograms was impossible; 114 subjects remained for data analysis (47 female, 67 male). The age range was 9.5 to 23.9 years (mean, 15.9 years; SD, 4 years). Patients aged 9 years and older were included in this study because calcification can be late in those with hypodontia.21,22 From each subject, a standardized record was obtained, including a detailed clinical examination. Presence or absence of heart disease and hypothyroidism was recorded. Panoramic radiographs were taken, and written parental informed consent was obtained. If this was not possible, a standardized roentgen set was made. Third molars were not included. Permanent teeth that were hypoplastic or radiographically observed but not yet erupted were considered present. In addition to agenesis, maxillary canine and first premolar transpositions, and impaction of canines were determined.

Statistical analysis

The FDI numbering system was used.23 Absent teeth were registered by tooth number. In addition, the tooth agenesis code (TAC) was calculated.24 With the TAC method, it is easy to represent combinations of tooth agenesis per quadrant; especially, the combination TAC values expresses the severity of the hypodontia per quadrant and gives valuable information to enable a rapid estimate for treatment planning (Table). However, the TAC obscures the symmetry of absent teeth between quadrants. Symmetric absence of teeth can be better represented by the percentage of agenesis by tooth type for the oligodontia and the nonoligodontia groups (Figs 1 and 2). For descriptive statistics, cross tables and histograms were made. To test for relationships between dichotomous variables, the Fisher exact test was used. To explain the chance of a patient having oligodontia, or being without oligodontia (with some agenesis), logistic regression was used. Also, logistic regression was applied for the relationships between agenetic teeth and congenital heart disease and retarded thyroid function. To compare the number of missing teeth between jaws or quadrants, the Wilcoxon signed rank test was used. To compare the numbers of missing teeth between groups, the Mann Whitney U test was applied with SPSS statistical software (version 16, SPSS, Chicago, Ill).

RESULTS

The prevalence of agenetic teeth in our subjects (n = 114) is shown in Figure 3. A total of 236 teeth were missing, from 0 to 13 per patient (median, 1; quartiles, 0 and 3 missing teeth). Of the DS patients, 59.6%
had at least 1 agenetic tooth. *Figures 1 and 2* show the agenesis by tooth type as percentages of absent teeth in both jaws for the oligodontia (n = 13) and nonoligodontia (n = 101) groups. In the nonoligodontia group, 33 patients had congenital heart disease, with a tendency toward a negative correlation with agenetic teeth (*P* = 0.093; odds ratio [OR], 0.49; 95% CI, 0.21-1.13). A tendency toward a positive correlation was observed between retarded thyroid function (13 patients) and agenetic teeth (*P* = 0.060; OR, 3.71; 95% CI, 0.95-14.60). In the oligodontia group, there was no significant negative correlation between congenital heart disease (4 patients) and agenetic teeth, because of the small group (data not shown). In these 13 patients, no retarded thyroid function was seen. Impaction of 1 or 2 maxillary canines was seen in 13 patients in the group of 101 nonoligodontia patients. No impaction was seen in the oligodontia group. No relationship was found between this type of impaction and the absence of 1 or 2 maxillary lateral incisors (*P* = 0.75).

The 13 oligodontia patients with DS (8 male, 5 female) were responsible for 101 agenetic teeth, ranging from 6 to 13 per patient (median, 7; quartiles, 6 and 9). In this group, there was a significant difference between the numbers of missing teeth in the maxilla (61; range, 2-8) and the mandible (40; range, 2-7; *P* = 0.025). There was no statistically significant difference in the number of absent teeth between the right and left

*Fig 1.* Distribution of percentages of agenetic teeth by tooth type in patients with DS and oligodontia (13 patients, 101 absent teeth). *Solid bars* are symmetric absent teeth; *shaded bars* are solitary absent teeth.
sides of the face (maxilla plus mandible), the maxillary right and left quadrants, and the mandibular left and right quadrants ($P = 0.453, 0.180, \text{ and } 1.00$, respectively). No impaction of canines was seen.

The nonoligodontia group contained 101 patients (59 male, 42 female). They were responsible for 135 agenetic teeth, ranging from 0 to 5 per patient (median, 1; quartiles, 0 and 3). There was no statistically significant difference in the number of agenetic teeth between the sexes ($P = 0.721$). No significant differences were seen in the numbers of absent teeth between the 2 jaws ($P = 0.755$), between left and right sides of the face ($P = 0.128$, or between the mandibular quadrants ($P = 1.00$). However, there was a statistically significant difference between the maxillary right (38 missing teeth) and left (29 missing teeth) quadrants ($P = 0.05$). When tooth numbers 31 and 41 were both agenetic in a child with DS, a positive relationship was obtained with oligodontia ($P = 0.001$; OR, 38.8; 95% CI, 8.66-173.79). This relationship was not seen for the combination of teeth 32 and 42 ($P = 0.228$; OR, 0.52; 95% CI, 2.88-16.04).

In the group with oligodontia, the most striking feature was that symmetric absence of teeth—absence in left-right symmetrical pairs—was more prevalent than solitary absence (Fig 1). Of the 101 agenetic teeth, only 10.9% were solitarily absent. The maxillary lateral incisors were most often symmetrically absent, closely followed by the second premolars in both jaws. The mandibular central incisors followed next and then the

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**Fig 2.** Distribution of percentages of agenetic teeth by type in patients with DS without oligodontia (101 patients, 135 absent teeth). Solid bars are symmetric absent teeth; shaded bars are solitary absent teeth.
maxillary second molars. Whereas symmetric absence of the maxillary canines was found, this was not the case in the mandible. In the maxilla, combination TAC 18 (27%) and 82 (23.1%) were the most common patterns (Table). TAC 18 represents a situation where the second premolar and the lateral incisor in the same quadrant are both absent; when the maxillary second molar is also absent, it is TAC 82. In the mandible, combination TAC 17 (26.9%) was found (absence of the second premolars and the central incisor). In the nonoligodontia group also, there was a pattern of symmetrical absence (Fig 2). The frequency of missing maxillary lateral incisors was higher, followed by the mandibular second premolars and the maxillary second premolars. Notable was the general absence of combination TAC scores; only TAC 18 was found more than once (6 times) in the maxillary right quadrant. In the mandible, combination TACs were completely absent.

Three patients had transpositions of a canine and first premolar, and 1 patient had fusion of the first and second premolars, all in the maxilla. The nonoligodontia group had no symmetric absence of maxillary first premolars and canines. In contrast, symmetrical absences of the mandibular canines and lateral incisors were found at higher frequencies than in the oligodontia group. In the nonoligodontia group, solitary absence of teeth (21 times in the maxilla and 15 times in the mandible) was more prevalent than in the oligodontia group.

DISCUSSION

Our finding of agenetic teeth (hypodontia) in 59.6% of the total DS group (n = 114) completely agrees with the prevalence of hypodontia (53.5%-63%) in recent studies of DS populations in different countries and was higher than in a study of an orthodontic population (38.6%). Variations in severity depend on the populations studied but also on variability in the categorizations of agenetic teeth. Our groups with oligodontia (n = 13) and nonoligodontia (n = 101) had different patterns in amounts and locations (Figs 1 and 2). In the nonoligodontia group, the frequencies of symmetrically agenetic maxillary lateral incisors and mandibular second premolars were higher compared with the maxillary second premolars; this pattern was the same as in other reports. These late-developing teeth, forming over longer periods of time, might be more susceptible to the effects of hypothyroidism. Threshold values required for the development of teeth might not be reached on time in children less than 5 years old, a time window that is observed in cancer treatment. Solitary absence of teeth (21 times in the maxilla and 15 times in the mandible) was more prevalent compared with the oligodontia group. In patients with DS and hypothyroidism, some are more affected than others, resulting in differences in effects and minor delays in timing during tooth development. Solitary absence of teeth can be the result. Notable was the general absence of combination TAC scores indicating a mild form of hypodontia. Describing patterns of tooth agenesis with combination TAC scores appeared to be a valuable method for discriminating mild from severe hypodontia (oligodontia). Only TAC 18 was found 6 times in the maxillary right quadrant in the nonoligodontia group, the site with significantly more agenetic teeth. This observation contrasted with the findings of
Russell and Kjaer, who found more agenetic teeth on the mandibular left side. The prevalence of oligodontia in our group was 11.4%, a factor 81 times higher than estimated in a white population, at 0.14%. Only 10.9% of the 101 agenetic teeth were solitarily absent. The most frequently symmetrically absent teeth were the maxillary lateral incisors. They were closely followed by the second premolars in both jaws, and the mandibular central incisors and the maxillary second molars. The latter were always absent in combination with other teeth (represented in TAC value 82), indicating a more severe tooth agenesis pattern, with more need for extensive treatment. TAC values 18 (27%) and 82 (23.1%) were the most common patterns in the maxilla. TAC 17 (26.9%) showed the highest prevalence in the mandible. In the maxilla, significantly more teeth were missing than in the mandible, a finding that agreed with others. In this group, a more fully developed symmetric pattern with more agenetic teeth and more combinations of agenetic teeth (TAC values) were found in the maxilla, with fewer solitarily absent teeth, than in the nonoligodontia group (Figs 1 and 2). Taken together, in the oligodontia group, in addition to quantitative differences, there were also qualitative differences. This indicated that they are a subgroup with a different phenotype. Yet unidentified genes alone or combined with other genes could play a role. Further research in a larger group of oligodontia patients with DS is necessary to determine interactions between genotype and phenotype. The genetic influence on dental agenesis is expected to dominate the environmental factor (if a tooth is already absent because of the gene, there can be no additional effect of the environment—eg, hypothyroidism). The nonoligodontia group had higher frequencies of agenetic mandibular canines and lateral incisors. In the absence of combination TAC scores (indicating solitarily absence of, for example, 43, 42, or 41 in the quadrant), tooth agenesis could occur through small variations in environment such as hypothyroidism. The absence of lateral incisors agrees with other findings (5.3%-9%). The absence of canines is rare, especially mandibular canines. Yet, absence of canines is a regular finding in patients with DS (low percentages). When teeth 31 and 41 were both absent, there was a considerable chance for the patient to develop oligodontia (logistic regression, $P = 0.001$). This result should provide an important reason for dental practitioners to make roentgen graphs at an early age for necessary treatment planning.

Thyroid deficiency can lead to delayed and prolonged proliferation of cells of the nervus trigeminus, resulting in a decreased rate of neuron production. This might explain the variety of agenetic front teeth. We suggest that the outgrowth of various small nerve branches is not timely. Dental trigeminal nerve fiber growth and patterning are strictly integrated with tooth morphogenesis. Failure of the nerve to establish the lingual branch can result in the absence of the mesenchymal dental follicle. This is the result of local epithelial-mesenchymal interactions. Such interactions can also be seen in trisomic Ts 16 mice with a small dental organ with hypoplastic nerves not housed in a well-defined bony canal. A small nervus plexus in variable intramandibular canals has also been reported.

In this study, 13 patients with DS (11.4%) were responsible for 19 impacted canines, a result (with no sex difference) between the findings of others (5.9%-15%). Several conditions predispose to impaction, such as delayed resorption of the deciduous canine, ectopic position of the germ, or a narrow maxilla. Impaction of maxillary canines often goes with agenetic or peg-shaped maxillary lateral incisors. However, we found no significant relationship between impaction of the maxillary canines and agenetic maxillary lateral incisors. We found no proof that the root of the lateral incisor would guide the canine during eruption. Rather, the lateral incisors might be responsible for yet more crowding in a small maxilla. Since there is no room, impaction of these late calcifying canines results. When no crowding of teeth occurred, as in the oligodontia group, no impaction of maxillary canines was observed. When the maxilla is already underdeveloped from birth, successor teeth compete for room (Fig 4); delayed eruption can further contribute to impaction. Thyroxine plays an important role in eruption. Accelerated eruption was seen in a boy with DS and hypothyroidism treated with...
vascular endothelial growth factor (VEGF) is located at the cytoplasmic calcium-binding protein NFATc1, which is a transcription factor of valve endothelial cells. Also, there is negative feedback control of VEGF and NFATc1 through NFATc1-mediated repression of VEGF expression. Restricted and tightly regulated patterns during discrete windows of time orchestrate this complex process. During deciduous tooth development at the cap stage in the human fetus (16-32 weeks), blood vessels are intensely positive for VEGF and its receptor VEGF-R2. Positive expressions were also observed in the inner enamel epithelium and the odontoblast layers. VEGF also promotes proliferation, survival, and axonal outgrowth of nerve cells, illustrating the presence of reciprocal paracrine control between nerves and vascular cells.

Children with congenital heart disease have elevated systemic levels of serum VEGF. We suggest that elevated levels of VEGF expression with diminished NFATc1 transcription during the correct time window will be favorable for angiogenesis and organogenesis of the tooth germ in development, resulting in fewer agenetic teeth in patients with DS and congenital heart disease.

The tendency of a negative correlation between congenital heart disease and agenetic teeth was an unexpected finding. The vascular and cardiac morphogenic defects most often found in patients with DS are the cardiac-cushion defects. Nuclear factor of activated T-cells cytoplasmic 1 (NFATc1) is a transcription factor required for heart valve formation. NFAT is dysregulated in patients with DS and is located at the DSCR1. Vascular endothelial growth factor (VEGF) is an upstream regulator of calcineurin signaling and NFATc1 activation, resulting in increased proliferation of valve endothelial cells. Also, there is negative feedback control of VEGF and NFATc1 through NFATc1-mediated repression of VEGF expression. Restricted and tightly regulated patterns during discrete windows of time orchestrate this complex process. During deciduous tooth development at the cap stage in the human fetus (16-32 weeks), blood vessels are intensely positive for VEGF and its receptor VEGF-R2. Positive expressions were also observed in the inner enamel epithelium and the odontoblast layers. VEGF also promotes proliferation, survival, and axonal outgrowth of nerve cells, illustrating the presence of reciprocal paracrine control between nerves and vascular cells.

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The tendency of a positive correlation between retarded thyroid function and agenetic teeth in the nonoligodontia group of patients with DS has not been reported before. Neonatal screening of children with DS showed that they have a specific thyroid (regulation) disorder that is unfavorable for brain growth and development. In rats, absence of the thyroid hormone, thyroxine, during odontogenesis results in smaller teeth. This is due to a decrease in the vascularization of dental structures with hampered proliferation and histo-differentiation of the epithelial tissues. The organogenesis of the permanent dentition starts in the 20th week of gestation, when nerve growth is critical and retardation is becoming evident in the embryo with DS. If hypothyroidism starts in this period and continues during the long period of tooth formation (22 years), this could well explain the microdontia in their permanent dentitions. In contrast, deciduous teeth in patients with DS are larger compared with those of patients without DS. In week 7 in utero, the fetus depends entirely on thyroxine of maternal origin. During the formation of the placodes for the deciduous enamel organ, the development of critical pathways is extremely sensitive to the triplicate gene-dosage effect of chromosome 21. A sufficient supply of thyroxine in that period together with the gene-dosage effect (factor 1.5) might result in larger deciduous teeth in patients with DS.

Obviously, analyses yielding results that are not statistically significant are a problem to the researcher. Ideally, a study should be designed to have sufficient power to ensure that “lack of statistical significance” is more or less the same as “a meaningful difference is not to be expected.” However, in this study, with a specific patient group, a sample size with ample statistical power could not be realized. This implies that, when no statistically significant difference is found, there is still room for a sizeable difference. Therefore, in this article, we intended to give the reader as much information as possible. Specifically, this means not only P values, but also estimates of the effects under study and 95% CI values of these effects. By doing so, we hope to eliminate the threat that is, especially in smaller studies, always present: that “difference not found” is translated by the reader into “it was found that no difference is present.”

The DSCR1 gene, also known as modulatory calcineurin-interacting protein 1, encodes a regulatory protein in the calcineurin-NFATc1 signal transduction pathway. DSCR1 expression in the developing endocardium is controlled by calcineurin-NFATc1 to ensure a proper feedback mechanism. However, DS is 1.5 times overexpressed in patients with DS; this leads to dysregulation, resulting in the well-known features of DS, often with the characteristic heart defects. The negative feedback of VEGF-NFATc1 through NFATc1 to repress VEGF might not take its proper course. Hence, favorable conditions with, for example, elevated VEGF values could be present during odontogenesis, resulting in no dental agenesis. The first steps for further research would be to increase the numbers of subjects with DS in a study and relate the different types of congenital heart diseases to the pattern of agenesis.

Neonatal screening of babies with DS showed that they have a specific thyroid regulation disorder: subclinical hypothyroidism with low-normal concentrations of thyroid hormone and high thyroid stimulating hormone. In some instances, this develops into real hypothyroidism. When threshold values required for the development of teeth are not reached on time in children.

Maxillary canine-premolar transpositions were observed in 3 patients (2.6%); twice in the left and once in the right jaws. This prevalence was too low to claim a genetic predisposition in patients with DS (Shapira et al). The tendency of a negative correlation between congenital heart disease and agenetic teeth was an unexpected finding. The vascular and cardiac morphogenic defects most often found in patients with DS are the cardiac-cushion defects. Nuclear factor of activated T-cells cytoplasmic 1 (NFATc1) is a transcription factor required for heart valve formation. NFAT is dysregulated in patients with DS and is located at the DSCR1. Vascular endothelial growth factor (VEGF) is an upstream regulator of calcineurin signaling and NFATc1 activation, resulting in increased proliferation of valve endothelial cells. Also, there is negative feedback control of VEGF and NFATc1 through NFATc1-mediated repression of VEGF expression. Restricted and tightly regulated patterns during discrete windows of time orchestrate this complex process. During deciduous tooth development at the cap stage in the human fetus (16-32 weeks), blood vessels are intensely positive for VEGF and its receptor VEGF-R2. Positive expressions were also observed in the inner enamel epithelium and the odontoblast layers. VEGF also promotes proliferation, survival, and axonal outgrowth of nerve cells, illustrating the presence of reciprocal paracrine control between nerves and vascular cells.

Children with congenital heart disease have elevated systemic levels of serum VEGF. We suggest that elevated levels of VEGF expression with diminished NFATc1 transcription during the correct time window will be favorable for angiogenesis and organogenesis of the tooth germ in development, resulting in fewer agenetic teeth in patients with DS and congenital heart disease.

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less than 5 years old, tooth agenesis results. Late-developing teeth, forming over longer periods of time, such as second premolars, are susceptible to the effects of hypothyroidism, and agenetic teeth can result. The first step in further research would be to precisely document the onset of hypothyroidism, the doses of medication, and the teeth that were affected.

CONCLUSIONS

We found that several parameters contribute to the prevalence of agenetic teeth. This information contributes to improved decision making and treatment planning for a young child with DS, and could provide lifelong benefits.

1. Oligodontia in patients with DS defines a subgroup with a different phenotype. A higher percentage (81 times) was found compared with a normal population. Further research on oligodontia in a larger group with DS is necessary to characterize the unique phenotype.

2. When teeth 31 and 41 are both absent, there is a considerable chance for the patient to develop oligodontia ($P = 0.001$; $OR = 38.8$).

3. With congenital heart disease in the nonoligodontia group, fewer agenetic teeth were expected ($P = 0.093$; $OR = 0.49$; 95% CI, 0.21-1.13).

4. With hypothyroidism in the nonoligodontia group, more agenetic teeth can be expected ($P = 0.060$; $OR = 3.71$; 95% CI, 0.95-14.60).

5. There is no relationship between the absence of 1 or 2 maxillary lateral incisors and impacted canines ($P = 0.75$).

6. The patterns of hypodontia differ in the groups with and without oligodontia.

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