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Maturation of teeth adjacent to dental agenesis site

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Abstract

Objective. The purpose of this study was to evaluate the developmental stage of teeth adjacent to the agenesis site in comparison to their antimeres. ***Materials and methods.*** Panoramic views of 39 patients with unilateral dental agenesis and 42 normal controls were evaluated. The dental developmental stage (normal or delayed) of the teeth adjacent to the agenesis site was determined for each patient using the Haavikko's method, while the overall dental age was determined by Becker's method. ***Results.*** No statistically significant difference was found in the developmental stage of teeth adjacent to the agenesis, compared to their antimere and to the same teeth in the normal control group. However, the prevalence of cases with no difference in development was almost double for the tooth distal to the agenesis site compared to the tooth mesial to the agenesis site in the hypodontia group (84.6% distal and 43.6% mesial; $p < 0.001$) and in the control group (83.3% distal and 52.4% mesial; $p < 0.002$). In most of the cases the tooth distal to the agenesis site was the 1st permanent molar. ***Conclusions.*** (1) No difference was found between the developmental stage of teeth adjacent to the agenesis site and their antimeres. (2) Teeth mesial to the agenesis site showed some delay in development compared to teeth distal to the agenesis site, in this study. (3) The 1st molars, which were in most of the cases the distal adjacent tooth to the site of agenesis, showed developmental stability. (4) Additional longitudinal studies are needed to examine the dental developmental pattern in patients with agenesis.

Key Words: *dental agenesis, dental developmental stage, dental age, antimere*

Introduction

Dental agenesis (DA) is the failure of tooth bud development, causing definitive absence of the tooth. It is the most common dental anomaly, affecting up to one-quarter of the general population [1], and is frequently associated with other dental anomalies such as microdontia, reduction in tooth size and/or malformation of other teeth. DA is included in the DAP (Dental Anomaly Pattern) recently summarized by Peck [2]. This well-established generalized phenomenon is accompanied by a reduced crown size in individuals with missing teeth [3,4] and, according to Garn et al. [5],a delayed tooth formation pattern takes place when one or more teeth are absent [5]. However, other authors found either no significant difference in the eruption timing of the teeth in patients with dental agenesis compared with a control group [6] or a delay of a few months that was not statistically significantly different [7].

Uslenghi et al. [8] suggested a localized pattern of delay, as indicated by delayed development of the teeth adjacent to the agenesis site, while Daugaard et al. [9] found that agenesis is associated with changes in maturation pattern within the developmental fields (like canine/premolar fields), although not necessarily with changes in other fields.

Although environmental factors can contribute to the phenotype of DA (multifactorial forms), in the majority of the cases it is inherited as an autosomal-dominant trait [10]. Its main cause is related to abnormal function of specific genes which play key roles during odontogenesis, particularly MSX1 and PAX9. Hundreds of genes are known to directly or indirectly be involved in the regulation of tooth development; however, mutations in these two genes appear to be more prevalent among affected individuals [10]. This may provide an explanation not only for the wide variety in agenesis patterns but also for

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associations of dental agenesis with other dental and oral anomalies [11,12].

Nonetheless, fluctuating asymmetry [13] in the normal population should be taken into consideration when comparing tooth development of both sides of the jaw. This is due to the fact that the presence of fluctuating asymmetry may obscure other differences in the developmental stage between the two sides.

Thus, the aims of this study were to (a) evaluate the dental developmental stage of an individual's permanent teeth adjacent to the agenesis site; (b) compare them to their antimeres (teeth on the contra-lateral side of the jaw—internal control), where no DA was observed; and (c) compare the bilateral dental development staging differences of individuals with DA to the normal control group (external control).

Materials and methods

Subjects

A total of 81 patients were recruited from the Orthodontic department in the HU-Hadassah SDM and a private orthodontic practice. The panoramic views of two groups of patients prior to orthodontic treatment were utilized.

DA group (n = 39). This group comprised patients mostly with one congenitally missing tooth per quadrant, provided that: (1) The adjacent permanent teeth within the quadrant were present; and (2) The antimere and its adjacent teeth were present.

Third molars were disregarded in this study due to their large variability. The central incisors and second molars were excluded since they do not have two adjacent teeth in the same quadrant. The antimere of the missing tooth and the two adjacent teeth, one on each side of the unaffected contra-lateral side, were evaluated (internal control).

Control group (external control) (n = 42). This group comprised individuals who were candidates for orthodontic treatment, with all teeth present, matched for chronological age.

Inclusion criteria for both groups were:

(1) No craniofacial and dental malformations (except agenesis in the DA group);
(2) Dental age prior to completion of the root development of the relevant teeth, i.e. the teeth adjacent to the site of absence before reaching the 'apex closure' stage;
(3) Good quality panoramic views, which allowed clear determination of the root developmental stage; and
(4) All relevant teeth were intact and without restorations.

Methods

Chronological age and gender were collected for participants in both groups and the number and type of missing teeth for the DA group were recorded.

All assessments were performed in three clusters: (1) the side with dental agenesis in the DA group; (2) the contra-lateral side in the DA group (internal control); and (3) the intact control group, both sides (external control).

The developmental stages of individual teeth adjacent to the agenesis site were assessed according to Haavikko's [14] method and compared with those of their antimeres (internal control). For example: if a maxillary lateral incisor was missing, the stage of development of the maxillary central incisor and the maxillary canine in that quadrant were compared with the corresponding teeth on the contra-lateral side.

Haavikko's [14] method is based on a study that was conducted in 1970, in which cross-sectional data from dental panoramic tomographs of 1162 Finnish children (615 boys and 547 girls), between the ages of 2–21 years, were used to assess 12 stages of tooth formation. Six of the stages relate to crown formation and six to root formation, with Stage 0 allocated to the appearance of a crypt of a tooth. Separate illustrations were given for single rooted and molar teeth. Maxillary and mandibular permanent teeth were considered separately, with the results from the right and left sides of the jaw combined. Third permanent molars were included and no score was allocated for missing teeth. In order to evaluate the possible influence of fluctuating asymmetry in normal dental development as it may appear in the external control group, the developmental stages (Haavikko's [14] method) of central incisors, canines, first premolars and first molars in both jaws were evaluated. The teeth selected for comparison matched the teeth adjacent to the sites of agenesis in the DA group and were referred to as 'mesial to agenesis' and 'distal to agenesis'.

The mean degree of tooth development by Haavikko's [14] staging of all 'mesial and distal teeth to the agenesis' were calculated and compared within the groups, i.e. DA side and antimeres in the study group and the two sides of the external control group. In addition, a comparison was also performed between the study group (DA) and the external control group.

In order to blind the investigator as to the origin of the teeth (DA side/intact side in the agenesis group or control group), the following procedure was adopted. The panoramic views were evaluated on a viewer in a dark room and were divided into right and left sides by alternate blocking of one side of the roentgenogram. The relevant teeth (the teeth mesial and distal to the site of agenesis and their antimeres) were manually traced on two separate sheets of tracing paper and

each tracing, for the right and left side, was coded independently.

The investigator then determined the dental developmental stage for individual teeth on each half-roentgenogram tracing, in random order. The determinations were performed twice within 3 weeks. The final score was obtained by calculating the mean of the two determination scores, provided the difference between them did not exceed one developmental stage. If the difference between the two scores was higher than one stage, a third determination was attempted with the help of one of the co-authors (IB) and the mean of the two closest scores was used.

Calibration. A calibration procedure was performed prior to scoring the radiographs. The examiner (DB) completed a series of recurrent determinations with another co-author (IB).

Overall dental developmental age (DDA). The DDA was recorded based on Becker's [15] method [16]. In this method, the overall dental developmental age is determined according to the combined basis of timing of eruption compared to standards and individual tooth development.

Statistics

The sample size was established based on the assumption that in 70% of the DA group the dental development of the teeth adjacent to the agenesis site will be retarded when compared with the contra-lateral side without DA (internal control), by at least one stage [8]. According to the sign test at least 37 patients were found to be included in the DA group when alpha is 5% and the power is 80%.

Cohen's Kappa value was calculated in order to indicate the extent to which agreement on tooth stage assessment exceeded chance agreement.

The chronologic age and DDA and the degree of development by Haavikko's [14] staging were assessed by Mann-Whitney U-test between the groups and within each group by Wilcoxon signed-rank test.

Developmental difference between the mesial and distal sites of agenesis was compared using the Chi square test.

Results

The reproducibility of the tooth stage assessment evaluated using the Kappa test for the repeated measurements was 0.84, indicating very good agreement.

The distribution of the missing teeth excluding the 3rd molars is presented in Figure 1. The absence of the second premolars (mandibular and maxillary) was most prevalent, followed by the maxillary lateral incisors. In most of the cases (60%) only one tooth per patient was missing.

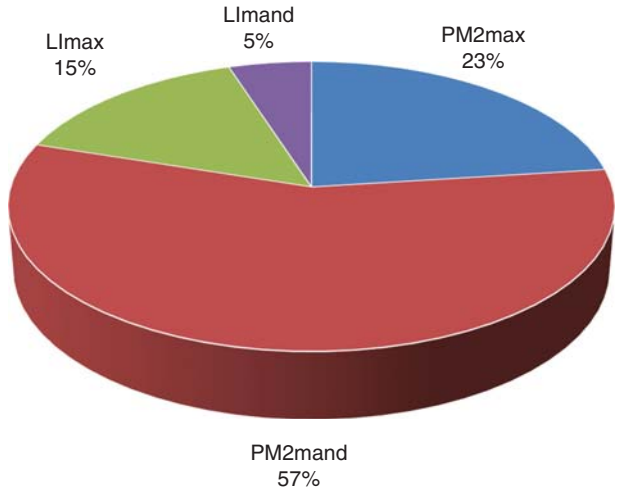

Figure 1. Distribution by tooth type of the DA in the experimental group. PM2mand, mandibular second premolar; PM2max, maxillary second premolar; LImand, mandibular lateral incisor; LImax, maxillary lateral incisor; PM1mand, mandibular first premolar.

The distribution of the patients by chronological age, DDA and gender is presented in Table I. No statistically significant difference was found between the chronologic and DDA and between the genders within each group and between the DA group and the external control group.

The comparison of individual dental developmental stages mesial and distal to the agenesis site is presented in Table II. The frequency of asymmetric teeth development in the DA and external control groups was not statistically significant both for the tooth mesial ($p = 0.429$) and for the tooth distal ($p = 0.875$) to the agenesis site. An examination of the developmental stages of the individual teeth adjacent to the agenesis site and comparing them to the contra-lateral intact side showed that they seldom exceeded one developmental stage. Two developmental stage differences were found only in one case of the DA group mesial to the agenesis of a maxillary second premolar (Figure 2A). In the external control group the highest inconsistency found in the comparison between the two sides was only one developmental stage.

The prevalence of cases with and without bilateral developmental differences is presented in Table III. When evaluating the intra-group differences in the dental development stage adjacent to the agenesis site, the percentage of cases where no difference was found was almost double for the tooth distal to the agenesis site (84.6%), compared to the tooth mesial to the agenesis site (43.6%) ($p < 0.001$) in the DA group. Consequently, the prevalence of asynchronic development (late or early) of the teeth distal to the agenesis site (15.4%) was significantly lower ($p = 0.031$)

Table I. Distribution of the patients groups by gender and chronological age and DDA (Becker) in the DA and the external control.

	DA group			Control group		
Group	*n*	Mean chronological age (SD)	Mean DDA (SD)	*n*	Mean chronological age (SD)	Mean DDA (SD)
Boys	24	9.9 (±2.3)	9.5 (±2.1)	21	9.8 (±1.3)	9.7 (±1.9)
Girls	15	10.1 (±2.2)	10.1 (±2.1)	21	9.7 (±1.8)	9.9 (±2.2)
Total	39	10.0 (±2.3)	9.7 (±2.1)	42	9.7 (±1.6)	9.8 (±2.0)

than that on the mesial side (56.4%) in the DA group (Table III). A similar and statistically significant finding was detected in the external control group ($p = 0.002$, Table III).

There was no statistically significant difference between the DA group and the external control group on both sides in the mean degree of tooth development when referring to the whole sample (Table IV) and when analyzing only the participants who presented missing second premolars (Table V).

Discussion

This study on dental agenesis focused on dental development of individual teeth adjacent to the agenesis site, in comparison to their antimeres, while other parameters such as overall dental age (DDA) were examined as well.

The mean chronological age of the DA group (9.97 years) in our study paralleled a developmental period for which one can assert, with relative confidence, that the determination of absence of a tooth bud is final. This, however, resulted in a relatively mature study group of patients which consequently presented some limitation to our study; namely, the developmental stage of the examined teeth relatively approximated root closure.

The chronological age and the overall DDA of the external control group were similar to each other and to those of the DA group (Table I). This similarity could be explained by the fact that the DA group consisted of patients with only a few missing teeth, and in most cases only one missing tooth. In such cases the possible effect of overall developmental delay, if present, might be limited, in contrast to situations with multiple congenitally missing teeth.

In this study the developmental stages of individual teeth were assessed according to Haavikko's [14] method. Several other methods of assessment of the dental developmental stage were published, including those suggested by Nolla [17], Demirjian and Goldstein [18], Williems et al. [19] and Cameriere et al. [20]. However, Haavikko's [14] 12 stages technique was chosen because the accuracy of the dental developmental stage was crucial in this study, which aimed to assess the developmental stage of teeth adjacent to the agenesis site in comparison to their antimeres. Recent scientific literature has advocated that Haavikko's method has been found to be more accurate compared to the other methods mentioned [21–24].

Although tooth agenesis is associated with a wide variety of alterations in the size, morphology and developmental timing of the remaining teeth, Odagami et al. [7] reported insignificant differences in DDA compared with the normal control group, probably due to diverse DA cases that were included in their study. This was confirmed by Ruiz-Mealin et al. [12] who found that, for every additional absent tooth, the dental age was delayed by 0.13 years. In our study, perhaps no significant delay was found in the overall DDA in the DA group compared to the external control group, because the DA group consisted of patients

Table II. Bilateral developmental differences in the DA group and in the external control group (by Chi Square test).

	Tooth mesial to agenesis site				Tooth distal to agenesis site			
	DA group		External control group		DA group		External control group	
Developmental difference	*n*	%	*n*	%	*n*	%	*n*	%
No difference*	17	43.6	22	52.4	33	84.6	35	83.3
Difference present—accelerated development**	10	25.7	15	35.7	2	5.2	4	9.5
Difference present—delayed development***	12	30.7	5	11.9	4	10.2	3	7.2
p-value	$p = 0.429$				$p = 0.875$			

* Tooth adjacent to DA presented with same developmental stage as its antimere.
** Tooth adjacent to DA presented with accelerated development compared to its antimere.
*** Tooth adjacent to DA presented with delayed development compared to its antimere.

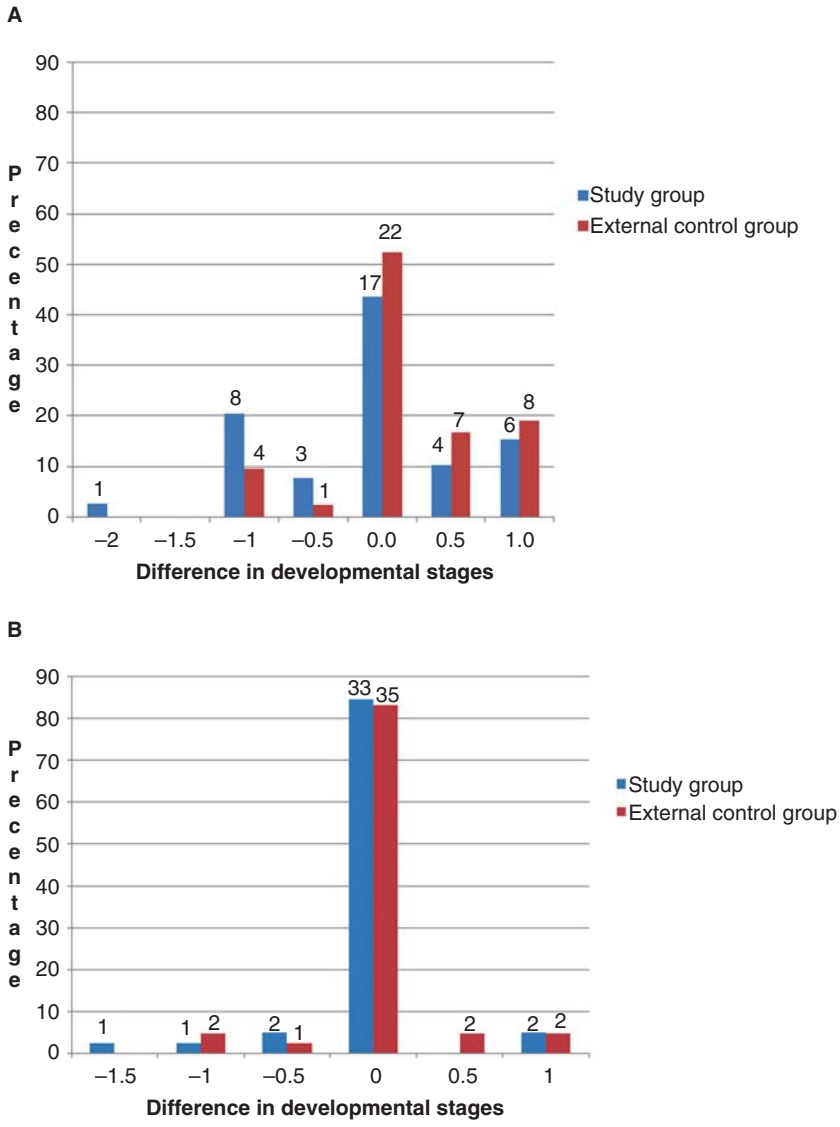

Figure 2. Distribution of the bilateral developmental differences of individual teeth: (A) Mesial to the agenesis site. (B) Distal to the agenesis site. The digits in the graph represent the number of teeth in each column.

with only several missing teeth (in most cases only one missing tooth), and thus the possible delay was not expressed.

Looking at the developmental stage of individual teeth adjacent to the agenesis site in comparison to the unaffected dentition, differentiation should be made between external and internal controls as well as between sites mesial and distal to agenesis. The employment of an internal control enables a differentiation between local influences on the timing of dental development in contrast to a general influence which can be studied by employing an external control.

Garn et al. [5], in their classical paper, stated that 'It is now more than evident that reduction in tooth number (hypodontia) is associated with a wide variety of alterations in the size, morphology and developmental timing of the remaining teeth'. Thus, although in our study no significant difference was found in the total DDA between the DA group and the external control (Table I), some tendency toward developmental delay could be ascertained in the DA patients (Table II). Breaking down the cases with developmental differences into early and late development, we found an even distribution within the mesial and distal sites of agenesis in the DA group, while in the External control group early development prevailed in teeth mesial to the agenesis site (Table II and Figures 2A and B). A similar attempt to compare the developmental stage of teeth adjacent to the agenesis site and the homolog teeth in an external control group was undertaken by Uslenghi et al. [8],who used the same methodology of Haavikko [14] to assess the developmental stages of the individual teeth as we used in our study. They found a statistically significant difference between the two groups, with the dental agenesis group demonstrating a mean delay in dental development of 1.51 years (±1.37 years).

Table III. Prevalence of cases with and without bilateral developmental difference: comparison of teeth mesial and distal to the agenesis site with their antimeres in the DA group and within the external control group (by Chi-Square test).

	DA group				External control group			
	Mesial		Distal		Mesial		Distal	
Developmental difference	*n*	%	*n*	%	*n*	%	*n*	%
No	17	43.6	33	84.6	22	52.4	35	83.3
Yes	22	56.4	6	15.4	20	47.6	7	16.7
p-value	$p < 0.001$				$p = 0.002$			

Table IV. Comparison of mean degree of tooth development according to Haavikko's [14] staging (by Mann-Whitney U and Wilcoxon signed-rank tests).

	DA group ($n = 39$)	External control group ($n = 42$)	*p*-value between DA and external control groups
Mesial to the missing tooth (SD)	9.51 (±1.58)	9.73 (±1.45)	0.646
The antimere tooth (internal control) (SD)	9.42 (±1.75)	9.89 (±1.27)	0.375
p-value within each group	0.430	0.101	
Distal to the missing tooth (SD)	11.06 (±1.46)	10.70 (±1.40)	0.116
The antimere tooth (internal control) (SD)	11.02 (±1.49)	10.71 (±1.39)	0.170
p-value within each group	0.595	0.862	

Table V. Comparison of mean degree of tooth development according to Haavikko's [14] staging, only in participants presenting missing second premolars.

	DA group ($n = 31$)	External control group ($n = 28$)	*p*-value between DA and external control groups
Mesial to the missing tooth (SD)	9.13 (±1.46)	9.04 (±1.11)	0.783
The antimere tooth (internal control) (SD)	9.00 (±1.64)	9.38 (±1.09)	0.302
p-value within each group	0.361	0.004	
Distal to the missing tooth (SD)	11.61 (±0.85)	11.36 (±1.09)	0.318
The antimere tooth (internal control) (SD)	11.66 (±0.67)	11.39 (±1.03)	0.248
p-value within each group	0.325	0.573	

The delay was greater for teeth adjacent to the site of agenesis and in subjects with increased severity of dental agenesis. This, however, cannot indicate the definite influence of a local factor, since a general factor could be involved as well, as long as only an external control is used.

A comparison of the developmental differences between the teeth adjacent to the agenesis site and an internal control of the antimeres was performed in our study for the whole sample and only for those who presented missing second premolars (as they were the majority of missing teeth in this study). Since a similar degree of mean tooth development was found in the DA and control groups in both comparison sets (Tables IV and V), it seems that a generalized delay could not be determined in our study group, supporting Odagami et al. [7] findings. However, seemingly there is no sufficient evidence today to clearly distinguish between local and general factors in dental development and definitive conclusions cannot be reached in this study.

Comparing the developmental differences on the mesial and distal sites to agenesis within the DA group, and the matching teeth in the external control group, revealed that the prevalence of asynchronic development (late or early) of the teeth distal to the agenesis site was significantly lower than that on the mesial side in the DA group and the external control ($p = 0.001$ and 0.002, respectively; Table III). Specifically, most of the teeth distal to the agenesis site (84.6%) and their matched external controls (83.3%) presented the same developmental stage

bilaterally. It should be pointed out that most of the missing teeth in our study (78%) were second premolars (mandibular and maxillary, Figure 1) and, consequently in most cases, the distal adjacent tooth was the first molar. Thus, a possible explanation for the different developmental behavior could be based on Butler's [25] field theory. Since the first and the second mandibular premolars belong to the same developmental field, the agenesis of the second mandibular premolar (the most prevalent missing tooth in our study) might have led to a developmental delay of the first premolar compared to dentitions without agenesis. However, the adjacent first mandibular molar belongs to another developmental field and as such is not related to the agenesis field. Furthermore, Dahlberg [26] referred to the most stable tooth in each field as the 'key tooth', i.e. the first within each tooth class (incisors, canines, premolars and molars). Those teeth showed the least phenotypic variation in size and symmetry [27]. The developmental antimeric stability of the first molars in our findings can be explained also by this concept.

Conclusions

(1) No difference was found between the developmental stage of teeth adjacent to the agenesis site and their antimeres.
(2) No difference was found in the dental developmental stage between individuals with DA and normal controls matched by age.
(3) Teeth mesial to the agenesis site exhibit a somewhat delayed developmental stage compared to those distal to the agenesis site in the clinical material employed in this study.
(4) The 1st molars, which were in most cases the distal tooth adjacent to the site of the agenesis, presented developmental stability.
(5) Additional longitudinal studies with younger patients and larger groups are needed to examine the dental developmental pattern in patients with agenesis.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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