Tooth agenesis and dental development in a Spanish population: a retrospective cross-sectional study

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Abstract

Background The purpose of this retrospective cross-sectional study conducted in a Spanish population, was to determine whether dental development is delayed in paediatric patients with agenesis. The comparative analysis of the average difference between chronological and dental age was carried out to assess the validity of maturation tables for the Spanish population. The study examined the potential influence of the following variables: sex, number of agenesis, location of the agenesis.

Results The study analysed a total of 114 panoramic radiographs, from children aged 5 to 16 years, with a mean age of 9.4 years (+/- 2.5 SD). The case group included 53 radiographs (26 boys and 27 girls with agenesis); the control group included 61 panoramic radiographs (27 boys and 34 girls without agenesis). Dental age was assessed applying Demirjian's method and specific maturation tables for the Spanish population. The mean age estimated using the Demirjian method for the Spanish population was lower than the chronological age of the sample in all groups (mean dental age: 9.054, mean chronological age: 9,354). The difference between chronological and dental age in the global sample was significantly delayed. The global difference was 0.3 years (0.2852 years in the girls group and 0.3151 years in the boys group respectively).

Conclusions Dental development in the studied sample representing Spanish population, is notably more delayed in children with agenesis, particularly among girls, despite earlier development. Dental development occurred earlier than expected. Dental development was studied using Demirjian's method with conversion tables for the Spanish population. Imprecise data was obtained in patients with agenesis as chronological age did not correspond to dental age. However chronological and dental age difference was minimal in patients without agenesis, determining the validity of the maturation tables for the Spanish population in this group of patients. Ultimately, the study concluded that later dental development of children with agenesis is influenced by gender, number of agenesis and location (posterior, lower).

KEYWORDS Age estimation, dental age, tooth development, Demirjian's method.

Background

Dental agenesis

Dental agenesis is a genetically determined heterogeneous disorder, manifesting as the congenital absence of one or more teeth [Meade and Dreyer, 2023; Vastardis, 2000]. One or more primary or permanent teeth are absent, due to the lack of formation or development of dental germs. There is a clinical and radiological absence of a tooth or tooth germ at an age when it should be present, with no history of tooth extraction or exfoliation. Dental number anomalies are relatively frequent alterations in the general population and have been studied by different authors. The disorder can cause aesthetic, functional or psychological consequences. Specifically, we categorise dental number anomalies as follows: hypodontia, which occurs when one to five teeth are missing; oligodontia, where more than six teeth are absent; and anodontia, which refers to the complete absence of all teeth. Hyperodontia, also known as the presence of supernumerary teeth, refers to the condition where an individual has more teeth than the normal count for primary or permanent teeth. This means that there are additional teeth beyond what is typically expected. Agenesis is the dental anomaly with the highest prevalence in the western population. However, there is significant variability in the prevalence rates reported by different researchers. The prevalence of agenesis ranges from 0.39% to 11.04%, although most authors estimate it to be approximately 6-7%, with a higher frequency in the permanent dentition and in women. The prevalence in the Spanish population is around 6% [Feijóo et al., 2012]. The mandibular second premolar is the most affected tooth, followed by the maxillary lateral incisor and the maxillary second premolar. Unilateral dental agenesis is more common than bilateral. However, bilateral maxillary lateral incisor agenesis is more common than unilateral agenesis. The overall prevalence of agenesis in the upper jaw (maxilla) is comparable to that in the lower jaw (mandible); however, the prevalence rates differ based on the type of tooth affected, such as incisors, premolars, canines, or molars. Third molar agenesis is the most prevalent;

the frequency range is between 23% and 28% [Vastardis, 2000]. In Europe, the prevalence is 4.6% in men and 6.3% in women [Polder et al., 2004].Agenesis has a variable inheritance pattern, frequently manifesting as autosomal dominant, and to a lesser extent autosomal recessive or X-linked. There are associations between the presence of dental agenesis and other abnormal dental features [Marra et al., 2020]. These conditions include microdontia, conical lateral incisors, ectopic eruptions of maxillary canines, ectopic eruption of first permanent molars, submerged deciduous molars, tooth dwarfism, incisor invagination, taurodontism, rotation of lateral incisors and upper premolars, enamel hypoplasia or hypocalcification. Dental embryogenesis involves more than 200 genes that encode growth factors, transcription factors, signaling molecule and proteins. The genes regulate cell activities and determine the position, number, and shape of teeth [Ravi et al., 2023]. Among the genes involved in dental development some of them belong to the Homeobox family (MSX1, MSX2 and PAX9) and others are related to syndromic alterations (AXIN2 and PITX2). MSX1 and PAX9 are recognised as causal factors of dental agenesis [De Coster et al., 2008]. Dental agenesis is related to later tooth development [Duke et al., 2023; Lebbe et al., 2016]. According to some studies, genetic factors could cause a delay in the development of other teeth in patients with agenesis. However, the literature presents various and often conflicting opinions regarding this matter.Dental agenesis is caused by the reciprocal and sequential interactions between epithelial and mesenchymal cells that lead to dental formation: it is expressed as an isolated trait in a sporadic or familial way. It can also be a feature of a set of more than 49 syndromes, including ectodermal dysplasia, Wiktop syndrome, Rieger syndrome type I, Down syndrome [Vastardis, 2000; Lan et al., 2022].

Dental development

Embryologically, human dentition arises from two of the three germ layers: ectoderm and mesoderm, which interact through the neural crest. The formation of these structures begins around the fourth week of gestation, [Sharpe, 2001; Miletich and Sharpe, 2004]. The ectomesenchyme plays a fundamental role in developing dental structures. It derives from the neural crest cells that migrate towards the gill arches and palatine processes (mesenchyme). From the epithelial-mesenchymal interaction, a continuous band of thickened epithelium is formed, serving as the precursor of dental arches. Some dental tissues originate from the mesoderm and neural crest (dental papilla, odontoblasts, fibroblasts, and cementoblasts) while the enamel organ and ameloblasts originate from the ectoderm [Feter et al., 2017]. The epithelial band that appears between 4 and 6 weeks of development is divided into the vestibular lamina (which will give rise to the vestibule) and the dental lamina (from which dental formation will proceed). The epithelium continues to proliferate locally in the underlying ectomesenchyme, leading to tooth formation. Subsequently, during the 3 stages of development (bud, cup and bell), the morpho- and histo-differentiation of the dental organ occurs. After the bell stage, the formation of the crown (enamel and dentin) and the root takes place, thanks to the epithelial cells that initiate the differentiation of the odontoblasts. These cells, found in the internal and external dental epithelium, proliferate to form Hertwig's epithelial root sheath, which extends around the pulp to shape the root [Feter et al., 2017].

Methods of study of dental formation

The formation of permanent teeth is significant for various reasons. From a clinical perspective, the analysis of dental maturation is a fundamental diagnostic tool. The degree of dental development is essential for making a diagnosis, establishing the treatment plan and assessing the prognosis of certain pathological processes [Cadenas et al., 2014]. Additionally, estimating dental age is vital in routine corpse identification and is fundamental in criminal investigations and accident assessments [De Donno et al., 2021]. It can serve as evidence in cases of unknown date of birth (immigrants, refugees, adopted children of unknown age), especially in cases where chronological age is necessary to access civil rights and social benefits. Chronological age is important in most societies for aspects related to schooling, employment, and marriage. Dental maturity has played an important role in estimating the chronological age of individuals due to its low variability. Compared to other tissues, developing teeth are less affected by endocrinopathies and other environmental insults, such as poor nutrition or other pathological changes.

Study of dental development

For many years, clinical eruption was the only criterion used to determine dental age. However, this method can be influenced by local factors and can be applied within a very limited timeframe. Tooth formation is considered a reliable measure due to its hereditary influence, low coefficient of variation and resistance to environmental effects [Verma et al., 2019]. There are many methods proposed for the study of tooth formation in permanent dentition, and most are based on the degree of dental calcification in radiographic records. Many authors have described different methods to classify the stage of dental formation. Various authors have defined different stages of development, such as Nolla in 1960, Gleiser and Hunt in 1955, Moorres et al in 1963, Haavikko in 1970, Liliequist and Lundberg in 1971, Demirjian et al in 1973, Gustafson and Koch in 1974, Nortje in 1983, Harris and Nortje in 1984, Kullman et al in 1992, Köhler et al in 1994 among others [Cadenas et al., 2014]. The differences between the different methods are due to two types of reasons: on one hand, to the calcification scales proposed by the authors as a comparative reference, and on the other hand, to technological advances in radiology, with routine incorporation of orthopantomography. This led to the decline in the use of many methods, including the one proposed by Nolla [Paz Cortés et al., 2020]. Currently, panoramic radiograph is used for these studies, and researchers choose among reference scales proposed by the different authors to evaluate dental development. The stages of development are easily recognisable, from the beginning of calcification to the final mature shape of the tooth. The stages are indicators of maturity, not size [Verma et al., 2019]. The stages defined in these classifications are sometimes numerous and difficult to compare. When the stages include fractions of crown and root growth, the evaluation is more difficult and subjective. An uncertain future crown height or indeterminate root length must be estimated accurately [Willems 2001]. Each tooth receives a score based on the degree of maturation of the tooth. The score, or the sum of the scores, is then converted to dental age. The mean dental age is compared with the chronological age [Cadenas et al., 2014]. The accuracy of dental age is not uniform from birth to maturity. Accuracy is greater at an early age because there is a greater number of teeth in formation and the morphological stages are shorter

[Cadenas et al., 2014].

Recent studies show that methods based on tooth size or crown or root growth fractions can make the assessment less accurate. [Olze et al., 2006]. According to several authors, errors in age prediction increase after 10 years of age and increase even more after 14 years. This is because all the teeth are in the process of completing their apical formation. Root formation can be considered complete in women and men at 16 and 17 years of age, respectively. For this reason, the models to estimate dental age do not include third molars, except Nolla's ones [Koç et al., 2021; Paz Cortés et al., 2020; Nolla, 1960].

Demirjian's method

Numerous studies have been carried out in different ethnic groups, analysing European, Asian and North American children. The results suggest possible differences in patterns of dental maturation among different populations [Cadenas et al., 2014]. The Demirjian method is one of the most widely used to estimate dental age, especially in clinical and legal studies [Cadenas et al., 2014]. In 1973 Demirjian and collaborators presented a work where they described 8 distinctive stages, called A-H, defined by changes in shape and that do not depend on speculative estimates of length [Pereira et al., 2023; Demirjian et al., 1973]. Their sample consisted of 2,928 panoramic radiographs of 1,446 boys and 1,486 girls of French-Canadian origin without growth disorders, with complete mandibular dentition (erupted or not), with an age range of 2-20 years. They applied a maturation scale based on Tanner, Whitehouse and Healy method to estimate chronological age, obtaining a value for each stage per tooth, separately for boys and girls. All mandibular left permanent teeth (excluding the third molar) were evaluated. The sum of the scores of the 7 teeth provided a dental maturity score on a scale of 0 to 100, which could be directly converted into dental age using the tables and percentile curves provided by the authors [Cadenas et al., 2014; Olze et al., 2006]. Tooth formation using Demirjian's method differs among ethnical groups. Thus the original data and the maturation chronology tables proposed by Demirjian based on the French-Canadian population cannot be extrapolated to other population groups [Alqadi and Abuaffan, 2019; Lee et al., 2008; Cadenas et al., 2014]. There is no consensus regarding the origin of these discrepancies. Some authors attribute the differences to ethnic or genetic factors [Grgic et al., 2022; Pelsmaekers et al., 1997], while others argue that the variations are primarily rooted in socio-geographical influence [Feijóo et al., 2012; Schmeling et al., 2004; Schmeling et al., 2000].

Studies in European populations

The main objective of the studies that apply Demirjian's method is to apply it to specific population groups to determine the validity of the original study in populations other than French-Canadian, with the aim of developing specific conversion curves and tables [Feijóo et al., 2012]. These types of study were carried out by Nyström et al. in 1988 in a Finnish population, Chaillet et al. in 2004 in a Belgian population, Frucht et al. in 2000 in a German population, Willems et al. 2001 in a Belgian-Caucasian population, Leurs et al. in 2005 in a Dutch population, Rózyło-Kalinowska et al. in 2007 in a Polish population. Specific maturation tables were prepared for the above mentioned studies (Table 1). Studies of dental development have also been carried out in the Spanish population [León Rubio et al. 2022; Paz Cortés et al.2020.], but using the original Demirjian's method. Differences in Spanish population compared to other population groups were reported [Feijóo et al., 2012]. In particular Feijóo et al., 2012, applying the original Demirjian method to the Spanish population, found that dental age in relation to chronological age was overestimated by 0.87 years in boys and 0.55 years in girls [Feijóo et al., 2012] and developed specific maturation tables for the Spanish population. In the different European population groups, there are studies that apply the original method of Demirjian, solely with the objective of comparing the dental age with the real chronological age (Table 2).

- Norwegian population: study by Nykänen et al. in 1998, in 261 Norwegian children (128 boys, 133 girls) between 5 and 12 years old, found that the discrepancy between chronological and dental age was 0.22 in boys and 0.38 in girls.
- English population: Liversidge et al. in 1999, applied Demirjian's method, calculating the dental age in two groups of 521 English children, one group of children of Bangladeshi origin and another of Caucasian origin. In both groups, significant differences were found between the chronological age and the estimated dental age. The difference was 0.74 years in the Caucasian boys, 0.70 years in the Bangladeshis boys, 0.44 years in the Caucasian girls and 0. 57 years in the Bangladeshi girl.
- Mitchell et al. in 2009 in another study on the English population, analysed 1722 OPGs of children between 4 and 24 years old and found a significant difference of 0.27 years in girls and 0.23 years in boys.
- Spanish population: Cruz-Landeira et al. in 2010 analysed a total of 308 radiographs of children between 2 and 18 years old, comparing the dental and chronological age of Galician children; the authors found that the estimated dental age was 0.76 years greater than the chronological age in boys and 0.88 in girls.

Author (year)	Mean difference DA-CA in females	Mean difference DA-CA in males
Nykänen (1998)	0,38	0,22
Liversidge (1999)	0,44 (caucasian) 0,57 (bangladeshis)	0,74 (caucasian) 0,70 (bangladeshis)
Mitchell (2009)	0,27	0,23
Cruz-Landeira (2010)	0,88	0,76
Feijóo et al. (2012)	0,55	0,87
Rózyło-Kalinowska (2007)	1,03	0,92
Leurs (2005)	0,60	0,35

TABLE 1. Mean differences between chronological (CA) and dental (DA) age in studies comparing dental with chronological age [Feijóo et al., 2012].

Goal

The purpose of this work was to study dental development in children with agenesis, applying for the first time Demirjian`s method with specific maturation tables for the Spanish population. Some studies have investigated the association between non-syndromic hypodontia and dental development: Ben-Bassat et al. 2014; Ruiz-Mealin et al. 2012; Uslenghi et al. [2006]; Tunç et al. [2011].

In a previous study by Uslenghi et al. [2006] a significant delay in dental development was found. The authors reported that isolated hypodontia can affect the development of the adjacent tooth, decreasing the dimension of the crown, and affecting the morphology of the crown and the root, causing delayed dental development or inducing taurodontism.

According to Dhamo et al. [2016], dental development is significantly delayed in subjects with agenesis. In particular, in the study by Tunç et al. [2011], the delay varies between 0.37 and 0.52 years of dental age between the groups with agenesis and without agenesis, and the difference in development is more pronounced in the lower second premolars, the lower first molar and the lower second molars.

Author (year)	Country	Females	Males	Sample size	Age (years)
Demirjian (1973)	Canada	1482	1446	2928	2 to 20
Nyström (1988)	Finland	1002	978	1980	0 to 25
Nykänen (1998)	Norway	133	128	261	7 to 12
Liversidge (1999)	England	258	263	521	4 to 9
Frucht (2000)	Germany	-	-	1003	2 to 20
Willems (2001)	Belgium	1188	1217	2405	2 to 17
Chaillet (2005)	Belgium	539	439	978	2 to 17
Leurs (2005)	Holland	451	225	226	3 to 17
Rózyło-Kalinowska (2007)	Poland	584	410	994	6 to 16
Mitchell (2009)	England	1722	992	730	4 to 24
Cruz-Landeira (2010)	Spain	157	151	308	4 to 17
Feijóo, Barberia, De Nova (2012)	Spain	525	485	1010	2 to 16

TABLE 2. Sample studies (in chronological order) of dental development in different populations (Demirjian method) [Feijóo et al., 2012]

However, other researchers report a statistically insignificant difference between children with agenesis and their controls without agenesis [Ben-Bassat et al. 2014]. These inconsistent results prompted us to conduct a pilot retrospective cross-sectional study in the Spanish population to assess whether dental development is delayed in paediatric patients with agenesis and to confirm the validity of conversion tables for the Spanish population. We studied the influence of the difference between chronological and dental age on dental development in a sample of children with dental agenesis. We compared dental development (dental age) with a control sample of healthy children without dental agenesis. We studied the influence of gender, number of agenesis (= 1, > 1), location of the agenesis (upper, lower, both upper and lower), location of the agenesis (anterior, posterior, both anterior and posterior).

Methods

Panoramic radiographs of children treated at the Postgraduate Master in Pediatric Dentistry at the Complutense University of Madrid, in the last 10 years, and who meet the study criteria, were analysed. The study was approved by the Ethics Committee of the San Carlos Clinical Hospital in Madrid.

Inclusion and exclusion criteria

The inclusion and exclusion criteria used in all tooth development studies have common aspects. Healthy children and high-quality radiographs are selected. Children with systemic diseases and developmental disorders are excluded.

Inclusion criteria

- Panoramic radiographs of children, who sought dental care at the UCM School of Dentistry between 2010 and 2015.
- Panoramic radiographs of children between 5 and 16 years old.

Exclusion criteria

- Radiographs of children with syndromes or systemic diseases that may alter the number of teeth.
- Panoramic radiographs with insufficient quality
- Radiographs of children who previously required orthodontic treatment.
- Radiographs of children with history of dental extractions.
- Radiographs of children with history of dental trauma including loss of permanent teeth.

One thousand sixty-five panoramic radiographs of children between 5 and 16 years old, treated in the Postgraduate Master in Pediatric Dentistry at the Complutense University of Madrid were reviewed. Agenesis was reported in 80 radiographs (5.0%). The prevalence of agenesis aligns with the rate of the prevalence reported in the Spanish population (6%) [Feijóo et al. 2012]. The total sample selected for the study included 114 panoramic radiographs, boys and girls between 5 and 16 years old, with a mean age of 9.4 years (+/- 2.5 S.D). The case group included 53 radiographs (26 boys and 27) selected from the 80 radiographs of patients with agenesis; the control group included 61 panoramic radiographs of patients without agenesis (27 boys and 34 girls).

Evaluation of dental agenesis

The examiner evaluated the presence of dental agenesis on panoramic radiographs, including cases in which at least one tooth was missing and there were no signs of formation or calcification [Cadenas et al., 2014].

Evaluation of the stage of dental development

The 7 left mandibular teeth were studied to assess the dental age, except the lower third molar. Each tooth was classified from A to H depending on the stage [Demirjian, 1973].

Determination of dental age

Once the different stages of development were assessed, a score was obtained for each tooth using specific conversion tables for boys and girls. A conversion table matched the total score (sum of each tooth scores) with the dental age of the patient [Demirjian, 1973]. In addition to the method originally described by Demirjian, Goldstein and Tanner, Demirjian and Goldstein presented a modification in which 4 teeth are used instead of 7 [Demirjian et al., 1976]. In this case, 4 periapical radiographs are used. The 4 teeth with less variability (1st premolar, 2nd premolar, 1st molar and 2nd molar) are studied.

However, this modification is less used and is preferred when a patient has bilateral agenesis of a mandibular tooth or when only periapical radiographs are available.

Variation of the method

We modified the method when evaluating the stage of development, according to the results obtained by Feijóo et al. 2012 in his study on Spanish population. In case of unilateral agenesis, the homologous tooth was taken as a reference from the contralateral quadrant. No statistically significant differences of the chronological appearance of stages were observed between homologous teeth of the first and second quadrant, and between homologous teeth of the third and fourth quadrant. In case of bilateral agenesis (e.g. 3.5 and 4.5) the same criteria was applied. No statistically significant differences were reported in the chronology of appearance of stages when comparing homologous teeth from the lower quadrant with the upper quadrant. So the corresponding tooth from the upper quadrant was selected. According to the study the chronology of development in both arches is comparable. Conversion tables for the Spanish population by Feijóo et al. 2012 were used to assess dental age, since Demirjian based his study on the French-Canadian population.

Statistical analysis

The statistical analysis of the data was performed with the SPSS 27.0 program for Windows. The statistical methods used were the following (IBM SPSS, 2020):

- Descriptive statistics of the quantitative variables (DESCRIPTIVE and EXPLORE procedure) for the description of the samples: mean, standard deviation, maximum, minimum, median, standard deviation of the mean, and Kolmogorov-Smirnov and Shapiro-Wilk normality test, etc.
- Descriptive statistics of the qualitative variables (FREQUENCIES procedure), to obtain the frequencies and percentages of the categories.
- Analysis of variance, ANOVA 2 factors (UNIANOVA procedure), for the comparison of multiple means on two conditions. The Bonferroni test was applied for the multiple comparisons of means within each factor.
- Student's t test (T-TEST procedure) for the comparison of two means in quantitative variables, assuming or not equal variances (parametric method). Normality in the data was assumed. The equality of variances was assessed using the Levene test (which assessed whether the test assuming equal or unequal variances was more suitable).
- Mann-Whitney non-parametric test (NPTESTS procedure) for the comparison of quantitative variables between two groups. Nonparametric tests were also performed because not all subgroups had equal variances. Only the parametric ones are indicated, because when there was significance in the parametric tests there was also in the non-parametric ones and vice versa.
- Analysis of variance, ANOVA (ONEWAY procedure), for the comparison of multiple groups. When the global value of Snedecor's F is significant, it means that the means in the groups are not equal. The Bonferroni test, which performs multiple comparisons between pairs of groups, was performed [Aranaz, 1996].
- Kruskal-Wallis non-parametric test (NPTESTS procedure) for the comparison of a quantitative variable between more than two groups [Aranaz, 1996].

Results

Characteristics of dental agenesis in our study

The study analysed a total of 114 panoramic radiographs, boys and girls between 5 and 16 years old at the time the radiographs were taken, with a mean age of 9.4 years (+/- 2.5 S.D). The case group included 53 radiographs (26 boys and 27 girls with agenesis); the control group included 61 panoramic radiographs (27 boys and 34 girls without agenesis). In each radiography, the analysis of maturation of all the permanent teeth was carried out (3192 teeth). The analysis of stages of dental maturation in incisors, canines, premolars and permanent molars of the third quadrant was carried out, applying the previously described variation of the method and the conversion tables for the Spanish population. Most of the patients had more than 1 agenesis (54.7%). In the case group, the frequency of posterior agenesis (from canine to molar) was 75.5%, while anterior agenesis (incisors and canines) was observed in 18.9% of the patients. Additionally, 5.7% of the patients exhibited agenesis in both sectors. 159 anterior teeth (from incisors to canines) were studied in 53 children with agenesis. 15.4% had unilateral agenesis of 1.2, of 1.2 and 2.2, of 4. and 23.1% unilateral agenesis of 4.2. No presence of canine agenesis was reported. 212 posterior teeth (from premolars to molars, excluding the third molar) were studied in 53 children with agenesis. Second lower premolars were the most affected teeth (3.5 had a 27.3% frequency and 3.5 and 4.5 had a 20.5% frequency). The frequency of mandibular, maxillary and mandibular/maxillary location was 62.3%, 17% and 20.8% respectively. 45.3% of the patients had a single agenesis, 54.7% had more than one tooth affected. The analysis of the univariate variance, performing a test of inter-subjects effects (CI 95%), indicated that gender does not have a statistically significant influence on the difference between chronological and dental ages (p=0.899) in both samples (cases and controls). A 2-factor ANOVA was performed to see if gender has an influence on the location (anterior, posterior, anterior and posterior, mandibular, maxillary, mandibular and maxillary) and the number of agenesis (agenesis of 1 tooth/agenesis of more than 1 tooth). Gender does not have a statistically significant influence (p=0.349; 95% CI) in the presence of agenesis in anterior or posterior sectors. Gender does not have a statistically significant influence (p=0.101; 95% CI) in the presence of agenesis in lower or upper sectors. Gender does not have a statistically significant influence (p=0.918; 95% CI) in the number of agenesis (1 tooth or more than one tooth).

Dental development in children with agenesis

In a subgroup of 44 children with posterior agenesis, the difference between chronological and dental age was positive in 33 children. Dental age overestimated chronological age (CA). On the other hand, in 11 children this difference was negative, underestimating the chronological dental age. In the subgroup of children with agenesis in the anterior sector, the difference between chronological and dental age (CA-DA) was positive in 9 children and negative in 4 children.

Comparison between chronological and dental age

The comparison of the average difference between chronological and dental age in the total sample (children with and without agenesis) was carried out. Dental age underestimates chronological age by 0.3 years (Table 5). T-student test was performed to evaluate the differences in

Girls	Anterior agenesis	Posterior agenesis	CA (years)	DA (years)	CA-DA (years)
1		3.5, 4.5	12.4	11.0	1.4
2		2.5	8.9	9.9	-1.0
3		3.5	11.0	11.1	0.1
4		2.5	7.8	8.0	-0.2
5		1.5, 3.5, 4.5	7.6	6.3	1.3
6	4.1		10.4	9.5	0.9
7	1.2, 2.2, 3.1, 4.1		8.8	8.5	0.3
8		3.5	10.3	10.1	0.2
9		3.5, 4.5	11.5	10.5	1.0
10	1.2, 2.2	3.5	6.0	6.1	-0.1
11	1.2, 2.2	3.5	6.0	6.2	-0.2
12		2.5	7.5	7.1	0.4
13		3.5	8.7	7.3	1.4
14	1.2	4.5	6.8	6.6	0.2
15		3.5, 4.5	10.2	8.0	2.2
16		3.5, 4.5, 4.7	6.3	5.9	0.4
17		3.5, 4.5	12.1	11.4	0.7
18		1.4, 1.5, 2.4, 2.5, 3.5	10.9	8.8	2.1
19		1.5, 2,5	7.7	7.3	0.4
20		4.5	8.4	7.5	0.9
21		3.5	11.8	9.6	2.2
22		3.5, 4.5	11.0	7.8	3.2
23	4.1		8.7	8.6	0.1
24	4.2		7.7	7.6	0.1
25		1.5, 2.5, 4.5	10.3	10.2	0.1
26		3.5	12.8	10.2	2.6
27		4.5	6.5	6.1	0.4

TABLE 3 Dental development in girls with agenesis.

Boys	Anterior agenesis	Anterior agenesis	CA (years)	DA (years)	CA-DA (years)
1		3.5, 4.5	11.3	9.3	2.0
2	2.2, 3.2		8.1	6.7	1.4
3		3.5	11.8	9.6	2.2
4		3.7, 4.7	8.2	5.9	2.3
5		3.5	8.9	7.6	1.3
6	2.2		5.3	5.7	-0.4
7		1.5, 2.5, 4.5	6.0	6.1	-0.1
8		4.5, 4.5	9.1	8.9	0.2
9		4.5	13.9	14.0	-0.1
10		3.5	12.6	12.4	0.2
11	3.2, 4.2		11.5	11.1	0.4
12		1.5, 2,5	5.8	6.0	-0.2
13		3.5	10.7	11.8	-1.1
14		3.5, 4.5	8.2	7.8	0.4
15		3.5, 4.5	5.4	6.3	-0.9
16		3.5	11.8	9.8	2.0
17		3.6	7.5	8.5	-1.0
18		1.7, 2.7	8.9	8.1	0.8
19	4.2		8.6	8.9	-0.3
20		1.5, 2.5	7.4	7.3	0.1
21	4.2		10.6	9.5	1.1
22		3.5, 4.5	7.3	7.5	-0.2
23		1.5, 3.5, 4.5	10.8	8.2	2.6
24		1.4, 2.4	10.2	9.1	1.1
25	1.2	3.6	12.7	10.0	2.7
26		4.5	12.6	10.1	2.5

TABLE 4 Dental development in boys with agenesis.

	CA	DA	CA-DA
N	114	114	114
Mean	9,354	9,054	0,2991
SD	2,4903	2,4786	1,32455

TABLE 5 Mean, standard deviation of the ages of the global sample (cases and controls).

	Grupo	N	Mean	SD (standard deviation)	P value
CA Case	Control	61	9,393	2,6916	
	53	9,308	2,2614		
DA Case	Control	61	9,489	2,8288	
	53	8,555	1,9082		
CA-DA Case	Control	61	-0,0951	1,39779	
	53	0,7528	1,07982		
					0,001**

**T-test: comparison between the average difference in chronological and dental age in the cases and in the controls.*
***significant value*

TABLE 6. Comparison between chronological and dental age between cases and controls.

the average difference between chronological and dental age, between the 2 groups (children with agenesis and without agenesis) (Table 6). Significant differences at 95% (t-student p=0.001) were detected between cases (dental development is delayed and chronological age overestimates dental age by 0.7528 years) and controls (dental development is not delayed and chronological age underestimates the age by 0.0951). In patients with agenesis, the differences were 0.7308 in boys and 0.7741 in girls. These differences are greater in girls than in boys, so dental development is more delayed in girls with agenesis than in boys. The estimated mean dental age in the cases was very close to the mean chronological age, thus dental development was not delayed in patients with agenesis (Table 6). The average differences between chronological and dental age in boys and girls were compared. (Table 7). In girls, the average difference between chronological and dental age was 0.2852 years, while it was 0.3151 years in boys. There are no significant differences at 95% (t-student p=0.905) between boys and girls (due to gender) in the difference between chronological and dental age (Table 7).

Comparison of dental development between cases and controls according to sex, location, number of agenesis

Table 8 shows the comparative analysis between CA and DA between controls and cases according to location of agenesis. The ANOVA detected statistically significant differences (p=0.004, CI 95%) between cases (posterior, anterior, posterior and anterior agenesis) and controls (Table 8). The multiple comparison test performed a posteriori (Student's T) to detect the differences between the subgroups, showed significant differences between the controls and the posterior agenesis group (p<0.001, 95% CI). We could conclude that posterior agenesis has an influence on the delay of dental development (Table 8).

When comparing the influence of the location (mandibular, maxillary, mandibular and maxillary) in the delay of dental development in children with agenesis, the ANOVA detected statistically significant differences (p=0.002, CI 95%) between cases (mandibular agenesis, maxillary, mandibular and maxillary at the same time) and controls. (Table 9). The post-hoc multiple comparison test (Student's T) to detect differences between subgroups detected significant differences in particular between controls and the mandibular agenesis group (p<0.001, 95% CI) and the mandibular agenesis group and jaws at the same time. (Table 9). The mandibular location thus influences the delay in dental development in children with agenesis. When comparing the influence of the number of agenesis (=1, >1) in the presence of agenesis, the ANOVA detected statistically significant differences (p=0.002, CI 95%), between cases (1 agenesis, > 1 agenesis) and controls (Table 10).

The multiple comparison test performed a posteriori (Student's T) to detect differences between subgroups detected significant differences between controls and the subgroup of > 1 agenesis (p<0.001, 95% CI) and between controls and the subgroup of 1 agenesis (p=0.025, CI 95%). Dental development is definitely influenced by the number of agenesis, regardless of the number agenesis (Table 10). When comparing the influence of gender on the presence of agenesis, the Student's T test detected statistically significant differences (p=0.003, 95% CI) between cases and controls (Table 11). Dental development is surely influenced by gender, but regardless of the specific gender (Table 11).

Discussion

When analysing the results, we found that overall (in children with and without agenesis) the mean age estimated using the Demirjian method for the Spanish population was lower than the chronological age of the sample across all groups (mean dental age: 9.054, mean chronological age: 9,354) (Table 8). In girls, the average difference between chronological and dental age was 0.2852 years; in boys was 0.3151 years. This data indirectly showed that dental development in our sample occurred earlier than in the sample studied by Demirjian. It also occurred earlier than what we expected in the Spanish population. Dental development was studied using Demirjian's method with conversion tables for the Spanish population. Imprecise data was obtained in patients with agenesis because the chronological age does not correspond to the dental age.This difference is minimal in patients without agenesis (dental age underestimates chronological age by 0.1 years). Applying Demirjian`s method with maturation tables for the Spanish population works in this subgroup: there is a correspondence between estimated dental age and chronological age in children without agenesis. The discrepancies obtained in the global sample, in the average difference between chronological and dental age in boys and girls, are not aligned with the results from other authors (Nykänen et al. 1998, Liversidge et al.1999; Cruz-Landeira et al. 2010; Feijóo et al. 2012; Rózyło-Kalinowska et al. 2007; Leurs et al. 2005; Mitchell et al. 2009) although all authors agree that directly applying the Demirjian method for calculating dental age leads to an over-estimation of chronological age. In contrast to other previously mentioned authors, the differences observed in the sample between chronological and dental age in girls are smaller than those reported by Nykänen et al.1998, Liversidge et al. 1999, Cruz-Landeira et al. 2010, Feijóo et al. 2012, Rózyło-Kalinowska et al. 2007 and Leurs et al. 2005 and greater than the ones reported by Mitchell et al. 2009. In boys, these discrepancies are smaller than the ones reported by Liversidge et al. 1999, Cruz-Landeira et al. 2010, Feijóo et al. 2012, Rózyło-Kalinowska et al. 2007 and Leurs et al. 2005 and greater than the ones reported by Mitchell et al. 2009 and by Nykänen et al. 1998. Among the studies we analysed, the age range of our samples is closer to that of the study by Cruz-Landeira et al. 2010. Our patients were between 5 and 16 years and between 4 and 17 years in Cruz-Landeira et al. 2010 study. The above study (157 girls and 151 boys), is the one whose sample size is closest to ours (61 boys and 53 girls). No presence of canine agenesis was found in our sample. Canines are fundamental teeth in the development of our dentition and the presence of canine agenesis has been rarely reported [Sivarajan et al., 2021]. On the other hand, a higher frequency of agenesis was reported in the posterior sectors (Table 4, Table 5). Second premolars are often among the most affected teeth [Meade et. Al 2023]. One of the limitations of the study is related to the size of the sample. Similar studies to be carried out in the future, in order to obtain a more homogeneous sample. The number of patients with anterior, posterior agenesis, upper and upper/lower agenesis should be increased. Although an association between the presence of agenesis and delayed dental development was found in this cross-sectional study, it has not been determined whether agenesis causes delayed dental development or vice versa. To better investigate this association in humans, genetic studies of the different pathways of PAX9, MSX1 and AXIN2 are needed.

	Sex	Mean	SD (standard deviation)	N	P value
Control	Girl	0,1029	1,50181	34	
	Boy	-0,0852	1,28294	27	
	Total	-0,0951	1,39779	61	
Case	Girl	0,7741	0,99173	27	
	Boy	0,7308	1,18381	26	
	Total	0,7528	1,07982	53	
Total	Girl	0,2852	1,36368	61	
	Boy	0,3151	1,29085	53	
	Total	0,2991	1,32455	114	0,905

**T-test: comparison between the average difference in chronological and dental age in boys and girls*

TABLE 7 Comparative analysis between chronological and dental ages in both samples in relation to gender.

	Localization	Number of boys/girls	CA-DA	SD (standard deviation)	P value
Control		61	-0,0951	1,39779	
Case	Anterior	10	0,6300	0,93220	0,095
	Posterior	40	0,8425	1,13677	<0,001**
	Anterior and posterior	3	-0,0333	0,20817	0,934
Total		114	0,2991	1,32455	0,004**

*T-test: comparison of the average difference between chronological and dental age of the cases with anterior, posterior, anterior and posterior agenesis with the average of the controls
** significant value.

TABLE 8 Comparative analysis between CA and DA between controls and cases according to location of agenesis.

	Localization	Number of boys/girls	CA-DA	SD (standard deviation)	T-test (P value)*
Controls		61	-0,0951	1,39779	
Cases	Maxilar	9	0,1111	0,64313	0,646
	Mandibular	33	0,8667	1,12017	<0,001**
	Maxilar and mandibular	11	0,9364	1,12541	0,014**
Total		114	0,2991	1,32455	0,002**

*T-test: comparison of the average difference between chronological and dental age of the cases with maxillary, mandibular, maxillary and mandibular agenesis with the average of the controls
**significant value

TABLE 9 Comparative analysis between CA and DA between controls and cases according to location of agenesis.

	Agenesis number	Number of boys/girls	CA-DA	SD (standard deviation)	T-test (P value)*
Controls		61	-0,0951	1,39779	
Cases	1 agenesis	10	0,5958	1,11491	0,025**
	>1 agenesis	40	0,8828	1,05155	<0,001**
Total		114	0,2991	1,32455	0,002**

**T-test: comparison of the average difference between chronological and dental age of the cases with 1 agenesis or >1 agenesis with the average of the controls*
***significant value*

TABLE 10 Comparative analysis between CA and DA between controls and cases according to number of agenesis.

	Sex	Number of boys/girls	CA-DA	D.E.	T-test (P value)*
Cases		53	0,7528	1,07982	
Controls	Boys	27	-0,0852	1,28294	0,003**
	Girs	34	-0,1029	1,50181	0,003**
Total		114	0,2991	1,32455	

**T-test: comparison of the average difference between chronological and dental age of the cases, the average of the controls in boys and the average of the controls in girls*
***significant value*

TABLE 11 Comparative analysis between CD and DU between controls and cases according to gender.

This set of genes acts both in hypodontia and in delayed dental development [Duke et al., 2023]. Understanding and knowing the maturation and development of the permanent dentition in children with agenesis is relevant from a clinical perspective and for therapeutic planning. If agenesis delays dental development [Dhamo et al., 2016], clinicians should consider this factor when making diagnoses and planning treatments.

Conclusion

The difference between chronological and dental age applying the Demirjian method with the maturation tables for the Spanish population, is significantly delayed, with an overall difference of 0.3 years. Statistically this difference is 0.2852 years in the girls and 0.3151 years in boys. Dental development in our sample representing Spanish population, was more delayed in children with agenesis, in particular in girls with agenesis than in boys, despite the earlier development of girls. Dental development occurred earlier than expected in the Spanish population. The difference between chronological and dental age was minimal in patients without agenesis, assessing the validity of the maturation tables for the Spanish population in this group of patients. The studied concluded that later dental development of children with agenesis was influenced by gender, number of agenesis and location (posterior, lower).

Declarations' section

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki. It is a retrospective cross-sectional study, and the protocol was approved by Ethical Committee of Hospital Clínico San Carlos in Madrid, Spain.

Consent for publication

All authors read and approved the final manuscript.

Availability of data and material. Data analysed in the current research (conversion tables for Spanish population) are openly available [Feijóo et al., 2012].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Francesca Dusio and Joaquín the Nova designed the study. Joaquín de Nova supervised the research. Alejandra Hernández Guevara reviewed the initial group of panoramic radiographs of children to select a sample with and without dental agenesis. Gonzalo Feijóo García tables for Spanish population were used.

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