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Sexual Dimorphism in Third Molar Agenesis in Humans with and without Agenesis of Other teeth

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Sexual dimorphism in third molar agenesis between individuals with and without agenesis of other teeth

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Abstract

AIM: The aim of this study is to investigate the sexual dimorphism in patterns and severity of third molar agenesis, in non-syndromic individuals with (Group A) versus without agenesis of teeth other than third molars (Group B).

MATERIAL AND METHODS: Group A consisted of 303 individuals of European ancestry (133 males, 170 females) and Group B of another 303 individuals matched one by one for ancestry, sex, and age (range: 12.5 – 40 years) to Group A. Tooth agenesis pattern was identified using panoramic radiographs. Rankings of the most common third molar agenesis pattern in males and females in Groups A and B were calculated. Sexual dimorphism of third molars agenesis within each group and between the two groups was compared using the Chi-square test and Fisher's exact tests. The average number of third molars agenesis per patient between sexes within each group and between the two groups was compared using the Mann–Whitney test.

RESULTS: Agenesis pattern of 18,28,38,48 has the highest rank of third molars agenesis pattern among females and males in groups A and B. Bilateral third molars agenesis is statistically higher in association with agenesis of other teeth (41.18%) in females and (35.34%) in males, compared to bilateral third molars agenesis without agenesis of other teeth (12.35%) in females and (12.03%) in males ($P<0.001$). Males and females show statistically significant increase in the number of third molars agenesis per individual in group A compared to group B ($P<0.001$).

CONCLUSIONS: Males and females show higher rate of third molars agenesis in presence of agenesis of teeth other than third molars compared to isolated third molars agenesis. In both sexes, bilateral agenesis of third molars in association with other teeth agenesis is higher compared to bilateral third molars agenesis without other teeth agenesis.

Introduction

Permanent tooth agenesis is the most prevalent craniofacial congenital malformation in humans. 22.6% of the population have at least one third molar agenesis (Carter & Worthington 2015), while agenesis of other permanent teeth, excluding third molars, is evident in 6.4% of the population (Khalaf et al., 2014). Primary dentition may also be affected, but with lower prevalence (from 0.5 to 0.9%). When a primary tooth does not develop, the secondary tooth is also missing (Matalova et al. 2008).

The phenotypic expression of tooth agenesis varies considerably between individuals either with or without considering third molars (Gkantidis et al 2017; Scheiwiller et al 2020). In the literature specific terminology has been used to indicate the severity of tooth agenesis. Hypodontia describes the condition of less than six missing teeth (80% lack only one or two teeth). Oligodontia is used when more than 6 teeth are missing and it is present in approximately 0.2% of the population (Khalaf et al. 2014). Finally, anodontia is a complete loss of the dentition and it is a very rare condition (Matalova et al. 2008)

Evidence suggests that individuals with tooth agenesis have significantly different craniofacial features from those without (Cocos et al. 2017; Oeschger et al. 2022 Oeschger, E.S.; Kanavakis, G.; Cocos, A.; Halazonetis, D.J.; Gkantidis, N. Number of Teeth Is Related to Craniofacial Morphology in Humans. Biology 2022, 11, 544). Facial size, but not cranial or cranial base size, has also been shown to reduce with a reduction in the number of teeth due to agenesis (Oeschger et al. 2020). The latter was also evident considering isolated third molar agenesis (Gkantidis et al. 2021 Gkantidis N, Tacchi M, Oeschger ES, Halazonetis D, Kanavakis G. Third Molar Agenesis Is Associated with Facial Size. Biology (Basel). 2021 Jul 12;10(7):650.).

Considering teeth other than thirds molars, gender dimorphism was observed in various studies, with females showing higher prevalence of non-syndromic permanent tooth agenesis than males (Khalaf et al., 2014). Agenesis patterns of teeth other than third molars have been also shown to differ between sexes. Non-syndromic males were less often affected by tooth agenesis, but they showed more severe patterns. Males had significantly higher numbers of congenitally missing first premolars (apart from #14), mandibular incisors (central and lateral), and maxillary left first permanent molar compared to females. On the other hand, agenesis of tooth #14 was more often evident in females (Heuberer et.al 2019; Arch oral Biol). To our knowledge the latter was the only study testing gender dimorphism in tooth agenesis patterns and it excluded third molars.

In a non-syndromic Japanese population with oligodontia, it was shown that there is No significant sex difference in the distribution of the number of agenetic teeth between males and females. However, sexual dimorphism was observed in the tooth agenesis patterns. the prevalence of agenesis of the maxillary second premolars was significantly higher in females ($P < 0.007$) and the prevalence of agenesis of the mandibular central incisors was significantly higher in males ($P < 0.007$) (A. Sato et al. 2021).

When considering third molars, females are 14% more likely than males to have agenesis of one or more third molars. Maxillary third molar agenesis has been found to be 36% more likely than mandibular agenesis in both sexes. Large differences in the prevalence of third molar agenesis are evident depending on geographic region (Carter et al. 2015).

Third molars have the highest variation in prevalence and they also show instability in terms of developmental integrity and timing (Carter et al. 2015; Koussoulakou et al. 2009; Soares et al 2015). So far, the existing studies on sexual dimorphism in tooth agenesis patterns are either focused solely on third molars, excluding individuals with agenesis of other teeth, or they ignore third molars when testing patterns of agenesis in teeth other than third molars.

Thus, previous studies suggest sex-specific effects on agenesis patterns of teeth other than third molars and they also suggest sexual dimorphism in third molar formation, when all other permanent teeth are present. However, the effect of agenesis on teeth other than third molars, in third molar formation on different sexes, remains largely unexplored. Based on previous findings (Scheiwiller et al 2020) we suspect that in presence of agenesis in teeth other than third molars, females will have more often and more severe third molar agenesis. On the other hand, based on another study (Heuberer et.al 2019; Arch oral Biol) the opposite might be true.

Therefore, the aim of the present study is to investigate the sexual dimorphism in patterns and severity of third molar agenesis, in a group without agenesis of teeth other than third molars compared to a group with agenesis of other teeth, additional to third molars agenesis.

Materials and Methods

Sample

This present retrospective data analysis was performed on an already available sample collected from orthodontic patient records, within a 12-year period (2006–2018), from the following orthodontic clinics: a) University of Bern, Switzerland, b) University of Athens, Greece, c) two private practices in Athens and two in Thessaloniki, Greece, and d) one private practice in Biel, Switzerland.

The study protocol was approved by the Ethics Commission of the Canton of Bern, Switzerland (Project-ID: 2018-01340) and the Research Committee of the School of Dentistry, National and Kapodistrian University of Athens, Greece (Project-ID: 281, 2/9/2016). Reporting is in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational studies.

Every patient included in the study was assigned a randomly generated code, and all identification information was immediately removed at the place of sample collection.

Sample collection aimed at forming the two following groups:

Group 1 (n=303). Non-syndromic individuals without agenesis of teeth other than third molars, aged between 12.5 and 40 years, white ethnicity, no systemic diseases or other defects that affect the craniofacial complex development, as reported in the subjects' medical records, adequate quality panoramic radiographs. The

Group 2 (n=303). Non-syndromic individuals with agenesis of teeth other than third molars, matched for age (within 6 months) and sex to Group 1. All other inclusion criteria for group 2 were the same to those mentioned above for group 1.

The patients where the cause of missing teeth or the diagnosis of tooth agenesis was unclear at the age of 12.5 years were excluded from the study.

Data extraction

All the patients' files (medical and dental history, intraoral and extraoral photos, radiographs) were reviewed and all data were recorded in an Excel sheet (Microsoft Excel, Microsoft Corporation, Redmond WA, USA) in a standardized manner, according to a previous protocol (Scheiwiller et al., 2020). Data extraction was performed previously by a single researcher and repeated for 40 randomly selected subjects following a 1-month washout period (https://www.random.org/). In case of disagreement, the radiographs were controlled by all authors and a consensus was reached. Adequate intra-rater agreement has been reported (Scheiwiller et al., 2020).

The following variables were also recorded: gender, date of birth, date of panoramic radiograph, congenitally missing teeth including third molars. All panoramic radiographs were viewed on screen to identify tooth agenesis. For this purpose, hard copy radiographs were scanned using an Epson Perfection V700 scanner with a resolution of 600 dpi at a scale of 1:1 and saved in .tiff (tagged image file format) format.

As previously published (Scheiwiller et al., 2020), to explore patterns of tooth agenesis, the TAC system was used (Van Wijk & Tan, 2006). This system assigns a binary value to each tooth providing a unique numeric value for each pattern. The combined values assigned to each dental quadrant (q1, q2, q3, and q4) represent a unique tooth agenesis pattern (Van Wijk & Tan, 2006).

Tested parameters

1. Sexual dimorphism in patterns of third molar agenesis within groups

2. Sexual dimorphism in severity of third molar agenesis within groups

3. Compare the sexual dimorphism in patterns and severity of third molar agenesis between groups

4. Sexual dimorphism in patterns of tooth agenesis of Group 2

Statistical analysis

All statistical analyses were conducted with SPSS software (IBM SPSS Statistics for Windows, Version 23.0; IBM Corp, Armonk, NY, USA). The two-tailed Pearson's Chi square test was used to assess differences in the frequencies observed between the two groups. The Spearman's correlation coefficient was used to investigate the relation of the number of agenesis of teeth other than third molars to the number of third molar agenesis, overall, as well as within quadrants.

The level of significance was set to 0.05. A Bonferroni correction was applied in case of multiple pairwise tests for similar outcomes to avoid false positive results.

Results

Sexual dimorphism in third molar agenesis with agenesis of other teeth (group A)

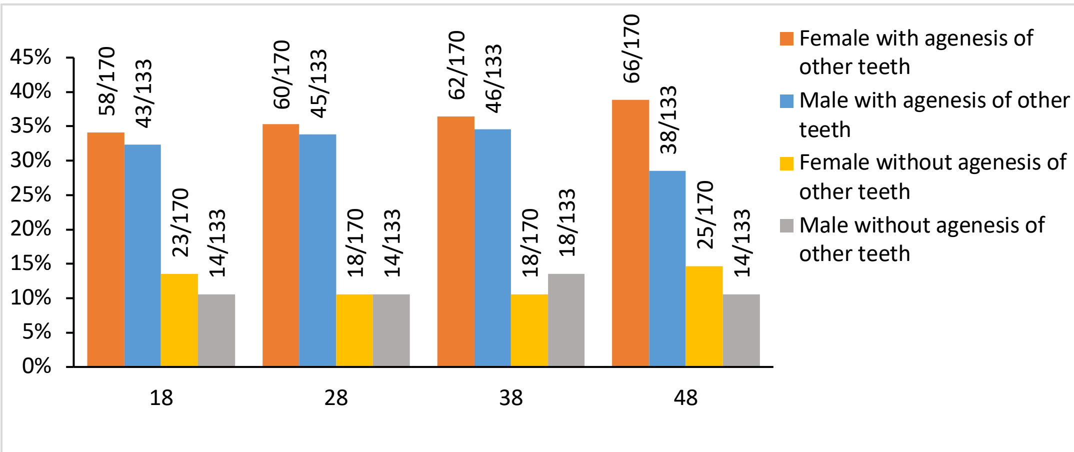
From a potential total sample of 532 third molars in males and 680 in females (133 male and 170 females participants), there were 172 (32.3%) and 246 (36.2%) third molars missing, respectively (P>0.01). There was no sexual dimorphism in third molar agenesis severity. The average number of third molar agenesis per individual was 1.29 ± 1.59 in males and 1.45 ± 1.60 in females (P>0.01). There was no sexual dimporphism evident when comparisons where performed within jaws or within quadrants (P>0.006, Table 1). Furthermore, there were no differences within sexes in the type of third molar missing when comparisons were performed between or within jaws (P>0.01, Figure 1).

Table 1. Distribution of symmetry patterns of third molar agenesis per jaw, in males and females **with** agenesis of teeth other than third molars, overall and for each quadrant.

Gender	Present bilaterally (%)	Missing Right side (%)	Missing Left side (%)	Missing unilaterally (%)	Missing bilaterally (%)	Total number of patients with agenesis	Average missing per patient	Total number of missing third molars
				Upper jaw				
Male	83/133 (62.4%)	5/133 (3.8%)	7/133 (5.3%)	12/133 (9%)	38/133 (28.6%)	50/133 (37.6%)	0.66 ± 0.90	88/266 (33.08%)
Female	102/170 (60%)	8/170 (4.7%)	10/170 (5.9%)	18/170 (10.6%)	50/170 (29.4%)	68/170 (40%)	0.69 ± 0.90	118/340 (34.71%)
P-value	0.669[3]	0.427[3]	1.000[3]	0.701[3]	0.872[1]	0.669[1]	0.725[2]	0.6751[1]
				Lower jaw				
Male	85/133 (63.9%)	2/133 (1.5%)	10/133 (7.5%)	12/133 (9%)	36/133 (27.1%)	48/133 (36.1%)	0.63 ± 0.88	84/266 (31.58%)
Female	94/170 (55.3%)	14/170 (8.2%)	10/170 (5.9%)	24/170 (14.1%)	52/170 (30.6%)	76/170 (44.7%)	0.75 ± 0.90	128/340 (37.65%)
P-value	0.158[1]	0.009[3]	0.643[3]	0.211[3]	0.529[1]	0.141[1]	0.198[2]	0.120[1]

Note:
1Chi-square test, 2Mann-Whitney test, 3Fisher's exact test (adjusted level of significance $p < 0.006$)

Figure1. Third molars agenesis with and without agenesis of other teeth.



In group A, bilateral third molar agenesis is present statistically more often than unilateral agenesis in both sexes (P<0.001). The incidence of bilateral agenesis third molar is 2.6 and 3.7 times higher than unilater agenesis in males and females, respectively (P=0.300, table 2). The most common third molar agenesis pattern was agenesis of all third molars (20.3% in males and 18.8% in females), followed by bilateral agenesis of lower third molars (6% in males and 6.5% in females). As evident in table 2, there was no sexual dimporphism in the bilateral versus unilateral occurence of the most common patterns.

Table 2. Five most common third molar agenesis patterns in individuals **with** and **without** agenesis of teeth other than third molars.

Gender	Most common patterns	Frequency (%)	Missing third molars	Bilateral	Unilateral
		With other teeth agenesis			
Females	1	32/170 (18.82%)	18,28,38,48	*	
	2	11/170 (6.47%)	38,48	*	
	3	9/170 (5.30%)	18,28	*	
	4 - 6	6/170 (3.50%) each	38 OR 18,28,48 OR 28,38,48	**	*
Males	1	27/133 (20.30%)	18,28,38,48	*	
	2	8/133 (6.01%)	38,48	*	
	3 -4	7/133 (5.26%) each	18,28 OR 38	*	*
	5-6	5/133 (3.76%) each	28 OR 18		**

	Without other teeth agenesis				
Females	1	8/170 (4.70%)	18,28,38,48	*	
	2	6/170 (3.52%)	38,48	*	
	3	5/170 (2.94%)	18,48		*
	4 -5	3/170 (1.76%) each	28 OR 48		**
Males	1	9/133 (6.76%)	18,28,38,48	*	
	2	4/133 (3.00%)	38		*
	3	3/133 (2.25%)	38,48	*	
	4-5	2/133 (1.50%) each	18 OR 28 OR 18,28	*	**

	Females			**Males**			
	Bilateral	Unilateral	P-value*	Bilateral	Unilateral	P-value*	P-value[1]
With other teeth agenesis	70/170 (41.18%)	19/170 (11.18%)	< 0.001	47/133 (35.34%)	18/133 (13.53%)	< 0.001	0.300
Without other teeth agenesis	21/170 (12.35%)	16/170 (9.41%)	0.383	16/133 (12.03%)	10/133 (7.52%)	0.215	0.932
P-value	<0.001	0.592	-	<0.001	0.109	-	-

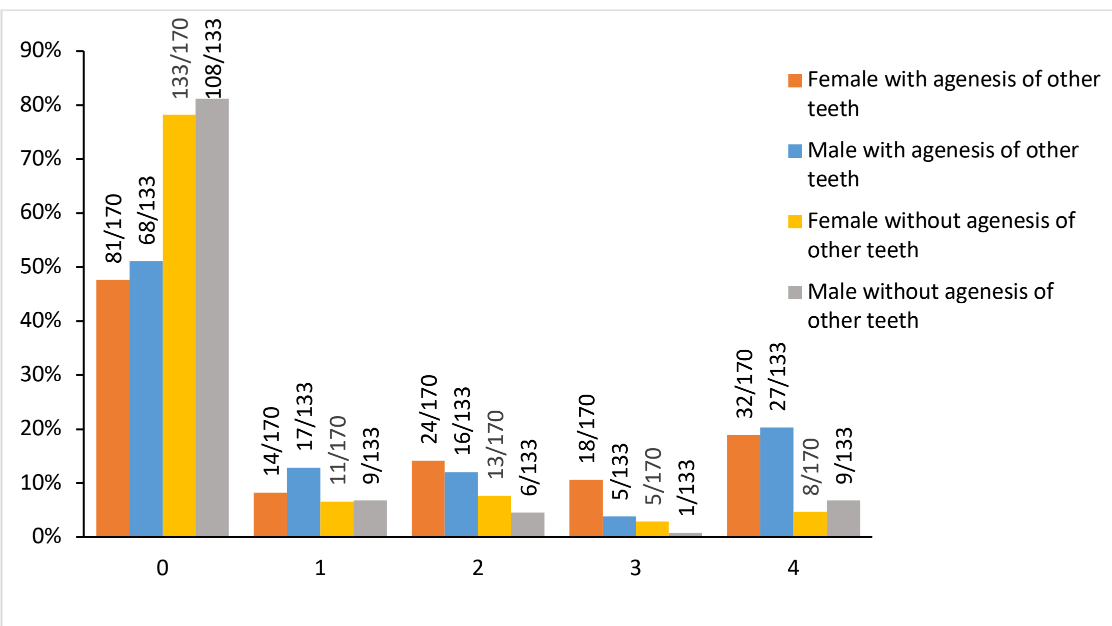
Note:

*Bilateral or Unilateral third molar agenesis

[1] Sexual dimorphism in bilateral agenesis of third molars with and without agenesis of other teeth

There was no sexual dimorphism in the incidence of third molar agenesis, when distinct groups were formed per agenesis severity considering all possible categories (0, 1, 2, 3, or 4 missing molars, Figure 2, Supplementary table).

Figure 2. Total number of missing third molars with and without agenesis of other teeth.



When all teeth are considered, the most common single tooth missing was the lower second premolar (38.7% in males and 38.5% in females), followed the lower third molar (31.6% in males and 37.6% in females), the upper third molar (33% in males and 34.7%

in females) and the upper lateral incisor (29.7% in males and 26.2% in females) (Figure 3). For all single teeth, there was no difference in the distribution between right and left sides, as well as no sexual dimorphism (P>0.001). The most common patterns in the maxilla and in the mandible were ranked for both sexes in table 3.

Figure 3. Number of missing teeth considering all teeth in the dentition including third molars.

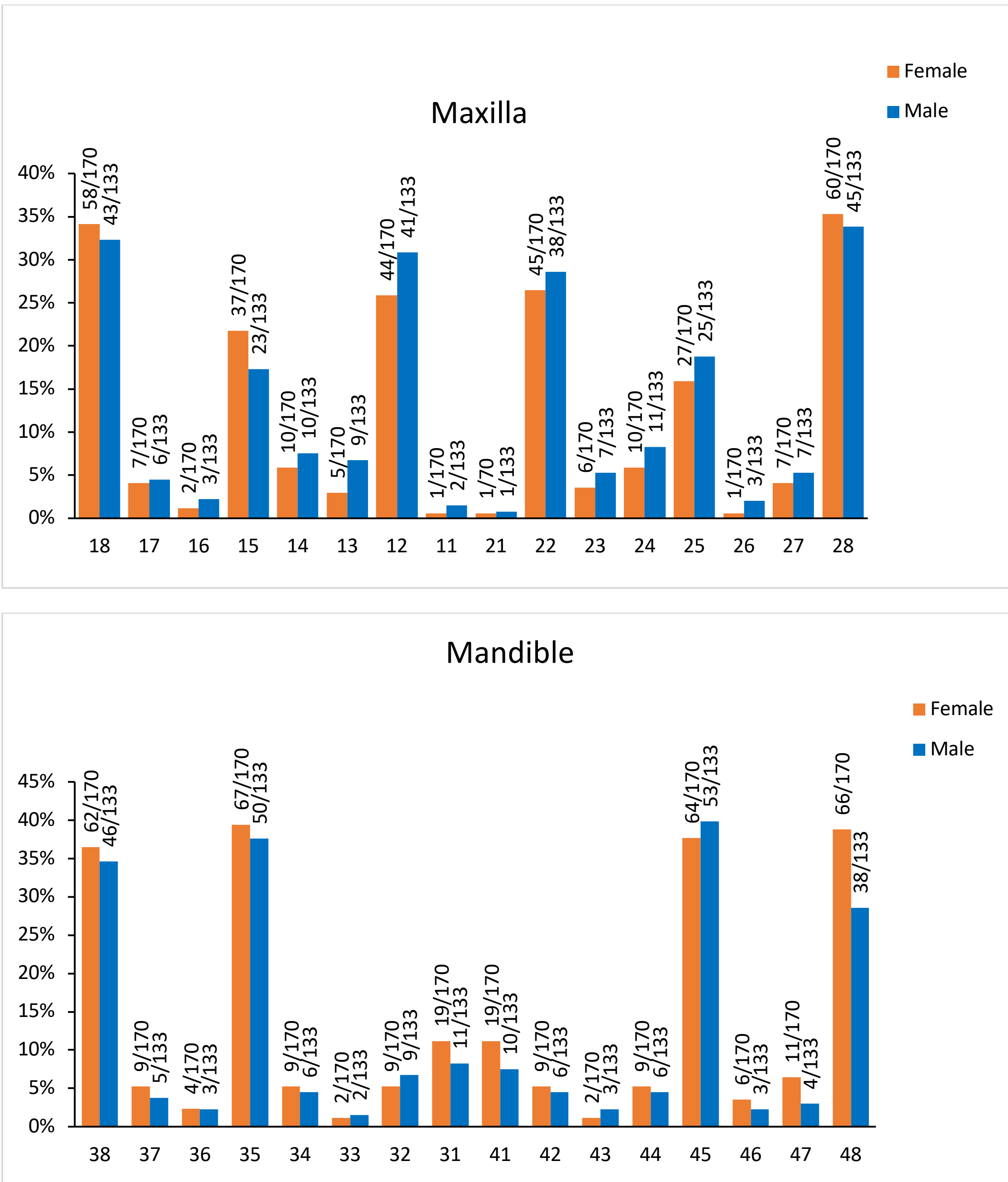


Table 3. Five most common teeth agenesis patterns in individuals **with** agenesis of teeth other than third molars, considering all teeth of the dentition.

Gender	Most common patterns	Frequency (%)	Missing teeth	Bilateral	Unilateral
		Upper jaw			
Females	1	19/170 (11.18%)	18,28	*	
	2	16/170 (9.41%)	12,22	*	
	3-5	8/170 (4.71%) each	22 OR 12 OR 18,15,25,28	*	**
Males	1	15/133 (11.28%)	12,22	*	
	2	11/133 (8.27%)	18,28	*	
	3	9/133 (6.77%%)	22		*
	4	8/133 (6.01%)	12		*
	5	4/133 (3.00%) each	28 OR 18,12,28 OR 18,12,28,22 OR 18,15,28,25	***	*
		Lower jaw			
Females	1	17/170 (10.00%)	35,45	*	
	2	16/170 (9.41%)	35		*
	3	10/170 (5.88%)	38,35,48,45	*	
	4	8/170 (4.70%)	45		*
	5	7/170 (4.12%)	38,48	*	
Males	1	13/133 (9.77%)	35,45	*	
	2	12/133 (9.02%)	45		*
	3	10/133 (7.52%)	38,35,48,45	*	
	4	9/133 (6.77%)	38,48	*	
	5	8/133 (6.01%)	35		*

Note:
*Bilateral or Unilateral third molar agenesis

Sexual dimorphism in third molar agenesis between group A and group B.

In group B, which was matched for age and sex to Group A, but included individuals without agenesis of any tooth apart from third molars, 60 third molars were missing in males (prevalence 11.3%) and 84 in females (prevalence 12.4%) ($p=0.592$). Within sexes there were no differences when comparisons were performed between or within jaws ($P>0.006$, table 4).

The average number of third molar agenesis per individual in group B was 0.45 ± 1.10 in males and 0.49 ± 1.07 in females. Similar to group A, also in group B there was no sexual dimorphism considering the distribution of third molar agenesis in different quadrants (P > 0.01, table 4).

Table 4. Distribution of symmetry patterns of third molar agenesis per jaw, in males and females **without** agenesis of teeth other than third molars, overall and for each quadrant.

Gender	Present bilaterally (%)	Missing Right side (%)	Missing Left side (%)	Missing unilaterally (%)	Missing bilaterally (%)	Total number of patients with agenesis	Average missing per patient	Total number of missing third molars
Upper jaw								
Male	116/133 (87.1%)	3/133 (2.3%)	3/133 (2.3%)	6/133 (4.6%)	11/133 (8.3%)	17/133 (12.9%)	0.21 ± 0.58	28/266 (10.53%)
Female	144/170 (84.7%)	8/170 (4.7%)	3/170 (1.8%)	11/170 (6.5%)	15/170 (8.8%)	26/170 (15.3%)	0.24 ± 0.66	41/340 (12.06%)
P-value	0.537[1]	0.358[3]	1.000[3]	0.616[3]	1.000[3]	0.534[1]	0.558[2]	0.555[1]
Lower jaw								
Male	114/133 (85.7%)	1/133 (0.8%)	5/133 (3.8%)	6/133 (4.6%)	13/133 (9.8%)	19/133 (14.4%)	0.24 ± 0.62	32/266 (12.03%)
Female	141/170 (82.9%)	11/170 (6.5%)	4/170 (2.4%)	15/170 (8.9%)	14/170 (8.2%)	29/170 (17.1%)	0.25± 0.60	43/340 (12.65%)
P-value	0.011[1]	0.015[3]	0.512[3]	0.174[3]	0.687[3]	0.618[1]	0.591[2]	0.818[1]

Note:
[1]Chi-square test, [2]Mann-Whitney test, [3]Fisher's exact test, (adjusted level of significance p < 0.006)

The incidence of third molar agenesis in group A (36.2% in females and 32.3% in males) was for both sexes statistically higher than the incidence in group B (12.4% female and 11.3% male) (P<0.001).

In contrast to group A, in group B there was no difference in the incidence of bilateral versus unilateral third molars agenesis in both males and females (P > 0.001). For both sexes, the incidence of bilateral agenesis of third molars in group A was statistically higher than in group B (P < 0.001).

In males, the incidence of bilateral agenesis of third molars in group A was 2.9 times higher than in group B, while in females it was 3.3 times higher. In group B, there was no sexual dimorphism in the prevalence of bilateral agenesis (P =0.932, table 2).

In group B, the most common agenesis pattern was agenesis of all third molars, in both males and females (6.8% and 4.7%, respectively), followed by unilateral agenesis of lower left third molar in males (3%) and bilateral agenesis of lower third molars in females (3.5%). In group B, similarly to group A, there was no sexual dimporphism in the bilateral versus unilateral occurence of the most common patterns (Table 2).

In group B, as in group A, there was no sexual dimorphism depending on the total number of missing third molars per individual when distinct groups were formed per agenesis severity (0, 1, 2, 3, or 4 missing molars, figure 2, Supplementary table). In all individual categories, Group A tended to have higher third molar agenesis prevalence than group B, although this did not always reach the level of significance ($p<0.01$).

Discussion

The primary outcome of the current study was to investigate the sexual dimorphism in patterns and severity of third molar agenesis in a large modern European (white) sample with and without agenesis of other teeth. The prevalence of third molar agenesis, in presence of other tooth agenesis, was 32.3% in males and 36.2% in females, while the prevalence of third molar agenesis without agenesis of other teeth was 11.3% and 12.4%, respectively. Thus, no sexual dimorphism in the incidence of third molar agenesis was observed within groups. Sexual dimorphism in the different patterns of third molar agenesis, as well as in symmetry, was also investigated, and no sexual dimorphism was detected in both tested groups. To our knowledge, the available evidence in the topic is scarce, since we were not able to identify any previous study investigating this topic.

A meta-analysis performed on studies with different geographic backgrounds reported that women are 14% more susceptible to third molars agenesis than men, and that maxillary third molars agenesis occurs 36% more often than mandibular (Carter & Worthington, 2015). This is in contrast to our results and it might be attributed to the geographic variations and the uncontrolled higher female representation in the individual studies included in the meta-analysis. Moreover, the above mentioned study reported the occurrence of third molars agenesis in Europeans to be 21.6%, while our study found only 11.3% of isolated third molars agenesis in males and 12.4% in females. The incidence of third molar agenesis was much higher in our study in presence of agenesis of other teeth (32.3% in males and 36.2% in females). However, even if we adjust our findings for this considering a 7% tooth agenesis incidence in the European population (Khalaf et al., 2014) the inconsistency is still high. Another factor that might have contributed to this inconsistency might be the inclusion of undiagnosed syndromic individuals in certain studies included in the meta-analysis, which could increase the incidence of third molars agenesis. Finally, our sample consisted of orthodontic records, which included a thorough medical and dental history, and the diagnosis was performed by trained orthodontists reducing the possibility of misdiagnosis (Anthonappa et al.

2013 Anthonappa RP, King NM, Rabie AB. Prevalence of supernumerary teeth based on panoramic radiographs revisited. Pediatric dentistry. 2013 May 1;35(3):257-61).

Our results clearly demonstrated that the prevalence of third molars agenesis is almost three times higher in both sexes with concurrent agenesis of other teeth. This points in the same direction with previous studies of different design that showed an increased prevalence of agenesis of other teeth in individuals with third molar agenesis (Bredy, Erbring & Hubenthal, 1991; Celikoglu, Bayram & Nur, 2011; Endo et al., 2015).

Symmetry distribution of third molar agenesis and occurrences within quadrants were also possible to be evaluated in our large sample of 303 individuals per group, selected out of a total of around 10,000 records. Such a large sample considering all teeth in the dentition is presented for the first time in the literature. No sexual dimorphism was found in the bilateral distribution of third molars agenesis in both groups. In accordance to previous studies (Scheiwiller et al. 2020), bilateral third molar agenesis was more often present than unilateral agenesis in both sexes when there was concurrent agenesis of teeth other than third molars (2.6 times higher in males and 3.7 in females). On the contrary, there was no difference in the incidence of unilateral versus bilateral occurrence of isolated third molar agenesis. Bilateral third molar agenesis occurred 2.9 times higher in males and 3.33 times higher in females when agenesis was also present in other teeth in the dentition.

Regarding the sequence of the number of missing third molars per individual, no sexual dimorphism was found between and within the groups. The most common amount of missing third molars with concurrent agenesis of other teeth was four, followed by two and one third molar, while in the control group without agenesis of other teeth the highest prevalence of third molar agenesis was one missing third molar, followed by two, and four missing third molars. This finding is similar to the findings of a previous study (Schweiwiller et al. 2020) and the findings of the control group are also similar to that of a meta-analysis (Carter & Worthington, 2015), which however did not consider sexual differences.

The aforementioned findings clearly show that the presence of agenesis in teeth other than third molars has a considerable effect on third molar agenesis patterns. Especially, the probability to have four missing third molars increases. This suggests that the third molars might be more vulnerable to genetic factors involved in tooth agenesis, as compared to other tooth types. Indeed, this is also supported by the increased number of missing third molars in the agenesis sample compared to that expected by chance (Schweiwiller et al. 2020). A recent study (Trakinienė et al., 2018) investigating 172 monozygotic twins and 112 dizygoitc twins found that the formation of third molars is highly affected by additive genetic factors, which can also explain increased third molar agenesis incidence in cases with agenesis of other teeth. A previous study suggests an association between third molars agenesis and reduced facial size, and reduced maxillas and mandibles , as an evolution mechanism observed in modern humans. (Gkantidis et al. Biology 2021).

Our study emphasizes the importance of accurate treatment planning in young patients with severe tooth agenesis. In these demanding cases, clinicians should take into consideration that third molars have also higher chances to be missing, and in many cases bilaterally. Thus, more complex multidisciplinary approaches might be required for successful management, considering the possibility that the third molars might also be absent (Carter NE et al. 2003).

A secondary outcome of the present study was to evaluate the sexual dimorphism in the agenesis patterns of all teeth, including third molars, in individuals with agenesis of teeth other than third molars. The most common missing tooth was for both sexes the lower second premolar. When considering teeth other than third molars no sexual dimorphism was evident in our sample. This finding is inconsistent with a previous study in the literature, where sexual dimorphism was detected in an agenesis population without considering third molars (Heuberer et al. 2019). Males showed higher agenesis incidence compared to females on teeth #24, #34 and #44, the mandibular incisors (central and lateral), and tooth #26, whereas tooth #14 was more often absent in females (Heuberer et al. 2019). One of the limitations of the aforementioned study is that males were underrepresented in the sample (40.1% males vs. 70.4% females). potentially undetected syndromic patients with full expression or subtypes might have been included, as genetic tests for certain syndromes was performed only for the patients included in the syndromic group but not for all the patients included in the non-syndromic agenesis group. Furthermore, the average number of missing teeth, without considering third molars was 5.5 per individuals, whereas in our group it was 2.68 ± 2.90 per individuals in males versus 2.60 ± 2.40 per individuals in females. The differences in reporting other teeth agenesis excluding third molars is inconsistent and not comparable. The fact that our sample was derived from orthodontic patient, which are thoroughly documented and follower over time, reduces the possibility that certain severe cases might represent non diagnosed syndromes. Therefore, this inconsistency can be attributed to any such confounder.

Sexual dimorphism was also found in non syndromic oligodontia in Japanese patients (Sato et al. 2021). In that study, without considering the third molars, the number of missing teeth per individual ranged from 6 to 19, while in our study only 27 cases presented with 6 or more teeth missing (8.9% of the agenesis sample). Thus, this inconsistency could be attributed to the large differences in agenesis severity between the two studies. The different geographic origin of the samples might be another reason for this (Khalaf et al. 2014, Carter et al. 2015). In agreement to our study, another study in Japanese patients (Hirakata et al. 2016), tested sexual dimorphism in teeth other than third molars in a group of individuals that had either agenesis of both mandibular third molars or all of all third molars and found no differences between sexes. However, the strict selection criteria applied in this study limit the generalizability of the findings.

The participants in our study were chosen to range from 12.5 to 40 years old. According to previous studies, till 12.5 years, Demirjian`s stage A is observed in the third molars in the vast majority of cases (95%). At this stage, the mineralization of the third molar cusps prevents a false-positive agenesis diagnosis in panoramic radiographs (Caldas et al., 2011; De Oliveira et al., 2012; Karatas et al., 2013; Soares et al., 2015; Zandi et al., 2015). The 40 years limit was chosen to minimize misdiagnosed tooth agenesis of originally extracted teeth or of teeth lost due to caries or other reasons.

One limitation of our study can be the inclusion of orthodontic patients, which may vary in the severity or the incidence of tooth agenesis than the normal population. According to several previous studies, teeth agenesis and malocclusion are endemic in the recent years and tooth agenesis outcomes in orthodontic patients are not expected to vary from the normal population (Gkantidis et al., 2017; Oeschger et al. 2022; Carter & Worthington, 2015).

Finally, as mentioned before, teeth agenesis can vary in severity and pattern depending on the geographic area or ancestry. Therefore, to minimize possible confounding, only white European subjects were included in our study, since they consisted the majority of individuals present in the searched archives. Therefore, the findings need to be confirmed in other populations.

Conclusions

This study showed no sexual dimorphism in patterns or severity of third molars agenesis. Both males and females showed higher rate of third molars agenesis in presence of agenesis of teeth other than third molars compared to isolated third molar agenesis. No sexual dimorphism was found in single tooth agenesis of all teeth including third molars.

In both sexes, in presence of other teeth agenesis, bilateral agenesis of third molars is higher than in individuals without other teeth agenesis. This indicates that the third molars might be more vulnerable to genetic or epigenetic factors involved in agenesis of other teeth and they are often affected as a whole. This seems to be associated with the evolutionary trend in humans towards reduced number of teeth.

Treatment planning of young patients with severe tooth agenesis, should consider the higher possibility of agenesis also in third molars.

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