Taurodontism in Brazilian patients with tooth agenesis and first and second-degree relatives: A case–control study

Raquel R. Gomes, Clarissa D. Habckost, Larissa G. Junqueira, André F. Leite, Paulo T. Figueiredo, Lilian M. Paula, Ana C. Acevedo

Oral Care Center for Inherited Diseases, University Hospital of Brasilia, Department of Dentistry, School of Health Science, University of Brasilia, Brazil

A B S T R A C T

Aim: An association between tooth agenesis and taurodontism has been suggested. To verify if tooth agenesis and taurodontism are associated within families and specific patterns of tooth agenesis, this study aims to compare the frequency of taurodontism in patients with nonsyndromic familial tooth agenesis, their first and second-degree relatives with complete permanent dentition and a control group of unrelated healthy individuals with complete permanent dentition.

Materials and methods: Panoramic radiographs of patients with nonsyndromic familial tooth agenesis, their first and second-degree relatives and a control group of individuals with complete permanent dentition were examined. Taurodontism was assessed on permanent mandibular first molars. The difference in the frequency of taurodontism among the studied groups was tested with Fisher’s Exact Test.

Results: Seventeen families with nonsyndromic familial tooth agenesis were studied. The frequency of taurodontism was 29% in patients with tooth agenesis, 10.3% in their first and second degree relatives, and 6.6% in the control group. A significant statistical difference among the studied groups was observed (p = 0.002). Taurodontism was proportionally more frequent in patients with a higher number of absent teeth. It was mainly observed in patients from families in which the proband was diagnosed with oligodontia.

Conclusions: Taurodontism is more frequent in nonsyndromic familial tooth agenesis. Individuals in families with second premolar and molar oligodontia are more likely to have taurodontism, even the individuals with complete dentition. This association could define a subphenotype for future genetic studies of dental development.

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1. Introduction

Taurodontism (Online Mendelian Inheritance in Man (OMIM) No. 272700) is an alteration in the internal morphology of the pulp chamber resulting in an apical extension of the pulp chamber extending into the root area in a multiradicular tooth. Taurodontic teeth display proportionally short roots and enlarged pulp chamber. In the general population, the reported prevalence of taurodontism ranges from 0.2% to 11.3%, with no statistical difference between genders. Taurodontism affects molars and premolars in both primary and permanent dentitions. It may affect a single tooth or multiple teeth, either unilaterally or bilaterally.

Taurodontism has been found to occur as an isolated trait with familial tendency or as a feature in a wide variety of
multiple-system malformation syndromes, especially in conditions affecting epithelial-derived tissues such as Ectodermal Dysplasia, Trichodento-osseous (TDO) Syndrome, Down’s Syndrome,5–7 Klinefelter Syndrome8 and X-linked hypophosphatemic rickets.9 The trait has been suggested to be inherited as autosomal recessive,4 autosomal dominant10 and also has been pointed out as an association of taurodontism with X-chromosome aneuploidy.9 Taurodontism has been found in association with other dental anomalies such as amelogenesis imperfecta and tooth agenesis.5,11–18

The aetiology of taurodontism is still unclear. The consensus is that this condition results from a developmental disturbance in the Hertwig’s epithelial root sheath.5,9 Failure or delay of the ectomesenchyme to induce the epithelium of the root sheath, or failure of the response of the epithelium could result in the delay in the morphogenesis of roots of teeth.21 Root morphogenesis is under strict molecular regulation that determines cell lineage and fate, tissue composition and structure, and morphology.19,20 It regards a series of complex processes involving epithelial- and mesenchymal-derived tissues that interact through molecular signalling and develop terminally differentiated cells that secrete unique extracellular matrices and control the microenvironment so that the root-associated tissues can mineralize. Several mice studies indicate numerous transcription and growth factors that are expressed by cells involved in root morphogenesis, for example, Shh, Dlx2, Patched2, Patched1, Nfjc, Gli2 and Smoothen. Nevertheless, little is known about the molecular mechanisms of root morphogenesis.21 The genetics of taurodontism is likely to be polygenic. At present, mutations in the distal-less homeobox gene (DLX3) expressed during root morphogenesis have been associated with taurodontism in TDO Syndrome and in families with autosomal dominant amelogenesis imperfecta.10,22

Tooth agenesis is the most common developmental tooth abnormality in humans. It is defined as the lack of deciduous and/or permanent teeth due to disturbances on odontogenesis. It most commonly involves third molars, affecting 10–25% of the general population.23–25 Excluding third molars, the second most affected group of teeth is either the lower second premolars or upper lateral incisors with a frequency between 3.4% and 10.1% depending on the studied population. A higher significant prevalence of tooth agenesis in females has been suggested.24

The diagnosis of tooth agenesis in the permanent dentition should be made after the age of 625 excluding third molars, and after the age of 10 years if third molars are also studied.26 Tooth agenesis has a strong genetic component.17,27–29 It may occur as sporadic cases, as familial trait, as an isolated condition or as part of other syndromes.30 It may be classified as hypodontia, oligodontia, or anodontia. Hypodontia is a term used to describe the absence of one to six teeth, whereas the term oligodontia is applied to agenesis of more than six teeth excluding third molars.23 The absence of all teeth is termed anodontia and is a rare condition associated with syndromes.31–33 The expression ‘severe hypodontia’ is also used to describe the absence of four or more teeth.31–33

Several tooth anomalies have been reported to be associated with tooth agenesis: small tooth size,34–38 peg-shaped upper lateral incisors,39 malpositions of canines,40,41 rotation of premolars and maxillary lateral incisors42 and taurodontism.43 These anomalies were also observed at higher than normal frequency in relatives affected with hypodontia.17 It has been shown that the teeth in relatives of patients with oligodontia might show reductions in size, even in relatives with complete permanent dentition.43

The aetiology of tooth agenesis is suggested to be multifactorial, with involvement of environmental and genetic factors.44,45 The strong genetic basis of tooth agenesis is supported by molecular studies of familial autosomal dominant tooth agenesis associated with mutations in genes expressed in early tooth development such as PAX9, MSX1, AXIN2 and EDA.46 The reports of families with known gene mutations segregating with tooth agenesis do not describe associated taurodontism.

Therefore, in order to verify if tooth agenesis and taurodontism are associated within families and specific patterns of tooth agenesis, the aim of the present study was to compare the frequency of taurodontism in: (1) patients with nonsyndromic familial tooth agenesis, (2) their first and second-degree relatives with complete permanent dentition and (3) a control group of unrelated healthy individuals with complete permanent dentition.

2. Materials and methods

The present study was approved by the Research Ethics Committee of the Faculty of Health Sciences, University of Brasilia, Brazil. All participants in the present study have signed an informed consent.

2.1. Subjects

Patients with nonsyndromic familial tooth agenesis and their first and second-degree relatives with complete permanent dentition were examined. All subjects were examined in the Oral Care Center for Inherited Diseases, University Hospital of Brasilia, Brazil, from March 2002. Panoramic radiographs of 124 patients with tooth agenesis and their relatives were collected. Radiographs of patients of both sexes, with ages ranging from 11 to 41 years with permanent mandibular first molars presenting complete root formation were included. Radiographs with permanent mandibular first molars presenting image of extensive caries or restorations were excluded. Sixty radiographs were suitable for assessing taurodontism.

2.2. Controls

Panoramic radiographs of 180 unrelated healthy individuals with complete permanent dentition were used as control. The control group was paired by sex and age being three individuals from the control group to each patient and relative.

2.3. Diagnosis criteria

2.3.1. Taurodontism

Taurodontism was analysed on permanent mandibular first molars according to the criteria described by Seow and Lai.12
The tooth was considered as taurodontic when the crown body–root ratio (CB:R) was equal or greater than 1:1.10. The molars were classified as normal, hypotaurodont, mesotaurodont, or hypertaurodont depending on the amount of apical displacement of the floor of the pulp chamber (Fig. 1). A molar was classified as hypotaurodont if the CB:R was within the range 1.10–1.29. Mesotaurodontism was defined as a CB:R within the range 1.30–2.00 and hypertaurodontism if CB:R > 2.00. Pyramidal teeth, defined as molars with a fused, single conical root, were also analysed. To assess crown–root ratios, the radiographs were digitalized at a resolution of 300 dpi and the measurements were performed by one examiner (CHDB) using Image Pro-Express software version 5.0 (Media Cybernetics Inc., Bethesda, MD, USA).

2.3.2. Tooth agenesis
Tooth agenesis was registered when a tooth was absent on the panoramic radiograph, excluding a history of loss due to trauma or extraction. All permanent teeth were investigated, including third molars. Third molar agenesis was diagnosed to differentiate individuals with complete dentition from individuals with only third molar agenesis. Hypodontia was diagnosed when one to six teeth were absent, excluding the third molars. Oligodontia was diagnosed if more than six teeth were absent, excluding the third molars.

2.4. Statistical analysis
Data were analysed using the SPSS (Statistical Package Social Software) at a level of significance set at \( p = 0.05 \). The difference in the frequency of taurodontism among the studied groups was tested with Fisher’s Exact Test. The Relative Risk (RR) was used to measure familial aggregation of taurodontism. The RR was estimated with 95% confidence interval for patients with tooth agenesis and relatives with complete dentition also to be affected with taurodontism when compared with the general population using a prevalence rate of 1.6%.47 The difference in the crown body–root ratio among the studied groups was tested with One Way ANOVA Test (Post Hoc Tukey Test). The difference in the frequency of taurodontism between sexes was tested with the Chi-Square Test. To verify intraexaminer concordance 20% of the tooth measurements (permanent mandibular first molars) were reanalysed after 14 days by the same examiner. The Kappa statistic was used to determine intraexaminer concordance. The Kappa statistic for intraexaminer concordance was found to be 1 for the right permanent mandibular first molar and 0.86 for the left permanent mandibular first molar.

3. Results
Seventeen families with nonsyndromic familial tooth agenesis were studied. Nine families presented hypodontia and eight families had individuals diagnosed with oligodontia. Table 1 shows the distribution of the individuals in this study. In the families with hypodontia, the missing teeth were: one or more incisors in five families, second premolars and incisors in three, and both second premolars and second molars in one. In families with oligodontia, inter- and intra-familial variations in the number of missing teeth were observed, however all teeth groups were affected by agenesis, except for maxillary central incisors. The results of the frequency of taurodontism in the studied groups are summarized in Tables 2–5. A significant statistical difference in the frequency of taurodontism among the studied groups was observed \( (p = 0.002) \). The frequency of taurodontism was higher in patients with nonsyndromic familial tooth agenesis. The risk for a patient with tooth agenesis to have taurodontism was 18.12 times higher than for an individual from the general population (95% CI 5.43–60.45). Moreover, taurodontism in these patients’ first and second-degree relatives with complete permanent dentition was also more frequent than in the control group (Table 2). The risk for a relative with complete dentition to have taurodontism was 6.43 times higher than for an individual from the general population (95% CI 1.92–21.43). A statistical difference in the crown body–root ratio among the studied groups was observed \( (p = 0.019) \). Patients with nonsyndromic

### Table 1 – The distribution by sex of the patients with tooth agenesis, their first and second-degree relatives with complete permanent dentition and the control group.

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with tooth agenesis</td>
<td>17 (54.8%)</td>
<td>14 (45.2%)</td>
<td>31</td>
</tr>
<tr>
<td>First and second-degree relatives</td>
<td>15 (51.7%)</td>
<td>14 (48.3%)</td>
<td>29</td>
</tr>
<tr>
<td>Control</td>
<td>96 (53.3%)</td>
<td>84 (46.7%)</td>
<td>180</td>
</tr>
</tbody>
</table>

### Table 2 – The frequency of taurodontism by sex.

<table>
<thead>
<tr>
<th>Taurodontism</th>
<th>Male ( n ) (%)</th>
<th>Female ( n ) (%)</th>
<th>Total ( n ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with tooth agenesis ( (n = 31) )</td>
<td>4 (12.9%)</td>
<td>5 (16.1%)</td>
<td>9 (29.0%)</td>
</tr>
<tr>
<td>First and second-degree relatives ( (n = 29) )</td>
<td>3 (10.3%)</td>
<td>0 (0.0%)</td>
<td>3 (10.3%)</td>
</tr>
<tr>
<td>Control ( (n = 180) )</td>
<td>6 (3.3%)</td>
<td>6 (3.3%)</td>
<td>12 (6.6%)</td>
</tr>
</tbody>
</table>
Table 3 – The frequency of unilateral and bilateral taurodontism and the distribution of the types of taurodontism.

<table>
<thead>
<tr>
<th>Taurodontism</th>
<th>Unilateral n (%)</th>
<th>Bilateral n (%)</th>
<th>Hypodontia n (%)</th>
<th>Meso n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with tooth agenesis (n = 31)</td>
<td>5 (16.1)</td>
<td>4 (12.9)</td>
<td>7 (22.5)</td>
<td>2 (6.4)</td>
</tr>
<tr>
<td>First and second-degree relatives (n = 29)</td>
<td>2 (6.8)</td>
<td>1 (3.4)</td>
<td>3 (10.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Control (n = 180)</td>
<td>12 (6.6)</td>
<td>0 (0.0)</td>
<td>9 (5.0)</td>
<td>3 (1.6)</td>
</tr>
</tbody>
</table>

Table 4 – The frequency of taurodontism according to the classification of tooth agenesis.

<table>
<thead>
<tr>
<th>Classification of tooth agenesis</th>
<th>Taurodontism</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present n (%)</td>
<td>Absent n (%)</td>
</tr>
<tr>
<td>Third molar agenesis</td>
<td>1 (11.1)</td>
<td>8 (88.9)</td>
</tr>
<tr>
<td>Hypodontia</td>
<td>4 (26.7)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Oligodontia</td>
<td>4 (57.2)</td>
<td>3 (42.8)</td>
</tr>
<tr>
<td>Total</td>
<td>9 (29.0)</td>
<td>22 (71.0)</td>
</tr>
</tbody>
</table>

familial tooth agenesis exhibited CB:R higher than their first and second-degree relatives with complete permanent dentition and also higher than the control group. No significant statistical difference was observed between sexes. The unilateral and bilateral frequency of taurodontism is shown in Table 3. In the control group, only unilateral taurodontism was observed. There was no difference in the distribution of taurodontism between the left and the right side. Only hypotaurodontism and mesotaurodontism were diagnosed in the studied sample (Table 3). There was no case of hypertaurodontism, pyramidal or single-rooted permanent mandibular first molars. Taurodontism was proportionally more frequent in patients with a higher number of absent teeth (Table 4). It was mainly observed in patients from families in which the proband was diagnosed with oligodontia (Table 4). Table 5 shows the distribution of individuals within the families according to the classification of tooth agenesis, type of missing teeth and the presence of taurodontism. The frequency of taurodontism in nonsyndromic familial oligodontia was statistically higher than in the control group ($p = 0.001$). In this families, individuals with taurodontism had mainly second premolars, second and third molars missing. One family with the proband diagnosed with oligodontia presented tooth agenesis and taurodontism segregating in an autosomal-dominant inheritance mode (Fig. 2).

4. Discussion

In the seventeen families with nonsyndromic familial tooth agenesis in this study, taurodontism of one or two first permanent mandibular molars was more frequent in patients with tooth agenesis and their first and second-degree relatives with complete permanent dentition than in the control group. Whilst the frequency of taurodontism in patients with tooth agenesis in this study is comparable to the reported in Brazilian and other geodemographic patients with hypodontia and oligodontia that used the same taurodontism diagnostic criteria, the frequency of taurodontism in first and second-degree relatives with complete dentition was higher when compared to the control group, to another Brazilian populations and to the prevalence reported in the literature.

Several studies have investigated the association of other tooth anomalies in patients with tooth agenesis, however only a few have studied more specifically its association with taurodontism. Arte et al. studied the frequency of anomalies in familial incisor–premolar hypodontia. They concluded that hypodontia was associated with taurodontism because the frequency of taurodontism was statistically higher in both probands ($p = 0.003$) and family members with hypodontia ($p = 0.048$) compared to the control sample. They concluded that the results were not statistically significant in separate groups of relatives, however they did not distinguish between relatives with and without hypodontia when comparing first and second-degree relatives. In this study, patients with tooth agenesis were distinguished from relatives with complete dentition. The results showed...

Table 5 – The frequency of taurodontism within the families according to the classification of tooth agenesis.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Families with tooth agenesis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Taurodontism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Present n (%)</td>
<td>Absent n (%)</td>
</tr>
<tr>
<td>Complete dentition</td>
<td>0 (0.0)</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Third molar agenesis</td>
<td>0 (0.0)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Hypodontia</td>
<td>1 (12.5)</td>
<td>8 (78.5)</td>
</tr>
<tr>
<td>Oligodontia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>19</td>
</tr>
</tbody>
</table>

4. Discussion

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that the risk for a patient with tooth agenesis to have taurodontism was about 18 times higher than that of the general population and that the risk for a relative with complete dentition to have taurodontism was about 6 times higher. We found that taurodontism is more frequent in nonsyndromic familial tooth agenesis, even the individuals with complete dentition.

Two Brazilian populational studies did not find association between tooth agenesis and taurodontism, but these results may be explained because the studied samples were mainly composed of esporadic cases of hypodontia. Previous studies that suggested association between tooth agenesis and taurodontism imply that it is more likely observed in cases of severe tooth agenesis, which is in accordance to our

Table 6 – The distribution of individuals within the families according to the classification of tooth agenesis, type of missing teeth and the presence of taurodontism.

<table>
<thead>
<tr>
<th>Family</th>
<th>Tooth agenesis</th>
<th>Missing teeth</th>
<th>Complete dentition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \Delta )</td>
<td>Taurodontism</td>
<td>Present</td>
</tr>
<tr>
<td>Hypodontia</td>
<td>Family 1</td>
<td>2–4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Family 2</td>
<td>2–5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Family 3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Family 4</td>
<td>1–4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Family 5</td>
<td>2–5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Family 6</td>
<td>1–4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Family 7</td>
<td>3–9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Family 8</td>
<td>3–4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Family 9</td>
<td>4–9</td>
<td>0</td>
</tr>
<tr>
<td>Oligodontia</td>
<td>Family 1</td>
<td>1–19</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Family 2</td>
<td>5–11</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Family 3</td>
<td>1–17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Family 4</td>
<td>1–9</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Family 5</td>
<td>1–17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Family 6</td>
<td>2–12</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Family 7</td>
<td>6–13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Family 8</td>
<td>1–18</td>
<td>0</td>
</tr>
</tbody>
</table>

\( \Delta \) = variation of the number of missing teeth among the individuals in each family. Missing third molars were also counted. Mbl, mandibular incisors; MbCI, mandibular central incisors; MxLI, maxillary lateral incisors; C, canines; PM, premolars; Mx2 PM, maxillary second premolars; M, molars.

Fig. 2 – (A) Family Pedigree. (B) Panoramic radiograph showing the absence of nine permanent tooth (asterisks) and taurodontism of the permanent mandibular first molars. (C) Tooth number anomalies in the examined family members. Tooth agenesis is represented by black teeth and taurodontism by grey teeth. X represents teeth lost due to extraction.
results. The frequency of taurodontism in the different groups of this study points a correlation between taurodontism and number of missing teeth. Seow and Lai investigated whether taurodontism was associated with certain patterns of tooth agenesis. They found that 56.5% of the patients with taurodontism had six or more missing teeth. Also, Kan et al. found that children with multiple missing teeth were significantly more susceptible to taurodontism than children with a single missing tooth. These data suggest that increased prevalence and severity of taurodontism are correlated with increased number of missing teeth. Our results suggest that individuals in families with second premolar and molar agenesis are more likely to have taurodontism.

The occurrence of taurodontism is considered an indicator of developmental instability and tooth agenesis has been suggested as an expression of a general abnormality of dental development. Alterations in crown–root ratio may be subtle morphological differences probably followed by other major alterations. Whilst our understanding of the genes and specific processes related to tooth initiation and crown formation has advanced over the past several decades, root development remains less well-understood. As taurodontism has been reported to be more common in individuals with tooth agenesis, understanding the nature of this association may be of importance in determining the aetiology of both conditions. This association could define a subphenotype for future genetic studies of dental development.

Genes expressed in the early stages of tooth development, such as MSX1, PAX9, AXIN2 and EDA have been linked to tooth agenesis, whereas the gene DLX3 that was identified in taurodontism associated with syndromes is expressed later during root morphogenesis. These genes, which are expressed at two distinctly different points in time during the entire tooth formation process, are likely to link between tooth agenesis and taurodontism. For instance, the gene PAX9 has been linked to agenesis of second premolars and molars in families with oligodontia and it has been demonstrated that the reduction of PAX9 gene dosage in an allelic series of mouse mutants causes hypodontia and oligodontia where the missing molars are arrested at different developmental stages and posterior molars are consistently arrested at an earlier stage. This is indicative that a reduction of PAX9 gene dosage affects the dental field as a whole. A potential candidate gene to be linked to tooth agenesis and taurodontism in families is DMP1. This gene encodes dentine matrix protein-1 (DMP-1), a non-collagenous bone matrix protein with an important role in the development and mineralization of bone and teeth. Homozygous mutations in DMP1 cause an autosomal recessive form of hypophosphataemia with permanent and deciduous teeth displaying enlarged pulp chambers in affected individuals. Individuals with either homozygous or heterozygous mutations in DMP1 showed tooth agenesis. It has also been shown that the third molar is either missing or retarded in 10% of Dmp-1 null mice that exhibit enlarged pulp chambers.

The studies that reported gene mutations segregating in families with tooth agenesis did not describe associated taurodontism. The identification of families with specific associated dental anomalies would allow testing of the specific hypothesis that certain genetic factors contribute to that specific association. Molecular studies are necessary to verify the aetiology of taurodontism associated with tooth agenesis. Further sequence variations studies of individual with nonsyndromic familial tooth agenesis and their relatives would confirm a possible association between these anomalies and could also contribute to a better understanding of root formation.

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Competing interest

None declared.

Ethical approval

The present study was approved by the Research Ethics Committee of the Faculty of Health Sciences, University of Brasilia, Brazil. Protocol number: 18/2008.

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