Multiple agenesis and anhidrotic ectodermal dysplasia: a comparative longitudinal study of dental similarities and genetic differences in two groups of children

E. BARBERÍA, D. SAAVEDRA*, M. ARENAS, M. MAROTO

ABSTRACT. Aim Dental anomalies in shape and number may be present isolated or associated with other manifestations. In anhidrotic ectodermal dysplasia they occur more frequently and severely. The authors examined a group of children with similar dental anomalies but no other ectodermal or extra-ectodermal signs.

Methods This study makes a comparative evaluation of similarities and differences of dental anomalies between two groups: A anhidrotic ectodermal dysplasia and B similar dental finding but without extra-dental anomalies.

Results In group A, the average number of agenesis in primary teeth was 3.5 (upper) and 5.33 (lower); in permanent teeth it was 5.4 and 5.8, respectively. In group B, the average was 1.62 (upper) and 0.25 (lower) in primary teeth, and 4.0 and 4.25 in permanent teeth respectively, with no constant pattern of occurrence. The study of tooth morphology of both groups revealed numerous anomalies in both dentitions. No differences were found in the average number of agenesis and morphological anomalies in the permanent teeth between both groups, but in the primary dentition group B presented a lower degree of incidence.

Conclusion The presence of almost normal primary dentition (regarding to number), but with morphological anomalies, should lead to suspect their exacerbation in the permanent dentition.

KEYWORDS: Anhidrotic ectodermal dysplasia; Oligodontia; Multiple agenesis; Conical teeth; Ectodermal anomalies.

Introduction
Dental anomalies in shape and number have been widely described in literature, either isolated or associated with other manifestations, both of ectodermal and extra-ectodermal origin, as part of diverse syndromes [Schalk-van der Weide et al., 1992; McKusick, 1988; Stimson et al., 1997; Lucas, 2000; Goldemberg, 2000; Shashikiran, 2002]. It is in anhidrotic ectodermal dysplasia that these dental anomalies are observed with greater frequency and have been the topic of several researches, with publications analyzing and detailing various aspects of these patients both from a genotypical and phenotypical viewpoint [Crawford, 1991; McLaughlin, 1991; Vierucci et al., 1994; Guckes et al., 1998; Ohno and Ohmori, 2000; Ruhen et al., 2001].

Ectodermal dysplasias constitute a group of clinically and genetically heterogeneous entities which is steadily increasing. Its variability can be explained by the different degree of involvement of the structures deriving from the ectoderm: keratinocytes, melanocytes, hair, sebaceous glands, eccrine and apocrine glands, nails and teeth. In addition, there may be involvement of the lens, conjunctiva, anterior lobe of the hypophysis, nipples, inner ear, mucous membranes of the mouth, nose, rectum and their respective glandular structures, as well as the Central Nervous System and the adrenal medulla, as signs of diverse syndromes [Reed et al., 1970; Winter and Baraitser, 1996; Kupietzky and Houpt, 1995].

This complex nosological group has been defined, classified and periodically reviewed by Pinheiro and

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Freire-Maia [1994]. These authors propose the existence of two groups; one includes all the clinical conditions characterized by defects in at least two of the following classical ectodermal structures: hair, teeth, nails and sweat glands, with or without other associated malformations. The other group includes the clinical conditions with defects in only one of the four above-mentioned classical structures and at least one other ectodermal defect [Pinheiro and Freire-Maia, 1994].

A clinical condition characterised only by ectodermal signs is called Pure Ectodermal Dysplasia; if it combines ectodermal signs and malformations it is known as Ectodermal Dysplasia Syndrome or Malformation Syndrome with Ectodermal Dysplasia [Pinheiro and Freire-Maia, 1994].

The most common ectodermal dysplasia is the hypohidrotic or anhidrotic type, also called Christ-Siemens-Tourraine Syndrome, responsible for at least 80% of the cases. Men are affected more frequently and with greater severity than women. The affected men are of normal intelligence, with thin hair, eyebrows and eyelashes and no body hair; they do not sweat and frequently suffer episodes of high temperature in infancy. They present multiple agenesis and their teeth often have an abnormal shape. They often show pigmentation and dryness of the skin around the eyes and the majorities have a prominent forehead, saddle nose, protruding lips and a hoarse voice. Their secretion of saliva and tears is usually reduced. The women who are obligate carriers may have thin hair, but the best diagnostic signs, not always present, are dental anomalies and an abnormal pattern of sweat distribution. Definitive clinical diagnosis is performed by mean of skin biopsy which shows the characteristic histopathology [Norval and Van Wyk, 1988].

This condition is X-linked and recessive and the gene responsible has been located at Xq12-13 [Zonana et al., 1988]. The paternal origin of the mutation is 3.5 times more frequent than the maternal origin. Kere et al. [1996] showed mutations in the gene that codifies a transmembrane protein expressed in the keratinocytes, in the hair follicles and in the sweat glands.

In the course of their professional careers the authors have examined a number of child patients with similar anomalies in dental shape and number, which affected both primary and permanent teeth. Among them, one group has been diagnosed with anhidrotic ectodermal dysplasia, while another group does not show additional manifestations of this clinical condition; that is to say, they do not present any other affected ectodermal or extra-ectodermal structure.

The aim of the present paper is to make a comparative study, from 1998-2004 of these two groups of children, which underwent treatment in the “Program of Integral Odontological Care for Child Patients” at the Faculty of Dentistry in the Madrid Complutense University, with the aim of assessing the similarities and differences of the dental anomalies in both groups.

Materials and methods

The above mentioned patients were included in the study after a complete medical assessment including medical history, examination of the whole body and family history.

The dental findings observed were obtained both by direct and radiological examination. The general physical examination was carried out in order to detect anomalies in sweating, hair, skin, nails and salivary flow, as well as to discard the presence of associated extra-dental malformations. The complementary tests were obtained from the medical and family histories. Using these data the children were then divided into two categories:

Group A: patients with clinical characteristics and diagnosis of anhidrotic ectodermal dysplasia, confirmed by complementary methods such as sweat test, sweat pore count and skin biopsy [Sofaer, 1981; Happle and Frosh, 1985; Tso et al., 1985; O’Leary et al., 1986; Kargül et al., 2001];

Group B: patients with similar dental anomalies to group A, but without any other anomaly of the ectoderm or other tissues.

Given the age of the sample it was possible to study both the primary and permanent teeth in the majority of the patients. The evaluated parameters were: number of ageneses (excluding third molars), teeth involved, and internal and external morphological anomalies. We were able to assess agenesis even in very young children as all of them were in the Nolla stage, where the calcification of the teeth had already begun. By applying the chronology of dentition and the Nolla stages it was possible to discern the missing molar in doubtful cases. The distribution patterns of the dental anomalies were also evaluated.

Results

Group A included 6 patients, 3 boys and 3 girls, of which one boy and one girl were twins. This boy died at the age of 4 and the available data only refers to his primary teeth. Group B included 8 patients, four boys and four girls belonging to four unrelated families.
Figures 1 and 2 show examples of the facial appearance, and the dental arches of each group.

**FIG. 1** - *Images of dental arches and the face of a patient in group A.*

**FIG. 2** - *Images of dental arches and the face of a patient in group B.*
Figures 3 and 4 show the genealogies of the patients in each group. Figure 5 presents the odontograms of group A and Figure 6 those of group B.

For ease of comprehension, dental findings have
been grouped into: anomalies of number, distribution pattern of agenesis, morphological anomalies and other findings.

Anomalies of number. In all of the cases with anomalies of number these were due to agenesis.

In group A the number of ageneses in primary dentition ranged from 2 to 16. Generally the number was greater in the boys sub-group (16, 12 and 10 agenesis) than in the girls one (10, 3 and 2 agenesis) (Table 1). The average was 3.5 in the upper arch and 5.33 in the lower arch (Table 2).

The variation in the number of ageneses in permanent dentition ranged from 3 to 26. The two boys had 26 and 10, while the girls had 16, 11 and 3, with no relationship between higher number and sex of the patient. Although, in general, the number of agenesis was greater in the permanent dentition, this was not true for all the children. In the cases where an increase was observed, this was neither constant nor proportional (Table 1). The average number of ageneses in the upper arch was 5.4 and 5.8 in the lower arch (Table 2).

In group B, which included 8 patients, three of them (2 girls and 1 boy) had no agenesis in primary dentition; 2 (a boy and a girl) had only 1 agenesis;
other two (girls) had two ageneses and one girl had four ageneses, the highest number of the group (Table 3). The average number of ageneses in the upper arch was 1.62 and 0.25 in the lower arch (Table 2).

The children in group B had a number of ageneses in permanent dentition ranging from 2 to 13, although here again there was no constant pattern in the number of agenesis or relationship between these and the sex of the patient (Table 3). The average number for the upper arch was 4.0 and 4.25 in the lower arch (Table 2).

**Distribution pattern of agenesis.** Tables 4 and 5 show the data of the distribution of the agenesis in primary and permanent teeth and the relationship between both dentitions. It can be seen that there is no relationship either in group A or group B between the absence of a primary tooth and that of the corresponding permanent one.

When comparing the ageneses in the right hemiarch with the left one, both upper and lower, as well as any possible symmetry between the two arches, no constant or determined pattern can be observed. This is true for both the primary and permanent dentitions.

In group A none of the children had all their primary teeth.

### Table 3 - Number of ageneses in primary and permanent dentitions in patients in group B.

<table>
<thead>
<tr>
<th>Agenesis</th>
<th>Dentition</th>
<th>Patient and sex</th>
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<tbody>
<tr>
<td></td>
<td>1 m</td>
<td>2 m</td>
</tr>
<tr>
<td>Equivalence</td>
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<tr>
<td>Primary</td>
<td>Symmetry R-L</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>Upper Arch</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>Lower Arch</td>
<td>yes</td>
</tr>
<tr>
<td>Symmetry</td>
<td>Upper/lower</td>
<td>no</td>
</tr>
<tr>
<td>Permanent</td>
<td>Symmetry R-L</td>
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</tr>
<tr>
<td></td>
<td>Upper Arch</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>Lower Arch</td>
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</tr>
<tr>
<td>Symmetry</td>
<td>Upper/lower</td>
<td>yes</td>
</tr>
</tbody>
</table>

m: male f: female N: no agenesis

### Table 4 - Distribution pattern of agenesis in group A.

<table>
<thead>
<tr>
<th>Agenesis</th>
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<td>8 m</td>
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<td>Permanent</td>
<td>Symmetry R-L</td>
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<td></td>
<td>Upper Arch</td>
<td>yes</td>
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<td></td>
<td>Lower Arch</td>
<td>yes</td>
</tr>
<tr>
<td>Symmetry</td>
<td>Upper/Lower</td>
<td>no</td>
</tr>
</tbody>
</table>

m: male f: female N: no missing teeth

### Table 5 - Distribution pattern of agenesis in group B.
teeth in either the upper or the lower arch, while in group B three children had all their teeth in both arches and 7 had all their teeth in the lower arch.

With regard to permanent teeth, only one child in each group had a complete arch. In group A it was the upper arch and in group B the lower arch.

Dental anomalies. A study of the internal and external morphology of the teeth in both groups revealed multiple anomalies. The most significant data were found in the central and lateral incisors and molars in the primary and permanent dentitions (Tables 6 and 7).

In group A in the primary teeth, the central and lateral incisors, when present, almost always had an atypical shape, both in the upper and the lower arch. In group B only 3 of the 8 patients had anomalies of shape in the upper arch and 5 in the lower. Five of the 6 patients in group A had an upper molar with pyramidal roots or taurodontism; as regard the lower molars, 2 children had taurodontism, 2 had a normal shape and the other 2 had agenesis. In group B half of the patients had a molar with taurodontism and the other half had normal molars in both arches.

In the permanent dentition, the upper central incisors, when present, were always peg-shaped in both groups, except for 1 case in group A, which was

<table>
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<th>Dentition</th>
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<th>Tooth</th>
<th>Patient and sex</th>
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<td>Permanent</td>
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</table>

Table 6 - Distribution of dental anomalies in group A.

Table 7 - Distribution of dental anomalies in group B.
Discussion

With regard to family history, the genealogies of group A were consistent with an X linked recessive hereditary pattern, while in group B the pattern of dental anomalies was compatible with an autosomal dominant inheritance, although parents, grandparent and other relatives were affected to a lesser degree as they had only 1 or 2 conical teeth or agenesis and their whole dentition was smaller, showing that with the passing of the generations the gene had become more apparent (anticipation phenomenon).

It is worthy of note that although anhidrotic ectodermal dysplasia is recessive and X-linked, on occasions the propositus was a woman, which was unexpected. However, from the dental point of view, these anomalies do not differ significantly between men and women carriers, as has already been shown by some authors [Guckes et al., 1998; Ohno and Ohmori, 2000; McLaughlin, 1991], although the other signs are present but to a lower extent. This may be due to an irregular inactivation of the X chromosome in the womb [Aizpuru et al., 2001] and thus the “carriers” show the ectodermal dysplasia phenotype, but to a lesser degree.

In general, the dental findings for the group A patients, both for primary and permanent teeth, do not significantly differ from those reported in literature: in reference to the number of agenesis, internal and external morphological anomalies in the anterior or posterior sector [Llodra et al., 2002] and surprising when compared to the research carried out by the general population [Llodra et al., 2002] and surprising to an irregular inactivation of the X chromosome in the womb [Aizpuru et al., 2001] and thus the “carriers” show the ectodermal dysplasia phenotype, but to a lesser degree.

In group B, on the other hand, the analysis of the agenesis shows surprising differences between primary and permanent teeth. These children had few agenesis in primary dentition, while with regard to their permanent teeth they are similar to those in group A. These differences are not so marked in relation to anomalies of shape, where similarities are found both in the primary and permanent teeth.

Thus in relation to the number of agenesis or the degree of morphological anomalies in the permanent dentition, no clinically significant differences were found between the two groups, and the dental anomalies can be considered similar.

However, there were subtle differences in the primary dentition, as the children in group B had fewer agenesis at this stage, with three cases in which the primary teeth were totally normal.

It is important to underline the lack of correlation or symmetry right/left, upper/lower and primary/permanent teeth in the agenesis or in the morphological anomalies in both groups. It should also be emphasized that the presence of normal or almost normal primary teeth with regard to number, but with anomalies in the internal and external morphology should make us reject an exacerbation of the anomalies in the permanent teeth.

A decrease in the salivary flow rate has been described as one of the findings in anhidrotic ectodermal dysplasia [Nordgarden et al., 2001]. It is worthy of note that it is very difficult to intentionally stimulate salivary flow, especially in the youngest patients, which makes it difficult to measure it. The prevalence of caries found in these patients, both in group A and B, was lower than expected for the general population [Llodra et al., 2002] and surprising when compared to the research carried out by the authors in patients with a decreased salivary flow rate [Barbería et al., 1985]. No satisfactory justification for these findings has yet been found.

References


