Dental implications of tooth-nail dysplasia (Witkop syndrome): a report of an affected family and an approach to dental management.

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Tooth-Nail dysplasia is a rare genetic disorder, which is classified as an ectodermal dysplasia. Diagnostic differentiation from other conditions in this category is necessary for effective dental management and genetic counseling. The oro-dental and clinical manifestations of Tooth-Nail dysplasia in an affected male infant and his father are documented. Other family members have the condition and pedigree data are in keeping with autosomal dominant inheritance. A comprehensive approach to the dental management of an affected child is proposed.
J Clin Pediatr Dent 28(2): 107-112, 2004

INTRODUCTION

Witkop tooth and nail syndrome (TNS) [OMIM 189500]a, is a rare genetic disorder in which hypodontia, enamel hypoplasia and morphological changes in the teeth are associated with the dysgenesis of the nails. This condition is conventionally categorized as an ectodermal dysplasia.

The clinical manifestations of hypodontia (oligodontia) and retarded growth of the maxilla and mandible, make appropriate dental management of TNS particularly challenging. An important diagnostic determinant of this syndrome is the failure of development and eruption of the dentition and as a result, the diagnosis may be delayed until early childhood. For this reason, there is potential for confusion between TNS and other ectodermal dysplasias. The distinctive phenotypic features in this disorder have been documented by several authors[1-8,10] and these are summarized in logical sequence in Table 1.

In this article we document the manifestations of an affected child and his father, review relevant literature with regard to the genetic aetiology and clinical manifestations and suggest guidelines for the comprehensive dental management of an affected child.

Table 1. Clinical anomalies recorded as syndromic components or associated features of TNS1-,8,10.

1.	**Teeth**
	• Partial anadontia (hypodontia), or oligodontia of the primary and permanent dentition. Seldom are more than 20 permanent teeth missing, with hypodontia and infrequently anadontia of the permanent teeth. The permanent mandibular incisors, second molars and the maxillary canines are the teeth most frequently involved.
	• Teeth are often small and sharp, with conical narrow tapering crowns.
	• Taurodontia is not common in this syndrome.
	• Hypomineralization of the enamel and other dental abnormalities are rare.
	• The maxillary frenal attachment is prominent in most affected individuals.
2.	**Facies**
	• Pouting lower lip associated with reduced vertical dimension of occlusion.
	• Prominent ears.
	• Slight to moderate frontal bossing in about 25 per cent of affected persons.
3.	**Nails**
	• Nail dysgenesis, or spoon shaped nails (koilonychia), which are slow growing and prone to fracture.
	• The toenails are often more severely affected than the fingernails.
	• Nail abnormalities may be present or absent at birth.
	• Severity ameliorates with age, and may not easily detectable in adulthood.
4.	**Hair**
	• Fine thin, slow-growing scalp hair, with normal eyebrows and eyelashes.
	• Sparse hair and scanty eyebrows have also been recorded.

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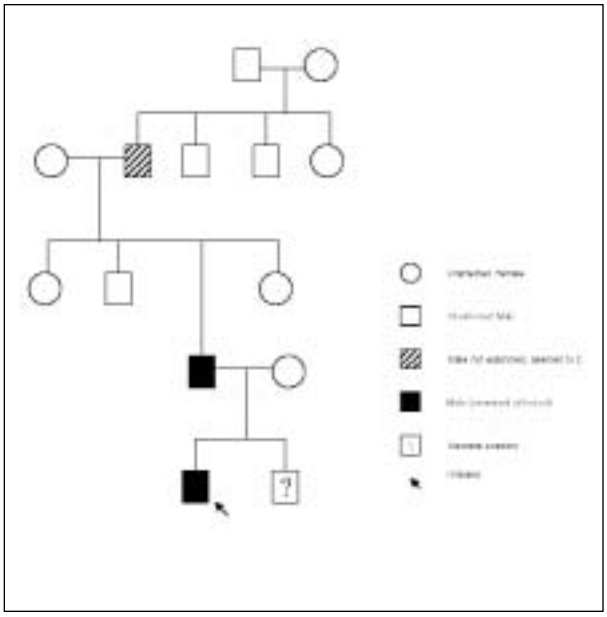

Figure 1. Pedigree of the affected family.

CASE REPORTS

TNS was diagnosed in the proband and his father, and reliably reported in his paternal grandfather. The proband's newborn brother was also possibly affected. Pedigree data were consistent with autosomal dominant transmission (Figure 1).

Patient 1

A male child born in 2000 was aged 2 years and 8 months when referred to the Dental Genetic Unit at Red Cross Childrens Hospital for assessment of abnormalities of his teeth and nails. His general health and development were normal and there had been no untoward factors in his mother's pregnancy. The teeth were conical in shape and he had dysplastic spoon-shaped nails on the fingers and toes (Figures 2, 3). The skin was dry, scaly and lightly pigmented, which appeared to be almost transparent, with the surface blood vessels being easily visible. The hair was fine, scanty and brittle and his eyebrows were sparse. Mild frontal bossing was evident (Figure 4). Sweating was normal and no other stigmata of ectodermal dysplasia were noted.

Intra-oral examination revealed a high maxillary frenal attachment. The eruption sequence was normal for the patient's chronological age. The maxillary deciduous canines (53,63) and the maxillary and mandibular second deciduous molars (55,65,75,85) were congenitally absent (Figure 5). The morphology of the primary incisors and canines were of particular note since these teeth were smaller in the mesio-distal dimension with sharp coniform, tapering crowns. Large inter-dental spaces were also present, especially in the maxillary arch. There was no evidence of enamel hypoplasia, or hypomineralisation.

Figure 2. Patient 1. Thin concave fingernails.

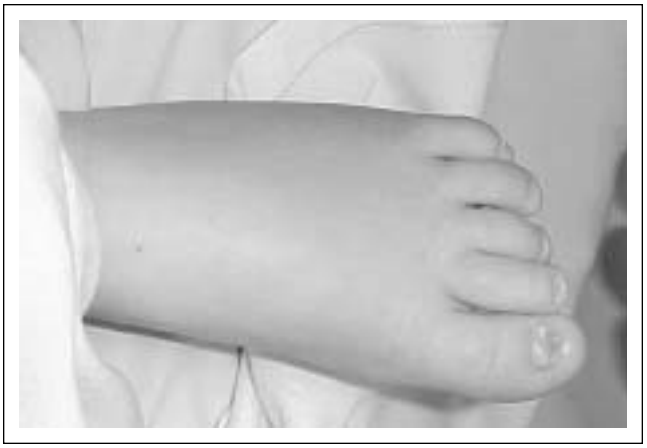

Figure 3. Patient 1. Thin concave toenails.

Figure 4. The affected father and son. Their hair is fine, and their eyebrows are sparse and mild frontal bossing is present.

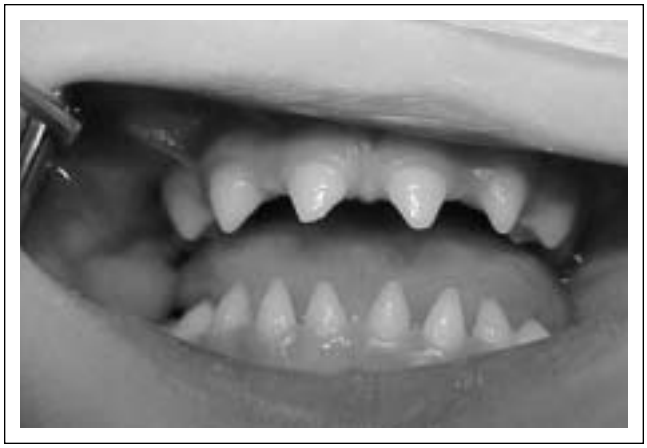

Figure 5. Patient 1. Conical tapering crown forms with large interdental spaces

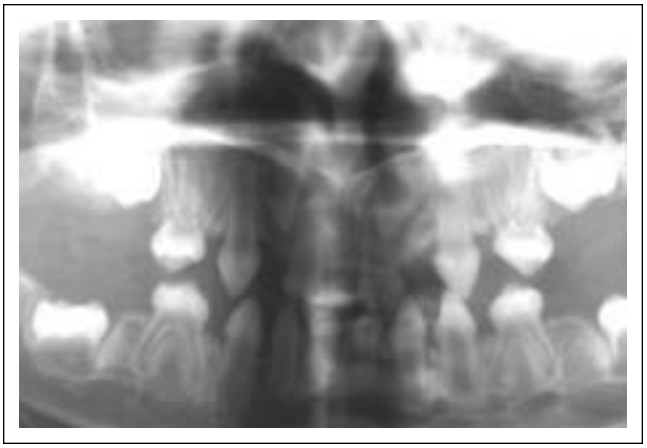

Figure 6. Patient 1. Dental pantomogram showing only 6 permanent tooth buds present (16,11,21,26,36,46). The maxillary central incisors (11,21) are developing into peg-shaped incisors. The distinctive morphology of the primary incisors, canines and molars (54,52,51,61,62,64 and 74,73,72,71,81,82,83,84) is evident.

The dental pantomogram (Figure 6) revealed that the first permanent molars (16, 26, 36, 46) were developing, and mineralized but not fully formed. The maxillary central permanent incisors (11,21) were developing into peg-shaped incisors. There was no evidence of any other tooth bud formation and no other pathology was noted.

Patient 2

The proband's father was 36 years of age when seen in 2002. He had been successfully treated for neoplasia of a submandibular gland 3 years previously and was in good health. On examination the nails of toes 3 to 5 was dysplastic, but his fingernails were normal. He also displayed mild frontal bossing and evertion of his lips (Figure 4). He could not recollect any abnormalities of his primary dentition. Some permanent teeth were congenitally absent (13,14,18,23,28,36,46) and the maxillary permanent lateral incisors (12,22) which were reportedly peg-shape, had been extracted. He wore dental prostheses, which replaced his missing teeth (12,13,14,22,23). The crown mesio distal widths of 25,31,32,41,42 appeared smaller, than the other dentition.

Other family members

The proband's grandfather wore a full complement of upper and lower dentures, and it was confirmed that he had the same pattern of dentition prior to the extractions, which left him edentulous. The second toenails were dysplastic.

At the time of the investigation the mother pregnant expecting another son. The baby (the probands brother) was born and examined a day after birth (Patient 3). The fingernails were normal, but the first toenail was spoon-shaped and the baby's skin was very dry and scaly (Figure 8).

Definitive diagnosis must await the eruption of the primary dentition and the evolution of the phenotype.

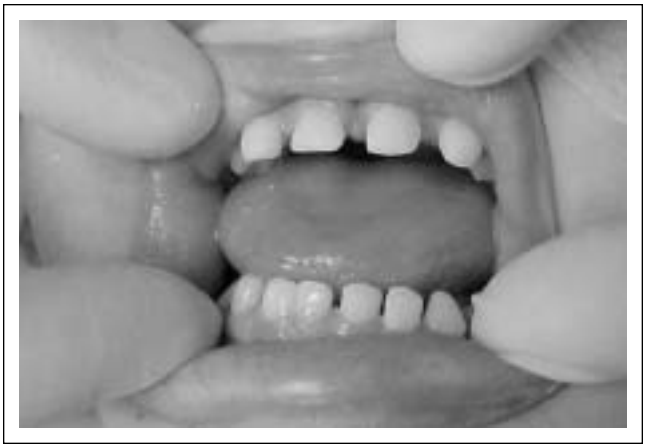

Figure 7. Patient 1. Teeth restored with composite veneers.

Figure 8. Patient 3. At the age of one day. The nail of toe 1 appears to be dysplastic.

Dental Management of the affected child (Patient 1)

Before an appropriate treatment approach was chosen, the patient was assessed as to whether he would be co-operative in the dental chair and whether this procedure could be completed in single visit. From the dental pantomogram the extend of tooth eruption could be seen and since primary root closure in the primary teeth was incomplete, it was decided that treatment should be delayed for three months. This interval would allow complete eruption of the primary teeth, which were to be restored prior to the restorative intervention. Since the patient was unco-operative and extrinsic remodeling of the dentition was necessary, and in view of local circumstances it was deemed preferable to undertake management of this young patient under general anesthesia.

The oro-dental strategy was to restore the dental esthetics to those of the norm by performing basic conservative restorations. In this way, prevention of any habits, speech, masticatory or psychological repercussions would be achieved. Since all the primary teeth, which were to be restored followed the normal chronological eruption sequence, and were fully erupted, a conservative approach taken. The material chosen for the restoration was a hybrid composite. Minimal preparation was required, with minor roughening of the outer enamel layer being necessary. The teeth were conditioned, after which the restorations were performed, conforming the peg-shaped teeth to match the normal structures (Figure 7). The rationale of this form of treatment is to maintain function of the primary dentition for as long as possible. The importance of oral hygiene was explained to the parents and periodical dental assessment was arranged.

DISCUSSION

Ectodermal dysplasias (ED) are collectively defined as genetic disorders in which there are congenital abnormalities of 2 or more structures of ectodermal origin, notably skin, nails, teeth, nerve cells, sweat glands, and components of the eye and hearing mechanisms.

Charles Darwin in 1860 first described ED, and subsequently more than 150 related syndromes were recognized.[b] Witkop and Brearley[5] in 1975, reported that the dental defects most often associated with ED were agenesis of teeth, microdontia, or hypoplastic conical teeth. Micrognathia and lip eversion were sometimes present.

The form of ED, which has been categorized as TNS, is characterized by true partial anadontia, which is often severe and may affect the primary as well as the permanent dentition, in association with nail dysgenesis. This disorder was described by Witkop[2] in 1965 and the eponymous designation "Witkop Syndrome" is sometimes used. Witkop[18], estimates the incidence to be about 1-2:10,000, hence this genetic disorder is rare. In TNS fewer than 20 permanent teeth are usually missing, and on rare occasions anodontia of the primary teeth has been documented.[1] Nail dysgenesis (koilonychia), or spoon-shaped nails are also a feature of the condition. The toenails are often more severely affected than the fingernails and may be absent at birth.[1,7] The severity of nail changes ameliorates with age, and may not easily be detected in adulthood.[7] Minor anomalies may also be syndromic components for instance, Jumlongras *et al*.[7] noted the prominence of the maxillary frenal attachment in most of the patients whom they studied. Affected individuals have a typical facies with everted lips or pouting of the lower lip, due to the lack of alveolar bone growth[7] and underdeveloped mandible. The ears may be prominent and slight to moderate frontal bossing is present in about 25 percent of persons.[5] The hair is usually of a fine texture, with sparse to absent eyebrows.[5,8,9] The sweat glands and heat tolerance are normal[5].

The child reported in this article is unusual, for in the literature it is noted that seldom are more than 20 teeth missing.[1,8] Calcification of the permanent dentition typically commences at the age of 3-4 months intrauterine and proceeds until the age of 7-10 years. In our patient, at the age of 2 years 8 months calcification up to and including the second permanent molar teeth should have begun. Since the rate of calcification is variable, it is difficult to assess the present extent of hypodontia in a child of this age. The fact remains, however, that only 6 permanent teeth are visible in the dental pantomogram, which is significant in this respect. The term "oligodontia" is defined by Stimons *et al.*[10] as the congenital absence of six or more teeth, excluding the third molars, which may have a reduction in the tooth size and form. When the number of missing teeth increases, the crown size reduction usually becomes greater.

A prominent maxillary frenal attachment was present in both the affected father and his son. Due to the fact that there are teeth missing, the alveolar bone is often hypoplastic. This is due to the fact that the alveolus never forms, which leads to under-development of the jaw(s) and reduced vertical dimension of occlusion.[11] This process is evident in our patients since the mandible appears smaller in proportion to the face in both the father and his son (Figure 3). This observation corroborates the contention that the mandible and maxilla are small in affected individuals.[12]

From a genetic view point Witkop[2], 1965 found this condition to be prevalent among Dutch Mennonites in Canada and his pedigree data supported an autosomal dominant mode of genetic transmission. Hudson and Witkop[1] subsequently reviewed the clinical details of 23 affected individuals in 6 families, documented several instances of male-to-male transmission and confirmed the pattern of inheritance. There is however, still some controversy in the literature concerning the mode of inheritance of TNS[10,13] and genetic heterogeneity cannot be excluded. In our Cape Town family male-to-male

transmission has occurred in three generations and the pedigree data entirely supports the conventional autosomal dominance inheritance.

At the molecular level Satokata and Maas[14] found a nonfunctioning MSX1 gene, which was responsible for a syndrome of cleft palate and facial and dental anomalies. Thereafter, using linkage analysis in a family with autosomal dominant agenesis of second premolars and third molars, Vastardis *et al*.[15] identified a locus on 4p16.1 where the MXS1 gene resides. Jumlongras *et al*.[7], established a linkage between TNS and polymorphic markers surrounding the MSX1 locus in a study of MSX1-knockout mice and the analysis of a 3-generation family affected by the disorder.[10] It has been shown that a nonsense mutation in MSX1 causes TNS and that MSX1 is crucial for both tooth and nail development.[7]

Genetic counseling of affected persons or parents is necessary so that they can be informed of the possible recurrent risks and the eventual dental problems that their offspring may encounter. The molecular data, which are now available, would facilitate antenatal diagnosis in an appropriate family setting but in view of the comparatively benign nature of TNS, procedures of this type are hardly warranted.

Dental management is multi-faceted,[16,17] spanning the various growing stages of the individual. It is important to plan the treatment prior to eruption of the permanent teeth, encompassing periodontal, orthodontic and finally prosthodontic measures. Previous management approaches have involved space maintenance, prosthetic appliances (partial dentures and over dentures),[11,13] and even implants[18] for the replacement of missing teeth. The approach to the management of our patient is largely governed by his age, and the necessity to ensure essential conservation of his dentition (primary or permanent). Equally, improvement of the patient's facial aesthetics and masticatory function are important in allowing him to integrate with others of his age. It is necessary to prevent any psychological repercussions, which may later establish themselves in the form of habits, tongue dysfunction or speech disorders.

Based on assessment of the cooperation of the patient, anxiety and fear as well as prior unsuccessful treatment attempts in the dental surgery, it was decided that this extensive treatment would be best done under general anesthesia. Furthermore, a single visit theatre session allows for stringent moisture isolation control, as well as efficient placement of restorations. In our patient, with the resources available and time constraints it was deemed best to perform the restorative dentiostry under general anesthesia.

With regard to the dental aesthetics in our patient, treatment options included the placement of composite cast crowns or crown construction with restorative material; the latter approach was undertaken. The material of choice was light activated hybrid compomer veneer restorations by virtue of its excellent esthetic, handling and physical properties (strength and the occlusal wear rate will be similar to that of normal deciduous tooth wear). This material also imparts fluoride into the surrounding environment, which is then incorporated into the tooth structure. Various interrelated factors determine the longevity of any restorations and the long-term outcome in our patient is uncertain. It is also relevant to mention that with the growth of the patient, modifications and repair of the restorations may be easily undertaken**.**

The vertical dimension of the dentition of the patient will be monitored during growth and it is expected that there will be a definite loss of occlusal functioning, which may result in lip eversion. For these reasons, the patient will be assessed at three monthly intervals. Although it is far to early for orthodontic intervention, on eruption of the first permanent maxillary and mandibular molars at the age of about six, a comprehensive orthodontic treatment plan will warrant consideration.

The fact that the dental features were milder in the father of the affected child (patient 2) is a reflection of the variability of phenotypical expression in this disorder. He underwent extensive prosthodontic bridgework in early adulthood with satisfactory results.

COMMENT

There is no general consensus on the dental management of the Witkop TNS, nevertheless it is evident that the treatment should coincide with the growth potential of the patient. Hence correctly timed treatment is imperative for successful results. It is appropriate that the management of the patient should be interdisciplinary, and relevant that long-term treatment may be necessary. Introduction and re-enforcement of oral hygiene from a young age is important so that affected persons may become accustomed to the dental environment.

ACKNOWLEDGEMENTS

It is also with gratitude that we thank Yolanda Erasmus for her diligence and enthusiastic assistance in the preparation of the manuscript. Thanks to Michael Wyeth of Medical Graphics, who processed and printed the illustrations used for this publication.

We appreciate the support received from the World Health Organization – University of the Western Cape Collaborating Center research fund, and the Special Dental Genetic Clinic -Red Cross Childrens Hospital.

Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), hppt://www.ncbi.nlm.nih.gov/Omim/ (for TNS [MIM 189500])

Hppt://www.nfed.org

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