Wolf-Hirschhorn Syndrome; Oro-Dental Manifestations and Management

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The major manifestations of the Wolf-Hirschhorn syndrome are developmental delay, short stature, mental impairment and epilepsy. Clefts of the lip and palate are sometimes present. Dental problems which are overshadowed by the major syndromic manifestations warrant appropriate management.
We have documented an affected South African boy, discussed his dental management and reviewed the oro-dental implications of the disorder.
Keywords: *Wolf-Hirschhorn, Syndrome, Cytogenetic,Dental,Genetic, Malformation*
J Clin Pediatr Dent 34(2): 173–176, 2009

INTRODUCTION

The Wolf-Hirschhorn Syndrome (WHS) [OMIM 194190], also known as the Deletion 4p-minus syndrome, is an uncommon but well recognized disorder.

Delineation of the WHS began in 1961 when Kurt Hirschhorn of the New York School of Medicine and his colleague HL Cooper documented a deletion of a B group chromosome, either 4 or 5, in a child with the condition which became known as the Cri du Chat syndrome.[4] Four years later, Ulrich Wolf and researchers at Freiburg, Germany reported a similar deletion of the short arm of a B chromosome in a child whose phenotypic features differed from those of the Cri du Chat syndrome.[5] With the advent of chromosomal banding techniques, it then became evident that the WHS deletion was on chromosome 4p while that of the Cri du Chat syndrome was on 5p. In the years that followed an accumulation of case reports of the WHS facilitated increasing definition of the syndromic manifestations. The single eponym 'Wolf' was employed by some authors[1], but by 1980 the conjoined eponym "Wolf-Hirschhorn" had become firmly established. During the past decade, increasing interest in the molecular basis of the condition has lead to the use of the title "Deletion 4p Syndrome" as an alternative to the eponymic version.

The WHS presents in the neonate with low birth weight, hypotonia and microcephaly. Developmental milestones are delayed, and growth is deficient. Intellectual impairment, which is variable but often severe, is a major problem. The diagnosis is suspected on recognition of the characteristic facies, and confirmed by laboratory demonstration of a partial deletion of the short arm of chromosome 4.

Cleft lip, with or without cleft palate, and micrognathia are present in a significant proportion of affected persons. Dental manifestations include hypodontia,[1,2] and taurodontism.[3] Mental retardation and a propensity to epilepsy impacts upon the dental management of the various oro-dental complications.

There is a paucity of reports in the literature concerning the oro-dental features of the WHS. Against this background we have described and depicted an affected South African child, discussed the practical significance of the oro-dental features and outlined an approach for dental management of the WHS.

Case report

A South African boy of mixed ancestry was born in 1996 at 42 weeks gestation with a weight of 2.44 kg, after an uneventful pregnancy. At the time of birth a cleft lip and palate was noted together with hypospadias and other minor dysmorphic features. His early course was characterized by feeding difficulties, failure to thrive, and the development of epilepsy at 9 months of age. The diagnosis of Wolf-Hirschhorn syndrome (WHS) was made clinically and

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confirmed cytogenetically at the age of 10 months by demonstration of a deletion of the short arm of chromosome 4(46XY), del (4) p16->pter). Both parents were shown to have normal chromosomes. He had global developmental delay, only walking at 8 years of age.

At the age of 10 years and 10 months, he was ambulant with a wide based, jerky gait. Mental impairment was severe and he was receiving hydantoin for epilepsy. His growth parameters were well below the 3rd centile with a height age of 6 years. He had the typical facial features of WHS with epicanthic folds, ocular hypertelorism, a prominent glabella and simple ears with bilateral pre-auricular pits. The surgical scar of a repaired cleft lip was evident (Figure 1). Micrognathia was present, with down-turning of the corners of the mouth (Figure 2). Structural cardiac and renal abnormalities were excluded by ultrasonic investigation.

Dental examination was extremely difficult due to the patient's mental handicap. Intra-oral examination was only possible once the patient had been sedated (7.5 mg Dormicum orally) and for this reason intra-oral radiographs were not recorded. Clinical examination revealed the surgical repair of the cleft palate, a high palatal vault with crowding of his anterior maxillary teeth and spacing of the mandibular incisors with evidence of microdontia (Figure 3).

The state of his oral hygiene was poor and several retained deciduous teeth were carious. Thereafter, prophylactic treatment was done and teeth 53, 64 and 74 were extracted under general anesthesia.

Recall visits for this patient will include re-educating the care-giver in oral hygiene methods including the use of automated toothbrushes and regular application of fluoride. Future dental management will be focused upon basic conservative restoration using materials that have high fluoride content. Periodic orthodontic consultations may be necessary but these will be undertaken at the discretion of the clinicians, especially with regard to the patient's mental and physical development.

DISCUSSION

In a study of 159 cases of the WHS, it was estimated that the minimum birth incidence was about 1 in 95,000, and that the infant mortality rate was approximately 20%.[6] Survival into adulthood is unusual but not unprecedented.

Children with the WHS bear a close facial resemblance to one another. Microcephaly, micrognathia, ocular hypertelorism, prominence of the glabella, flattening of the nose with asymmetrical nares, shortening of the philtrum and down turning of the corners of the mouth constitute a recognizable facies. Strabismus and facial clefting are variable features. The oro-facial manifestations of the WHS are listed in Table I. Other external syndromic features include high arched eyebrows, convex fingernails and simian palmar creases. Internal ramifications, which can influence the nat-

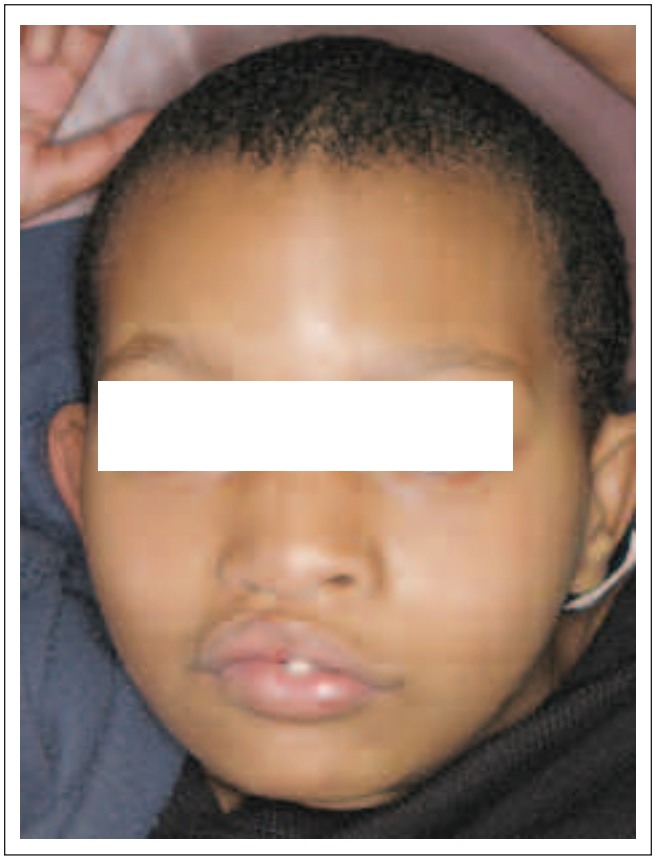

Figure 1. The affected boy at the age of 10 years. Ocular hypertelorism, epicanthic folds and the surgical scar of a repaired upper lip are evident.

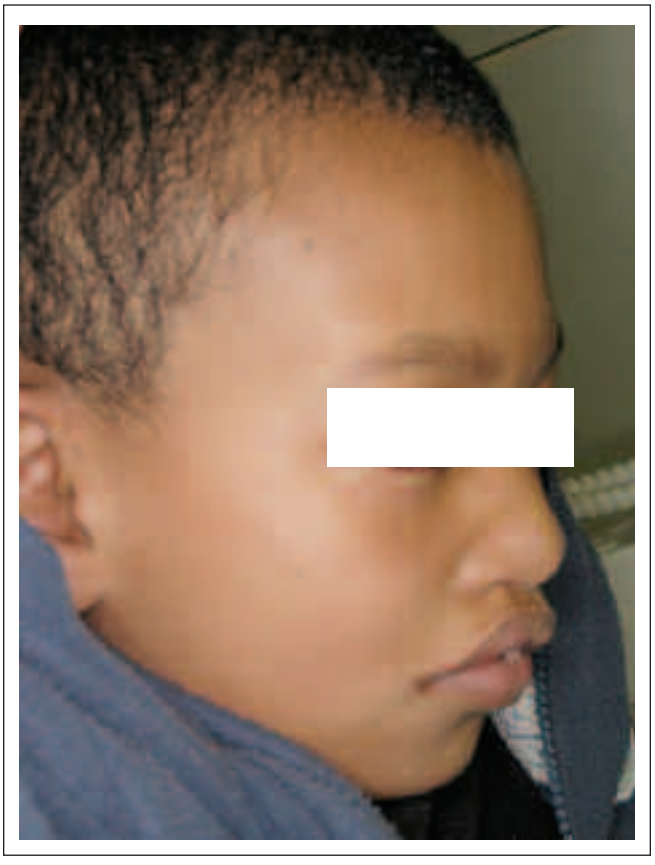

Figure 2. Pre-auricular ear pits and mandibular micrognathia are present.

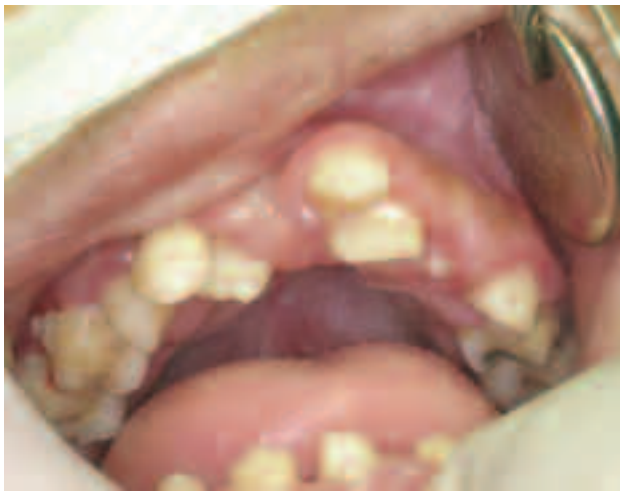

Figure 3. Intra-oral manifestations; a repaired cleft palate, a poorly arranged dental arch and microdontia of the mandibular incisors with interdental spacing are evident.

ural history of the condition, include renal, cardiac and skeletal abnormalities.

The WHS has features in common with other mental retardation-malformation syndromes, notably the Cri du Chat syndrome, from which it was originally delineated, and the Smith-Lemli-Opitz syndrome. Diagnostic precision is achieved by the demonstration of the underlying chromosomal defect on the short arm of chromosome 4 (4p16.3). The size of the deletion is inconsistent and if conventional cytogenetic investigations fail to reveal an abnormality, the fluorescent *in situ* hybridisation (FISH) technique may be informative.

Table I. Oro-facial Manifestations of the Wolf-Hirschhorn Syndrome

Characteristic features
Psychomotor and growth retardation
Microcephaly
Craniofacial asymmetry
High forehead
Wide nasal bridge with prominent glabella
Beaked nose
Hypertelorism
Epicanthal folds
Short philtrum
Downturned corners of mouth
Long, thin neck
Less common features
Midline scalp defect
Highly arched eyebrows
Ptosis
Downward slanting palpebral fissures
Facial angiomas
Divergent strabismus
Deep seated, poorly differentiated ears
Lobeless pinnae
Narrow external canals
Preauricular dimple or skin tag
Sensorineural hearing loss
Cleft lip and or palate
Microdontia
Hypodontia

The majority of persons with WHS have new mutations although in about 15%, one of the parents carries a balanced chromosomal translocation; these factors are important in genetic counselling.

At the molecular level, the critical region for WHS in the deletion on the short arm of chromosome 4 is about 146 kilobases in length.[7] Correlations between the genotype and the phenotype have been recognized.[8] In the oro-dental context Nieminen *et al* (2003)[9] documented 5 persons with WHS and significant oligodontia in whom one copy of the MSX1 gene in the region on 4p had been deleted. These authors pointed out that this gene was mandatory for normal tooth development. Thereafter, it was suggested that the cleft palate, microcephaly and mental retardation in the WHS were effectively the result of a contiguous gene syndrome.[10]

The most significant oral manifestations of the WHS are cleft lip with or without cleft palate, together with mandibular hypoplasia. Down turning of the corners of the mouth represent an important component of the characteristic facies. Involvement of the teeth is variable but the presence of hypodontia has been emphasized.[1] Radiographic investigation of a patient with the WHS revealed taurodontism.[3] An affected child documented by Babich *et al* (2004)[11] had agenesis of multiple permanent teeth, especially premolars and molars, taurodontism and retention of primary teeth. Another child with the WHS had severe hypodontia, late dental development, taurodontism of the primary molars, microdontia and spacing.[2]

In view of the potential severity of the mental retardation, dental caries and periodontal disease may be the consequence of defective oral hygiene. Treatment of concomitant epilepsy with hydantoin may lead to hyperplasia of the gingiva and further accentuate these problems. Swallowing difficulties have their basis in disturbed cortical functioning, and may lead to nutritional deficiency. Similarly, articulation and speech may be impaired.

The main general factors which influence dental management of the WHS are mental retardation and epilepsy.[12,13] Drooling and swallowing difficulties may also impact upon dental procedures, while small stature will be relevant to the choice of the dental chair. The potential presence of internal complications, especially in the cardiac and renal systems, warrants assessment prior to any dental procedure. In turn, these factors may determine the mode and type of anaesthetic. Prophylactic antibiotic therapy may be necessary if a structural cardiac defect is present. Finally, the magnitude and sophistication of dental procedures which are contemplated will be influenced by the natural history of the WHS and the potentially restricted lifespan.

It is evident that a wide range of oro-dental abnormalities may occur in the WHS. These warrant due care and attention, in the context of the overall management of this condition. As emphasised by Iwanowski et al (2005),[14] an affected

child has needs which require integrated support. Appropriate dental care represents an important component of this process.

ACKNOWLEDGEMENTS

We are grateful for support from the National Research Foundation and the Medical Research Council of South Africa. Greta undertook the literature search and preparation of the manuscript with her customary efficiency and goodwill.

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