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CLINICAL SECTION

Beware the solitary maxillary median central incisor

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The incidence of a solitary maxillary median central incisor (SMMCI) tooth in the general population is low, in either the primary or secondary dentition. The most common cause of a missing maxillary central incisor is trauma, or more rarely hypodontia. However, SMMCI is also a recognized genetic anomaly and affected individuals can be carriers for a potentially more serious condition affecting midline development of the brain and face, holoprosencephaly (HPE). The presence of an SMMCI of unknown aetiology is therefore considered a risk factor for HPE, even in the absence of any other clinical signs. The orthodontist may be responsible for diagnosing cases of SMMCI with no obvious cause, and in these subjects due consideration should be given to referral for the appropriate genetic testing and counselling.

Key words: Solitary median maxillary central incisor, genetic testing, orthodontics, sonic hedgehog

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Introduction

All syndromic conditions affecting the head and neck have a characteristic range of clinical features and nowhere is this more dramatic than in holoprosencephaly (HPE)[1] (Figure 1). HPE is a congenital malformation sequence, which involves impaired cleavage of the embryonic forebrain in association with varying degrees of facial dysmorphism.[2] In the most severe form of HPE, the early forebrain fails to divide into right and left cerebral hemispheres, the olfactory and optic tracts remain as single midline structures and the face exhibits cyclopia, with a proboscis or rudimentary nose sitting above a single midline eye.[3] In contrast, milder or microforms of this condition can present with normal brain morphology, but varying degrees of midline facial dysmorphogenesis, including clefting. The mildest manifestation of HPE is represented by normal development of the central nervous system (CNS) and face, but the presence of only a solitary maxillary median central incisor (SMMCI). This diverse range of clinical presentation can even occur within members of the same pedigree.[4] Importantly, individuals affected by SMMCI can be carriers for HPE, and the presence of unexplained SMMCI is therefore considered a risk factor even in the absence of any other clinical signs. The orthodontist may be responsible for diagnosing cases of SMMCI with no obvious aetiological basis, and in these subjects due consideration should be given to referral for the appropriate genetic testing.

HPE is a common cause of inherited birth defect

HPE is a surprisingly frequent condition in the human population, occurring with an incidence of 1 : 250 in early embryonic development and representing one of the commonest causes of embryonic lethality.[5] Because of this lethality, the incidence of HPE drops to around 1 : 16000 at birth.[6] HPE has a complex aetiological basis, with both genetic and environmental factors being involved.[7] In many cases a genetic cause can be established, through either chromosomal anomalies or gene mutation acquired sporadically or via Mendelian patterns of inheritance. In recent years, a number of HPE-associated genes have been identified, which include sonic hedgehog (*SHH*),[8–10] *SIX3*,[11,12] *TGIF*[13] and *ZIC2*.[14] A key question has been why the mutation of a single gene can produce such a wide range of clinical phenotypes within a single condition. In the case of *SHH*, it would appear that interference with activity of this signalling molecule at discrete, but crucial time points during both neural and facial embryonic

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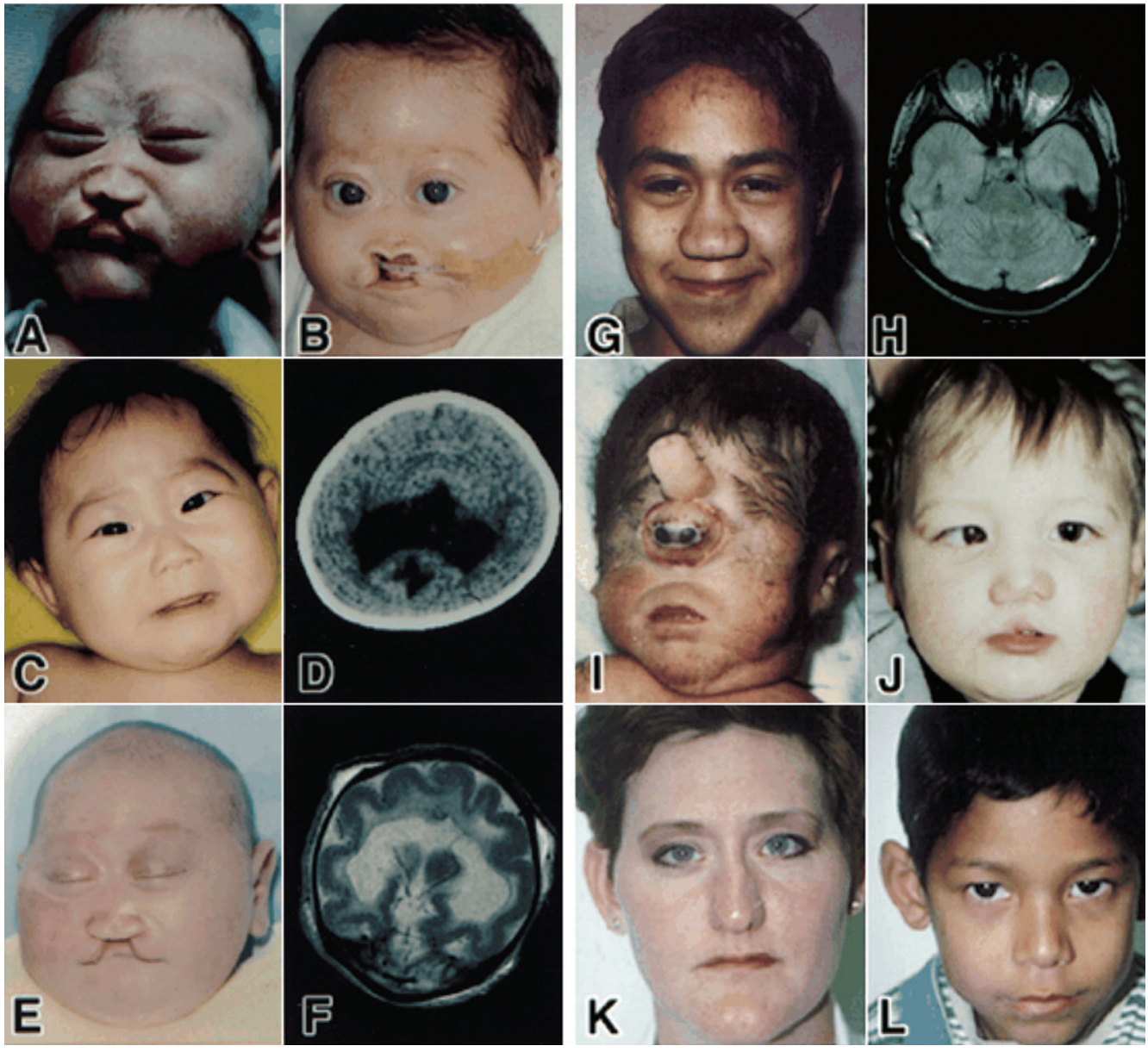
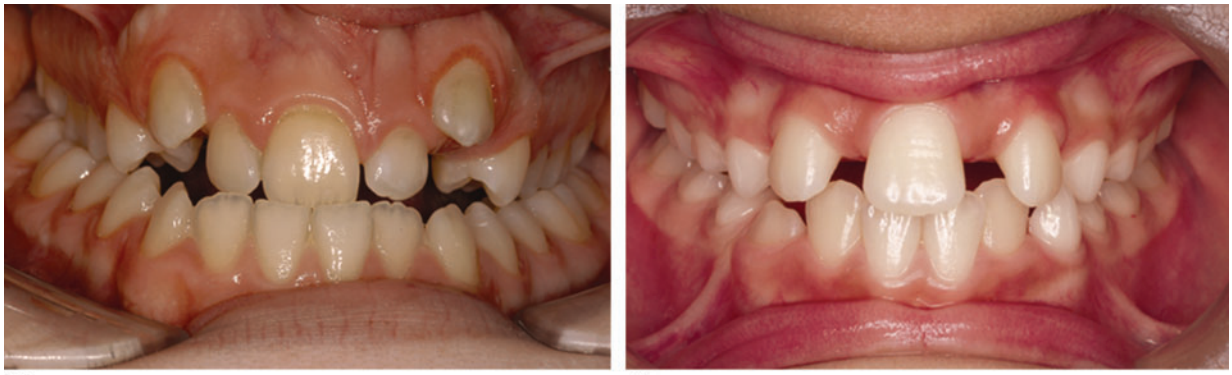


Figure 1 The clinical spectrum of HPE. (A) Microcephaly with absence of nasal bones and median cleft lip/palate. (B) Premaxillary agenesis and midline cleft lip/palate. (C,D) Severe semilobar HPE but relatively normal facies. (E,F) Microcephaly, premaxillary agenesis and cleft lip. (G,H) Microcephaly, ocular hypotelorism, flat nose and hypoplasia of the midface and lip philtrum, but normal brain scan. (I) Severe alobar HPE with cyclopia and midline proboscis above the eye. (J) Microcephaly, ocular hypotelorism, right-sided cleft lip and palate (repaired) and normal brain. (K) Microcephaly, philtrum hypoplasia and normal brain. (L) Lobar HPE, microcephaly and philtrum hypoplasia. All these individuals have mutations in the sonic hedgehog gene. Reproduced from Nanni *et al.*,[10] by permission of Oxford University Press

patterning can lead to such a spectrum of malformation severity.[15]

SMMCI is a feature of HPE

Solitary maxillary median central incisor can occur as one manifestation of a cyclopic phenotype associated with HPE, as part of a group of abnormalities unrelated to HPE or as an isolated condition in its own right.[16,17] Mutation in the human *SHH* gene has been associated with isolated SMMCI, and individuals with this condition demonstrating both normal intelligence and brain imaging, have been reported to have children affected with HPE.[16,17] The HPE spectrum can demonstrate incomplete penetrance and it is estimated that only 70%



(a) (b)

Figure 2 Similarities in presentation of a missing maxillary central incisor. (a) Loss of a single maxillary central incisor due to trauma, the symmetrical position of the remaining maxillary incisor is suggestive of SMMCI. (b) SMMCI as part of a spectrum of microform HPE. Brain imaging in this subject was normal

of obligate carriers show some clinical feature of this condition.[18] Therefore, the presence of SMMCI must be considered a risk factor for HPE, even in the absence of any other clinical signs.

A role for the orthodontist?

The absence of a maxillary central incisor is most commonly due to trauma (Figure 2a), especially when there is an increased overjet. Hypodontia affecting the primary dentition is very rare and in the permanent dentition congenital tooth absence more frequently affects the maxillary lateral incisor,[19] but rarely the central incisor can be affected. Therefore, in cases where SMMCI cannot be explained on the basis of the clinical history, it is suggested that the subject is referred for further genetic analysis (Figure 2b). Other clinical signs associated with SMMCI as part of the spectrum of HPE are a very symmetrical upper central incisor[20] and the presence of a prominent mid-palatal vomerine ridge.[21]

In the course of a career, the orthodontic clinician is likely to encounter many dental anomalies, most of which are localized and benign in nature. Solitary maxillary median central incisor is one dental anomaly that can have potentially more serious implications. It therefore warrants further investigation, including referral of the patient to a geneticist for testing and if necessary, genetic counselling.

More recently, it has been shown that a loss of function affecting the mouse *Gas1* gene is associated with microform HPE.[22] *Gas1* encodes a GPI-linked membrane protein that facilitates sonic hedgehog signalling at long range ans is important during normal development of midline structures in the craniofacial region. *Gas1*$^{-/-}$ mice have SMMCI, cleft palate and maxillary hypoplasia.

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