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Knobloch syndrome: novel intra-oral findings

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Introduction

Knobloch syndrome is a rare autosomal recessive disorder consisting of eye defects and a midline cranial defect. Genetic analysis of families with Knobloch syndrome has shown heterogeneity, with pathogenic mutation mapped to the *COL18A1* gene on the 21q22.3 chromosome KNO (OMIM: *120328, #267750) and a second unmapped locus KNO2 (OMIM: %608454)[1–4]. These mutations lead to deficiency of one or all collagen XVIII isoforms or endostatin[2]. Here, we report a case of Knobloch syndrome and suggest that the variety of craniofacial/dental anomalies present may be related to defective collagen synthesis.

Case report

An 8-year-old girl was presented to the Dublin Dental Hospital for emergency dental treatment. Many teeth had enamel defects, caries, or both. Her oral hygiene was poor, and she had not been cooperative for dental treatment in the past.

Dental assessment revealed distinctive extra and intra-oral features. In addition to the groove of frontal bone and the nasal lesion (Fig. 1a), nodular lesions on the lower lip were present (Fig. 1b). Intra-orally, there were multiple anterior lower frenae extending into the fibrotic lesions in the lower lip (Fig. 1c). Caries was evident in both the primary and permanent teeth (Fig. 1d). Enamel defects were present to varying degrees in both dentitions. Unusual vertical ridging of the enamel was present on the lower central permanent incisors, whereas the lateral incisors appeared normal (Fig. 2b). The upper right central incisor was rotated 90 degrees, and both upper central incisors had significant loss of enamel (Fig. 2a). The clinical issues identified are summarized in Table 1. This child demonstrated a poor attention span which resulted in poor cooperation and difficulty in establishing good home care.

Standard chromosome testing indicated a normal female karyotype, and FISH analysis of 22q11.2 showed no deletion. A diagnosis of Knobloch syndrome was made based on pigmentary retinopathy and other clinical findings. Referral to plastic surgery resulted in excision of the nasal skin lesion, where histology and CD68 staining confirmed the diagnosis of a juvenile xanthogranuloma (Fig. 1a).

Because of the poor cooperation and the extent of treatment required, comprehensive dental treatment was performed under general anaesthesia: extraction of five teeth and restorations of the permanent teeth. Intubation was difficult because of unusual anatomical features of the larynx, suggesting some connection with defects in the midline structure. Five teeth were sent for histological examination. Decalcified teeth showed accentuated scalloping in some areas (Fig. 2c). Teeth examined by ground section showed prominent lines of Retzius in both the primary and permanent dentition, indicating disruption of enamel formation (Fig. 2d). Because the clinical pattern of enamel defects is not chronological, it seems likely that the underlying collagen defect has given rise to a similar pattern of exaggeration of the normal Retzius lines.

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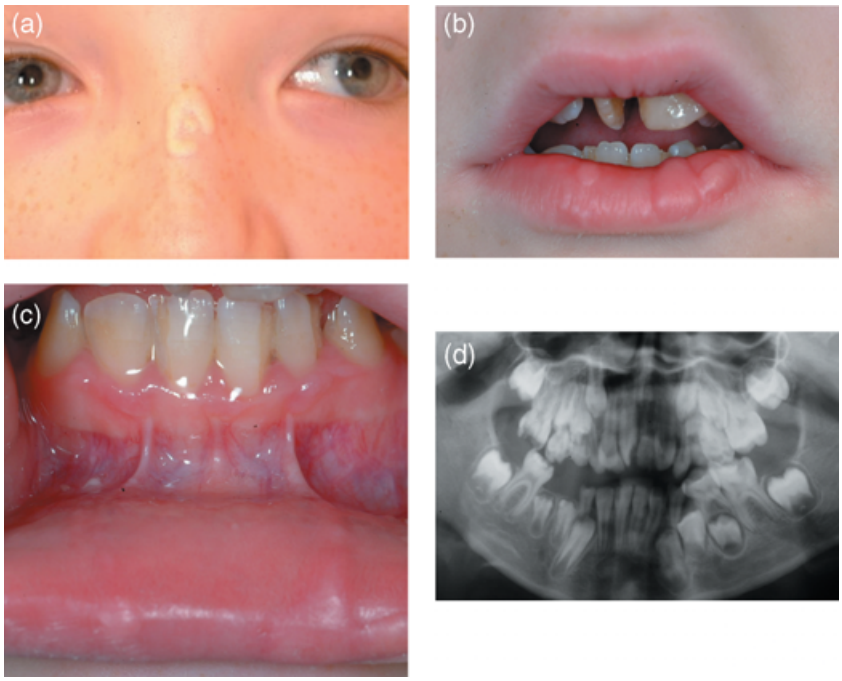

Fig. 1. (a) Juvenile xanthogranuloma which was excised at age 9 years. (b) Extra-oral view of the nodular lesions on lips. (c) Multiple fibrous labial frenae which seem to extend with submucosal bands into the nodules. (d) Orthopantomograph at presentation (age 8.5 years).

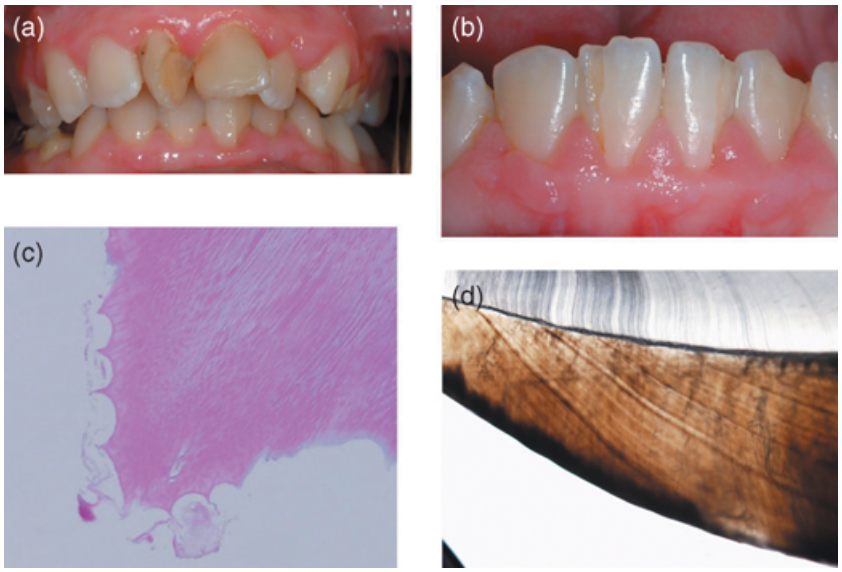

Fig. 2. (a) Rotated upper right central incisor; both incisors restored with composite resin with lateral incisors unaffected. (b) Vertical enamel fractures on lower incisors, with one intact lateral incisor. (c) High-power view of a decalcified section of the area of accentuated scalloping at the enamel–dentine interface on the crown of the primary canine. (d) Ground section of the first permanent molar showing exaggerated Retzius lines in the enamel.

Table 1. Initial problems identified.

Pain from lower left first molar
High caries rate
Poor oral hygiene
Enamel defects (contributing to caries, poor aesthetics, and plaque stagnation)
Rotation of upper right central incisor
Implications of early loss of teeth on orthodontic treatment
Previous poor dental experience
Poor cooperation for dental treatment
Scalp defect and nasal lesion
Fibrotic lesions of lip

A range of severity of enamel defects was observed (Table 2). The upper lateral incisors and second molar teeth were not affected, the premolars were mulberry shaped with islands of normal enamel, and there was progressive vertical chipping of the enamel defects on the upper and lower incisors (Fig. 3). Oral hygiene continued to be complicated by the enamel irregularities, but behaviour improved with advancing age. As a temporary measure, flowable composite restorations have been placed

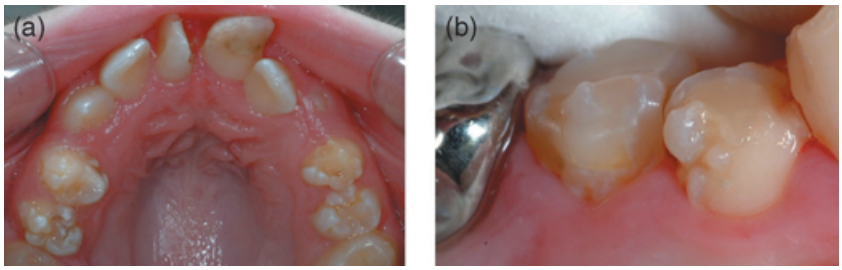

Fig. 3. (a) Extensive enamel defects on the erupting upper premolars. (b) Enamel defects on the erupting lower premolars.

Table 2. Pattern of enamel defects.

Thin enamel
Normal colour and hardness
Primary and permanent tooth enamel affected to varying degrees
Vertical ridging of permanent incisors and some primary teeth
Mulberry-shaped premolars
Chipping of enamel
Difficulty in bonding to defective teeth

on the affected teeth to facilitate dental hygiene and improve aesthetics. Currently, upper fixed appliances are being used to derotate the upper central incisor, and aesthetic restorations will be provided once derotation is complete.

Discussion

This patient's ocular and extra-oral features led to a clinical diagnosis of Knobloch syndrome. Additional anomalies are reported, including the xanthogranuloma, depressed metopic suture, rotated central incisor, and abnormal laryngeal anatomy. A range of enamel defects in both primary and permanent teeth was observed. Our patient also presented with caries and poor aesthetics; management has been complicated by poor cooperation, repeated tooth surface loss, difficulty in retention of composite resin, and abnormal anatomical form in some teeth.

Although collagen XVIII and laminin are present in developing teeth, it is unknown how defective collagen and endostatin affect the complex process of tooth development. Histological examination of the extracted primary and permanent teeth suggested structural change within enamel which is likely because of alterations in the collagen.

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