International Journal of Paediatric Dentistry 2006; **16:** 218–221

Apert syndrome with glucose-6-phosphate dehydrogenase deficiency: a case report

G. TOSUN & Y. SENER
Faculty of Dentistry, Department of Pediatric Dentistry, Selcuk University, Konya, Turkey

Summary. Apert syndrome is characterized by midface hypoplasia, syndactyly of the hands and feet, proptosis of eyes, steep and flat frontal bones, and premature union of cranial sutures. Maxillary hypoplasia, deep palatal vault, anterior open bite, crowding of the dental arch, severely delayed tooth eruption, and dental malocclusion are the main oral manifestations of this syndrome.

In this report, a case of Apert syndrome with glucose-6-phosphate dehydrogenase (G_6PD) deficiency is presented. The patient, a 4-year-old male and the fourth child of healthy parents, was admitted to our department because of delayed tooth eruption. He had all the cardinal symptoms of the Apert syndrome.

Clinical examination revealed that primary centrals, canines and first molars erupted; however, primary second molars and laterals had not erupted. The patient had no dental caries. Preventive treatments were applied, and subsequently, the patient was taken to long-term follow up.

Introduction

Apert syndrome (Mendelian Inheritance in Man #101200) was first described by French paediatrician Eugene Apert in 1906. The birth prevalence is 1 in 1 000 000 [1]. Apert syndrome is caused by an autosomal dominant mutation that is associated with mutations of the gene for fibroblast growth factor receptor 2 [2]. This mutation causes some of the bony sutures of the skull to close prematurely, referred to as craniosynostosis, which causes asymmetric growth and gives the head a distorted shape [3,4]. Typical craniofacial features characteristic of Apert syndrome include ocular hypertelorism, proptosis, down-slanting palpebral fissures, trapezoid-shaped mouth, depressed nasal bridge, and midfacial hypoplasia. Additionally, characteristic syndactyly of all four limbs occurs [4–6].

In Apert syndrome, the oral cavity is characterized by impaction, severe crowding, delayed eruption, thick gingiva, sometimes supernumerary teeth, or congenitally missing teeth. Other frequent oral cavity findings include class III malocclusion, anterior open bite, bilateral posterior cross-bite, unilateral posterior cross-bite but to a lesser degree, a midline deviation [7,8].

Glucose-6-phosphate dehydrogenase (G_6PD) deficiency is the most common red blood cells (RBC) enzyme disorder. This disorder is an X-linked hereditary deficiency, and men are affected hemizygously by this disorder [9,10]. Deficiency of G_6PD leads to haemolytic anaemia as a result of RBC destruction [11]. This is due to the fact that nicotinamide adenine dinucleotide phosphate (NADPH) is made only via the pentose phosphate pathway in RBC. NADPH is needed to keep glutathione in a chemically reduced state (free –SH group) so that it can keep iron chemically reduced in haemoglobin and to help maintain the membrane of RBCs – probably acting as an antioxidant [9,11].

The main problem in G_6PD deficiency is that haemolysis can be precipitated by a number of factors, such as oxidant drugs, eating fava beans, or intercurrent infection. Drugs that may induce haemolysis include sulphonamides, chloramphenicol, aspirin acetaminophen, penicillin, streptomycin, isoniazid, probenecid, and toluidine blue [12].

This is the first case cited in literature of Apert syndrome in parallel with G_6PD deficiency.

Case report

A 4-year-old boy with the diagnosis of Apert syndrome was seen for delayed eruption of his

This paper was presented at the 7th Congress of the Balkan Stomatological Society on 28–30 March 2002, Kuşadası, Turkey.
Correspondence: Dr G. Tosun, Faculty of Dentistry, Department of Pediatric Dentistry, Selcuk University, Campus/Konya, Turkey. E-mail: gultosun@hotmail.com

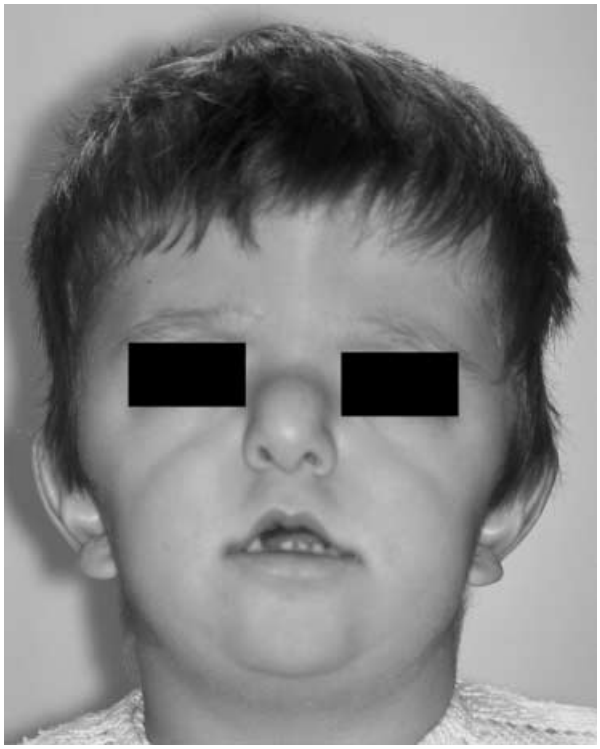

Fig. 1. Frontal view of the patient.

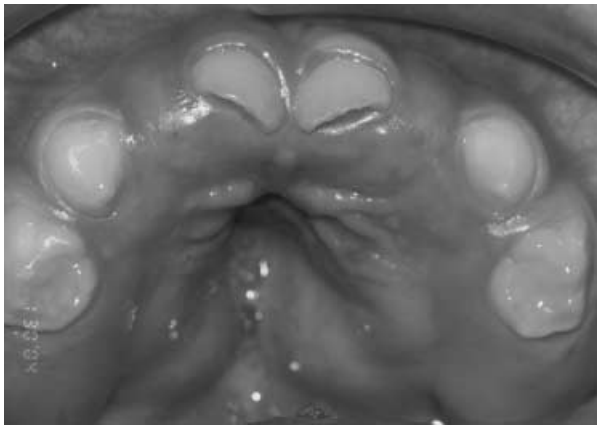

Fig. 2. Note marked swellings of palatal mucosa.

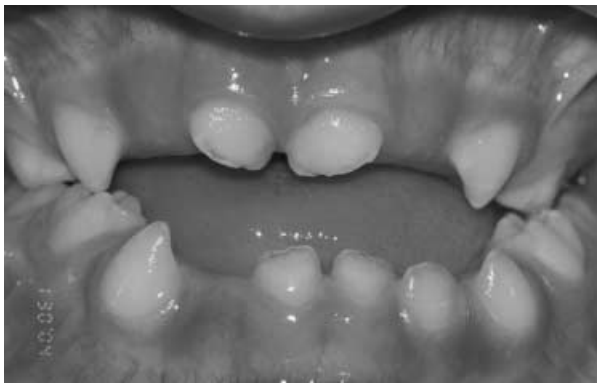

Fig. 3. Anterior open bite and bilateral cross-bite.

teeth. Our patient, his mother, and two brothers were diagnosed with G_6PD deficiency in haematology clinic and his sister is not affected.

Physical examination of patient showed cardinal features of Apert syndrome. During extraoral examination, it was observed that he displayed midface hypoplasia, a flat/steep forehead, an extremely short depressed nose, proptosis, trapezoidal shape of mouth (Fig. 1), and syndactyly of hands and feet digits. Prior to attending this consultation, he had had reconstructive surgery to separate the digits of his syndactyly hands.

Intraoral clinical examination revealed that centrals, canines, and primary first molars erupted; however, primary second molars and laterals had not erupted. The patient does not have carious teeth. The tongue appeared excessively large.

The maxillary arch was V-shaped with a midline pseudo cleft (Fig. 2). There appeared clefting of the palate because of lateral swellings on the palatal process. Examination of the occlusion revealed a bilateral cross-bite, class III malocclusion, and anterior open bite (Fig. 3).

Investigation of the panoramic radiograph (Fig. 4) revealed that all teeth were present except for mandible and maxilla premolar germs. In the lateral cephalogram, hypoplasia of the maxilla gave the appearance of a class III skeletal relationship (Fig. 5).

Preventive treatments included topical fluoride, and fissure sealant was applied to the patient's present teeth and oral hygiene instructions were given to assist his parents in patient's daily oral care.

Discussion

Apert syndrome is one of five craniosynostosis (premature fusion of cranial sutures) syndromes characterized by midface deformity and syndactyly of hands and feet. The unusual palate of patients with Apert syndrome is of interest. High-arched palate with lateral swellings is one of the characteristics of this syndrome [4,13]. Lateral swellings of the palatine process are observed on both sides of the midline. Solomon *et al.* [14] have described these lateral swellings on the palatine process as present in infancy and increasing in mass as the child ages. The patient described in this case

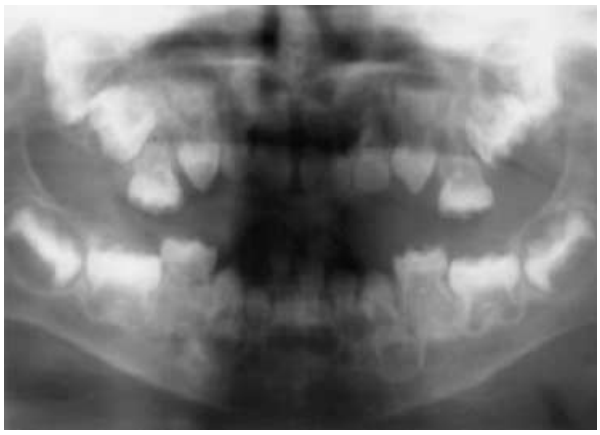

Fig. 4. Ortopantomogram of the patient.

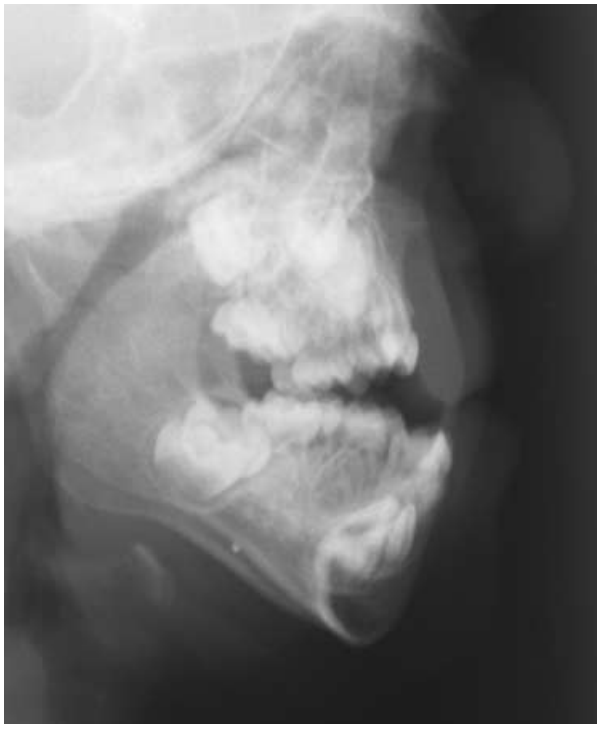

Fig. 5. Lateral cephalogram.

report has the classical signs of Apert syndrome. His palatal view may lead to a mistaken diagnosis of cleft palate. Coronal tomograms have shown the lateral palatal swellings to consist of soft tissue. Histological studies have revealed acid mucopolysaccharides deposits consisting predominantly of hyaluronic acid [14]. According to Cohen and Kreiborg, patients with Apert syndrome have ocular proptosis, down-slanting palpebral fissures, lateral canthi, ocular hypotelorism and the ears are mostly low set [4,15]. The nose is extremely short. The nasal bridge is markedly depressed [6]. The lips have a trapezoidal configuration in the relaxed state. In this syndrome, the appearance of patient is prognathic because the maxilla is hypo-plastic transverse, vertical with sagittal dimensions [7]. Delayed dental eruptions of both primary and permanent dentition have been noted [7,16]. Kaloust *et al*. [17] found that there was significant delay in the development of the Apert patient's dentition with an average delay of 0·96 year. In addition, they found a direct correlation between the amount of delay and the chronologic age of patient with an increase delay in dental development as individual with Apert syndrome grows older. Delay eruption on second primary molars and lateral teeth existed in this patient.

Aetiology of delay eruption in Apert syndrome is not clear. It may be explained, however, by recent genetic research of craniosynostosis syndromes. Mutations in the fibroblast growth-factor receptor-2 (FGFR2) gene, which codes for four types of human FGF receptors that are translated by alternative splicing, has been identified as a potential cause of four phenotypically distinct craniosynostosis syndromes [1]. It has also been associated with Crouzon's disease. The relationship between FGFR2 and tooth development has been described by Thesleff *et al*. [18].

G_6PD is the first enzyme involved in the pentose phosphate pathway. G_6PD catalyses the net transfer of a hydride ion to NADP+ from carbon 1 of glucose-6-phosphate (G_6P) to form 6-phosphogluconono-and-lactone and NADPH (a powerful reducing agent). G_6PD is specific for NADP+ and is strongly inhibited by NADPH. NADPH is a cofactor for glutathione reductase that plays a role in maintaining cellular protection against oxidation, including detrimental oxidation effects in RBC [9,10]. Red blood cells that are deficient in G_6PD are thereby susceptible to oxidation and subsequent haemolysis [11]. Although some G_6PD deficiencies are caused by drug-induced haemolytic anaemia, the presence of infection appears to have a profound influence over most haemolysis as a result of G_6PD deficiencies [19–21].

For the patient with Apert syndrome, oral hygiene is very important but can be very difficult. The hand deformities make it very difficult to floss and, often, to brush the teeth. Floss holders, the new generation

of electric tooth brushers, and fluoride mouth rinses may make the task easier.

Professional care including frequent dental examinations, oral hygiene prophylaxis, fluoride treatments, and dental sealants are very important. Because of the severe consequences of either drug-induced haemolysis or infection, the dentist must avoid drugs that potentially induce haemolysis as result of G_6PD deficiency.

What this case report adds

- Although birth prevelance of the Apert syndrome is in 1 in 1 000 000, Apert syndrome in parallel with G_6PD deficiency is first described in this paper.

Why this paper is important for paediatric dentists

- In patients with Apert syndrome oral hygiene can be very difficult due to hand deformities, therefore, professional care is necessary and care must be taken for either drug induced haemolysis or infection, as a result of G_6PD deficiency.

References

1 Cohen MM, Kreiborg S Jr, Lammer EJ, *et al*. Birth prevalence study of the Apert syndrome. *American Journal of Medical Genetics*. *Part A* 1992; **42**: 655–659.

2 Wilkie AO, Slaney SF, Oldridge M, *et al*. Apert syndrome results from localized mutations of FGFR2 and is allelic with Crouzon syndrome. *Nature Genetics* 1995; **9**: 165–172.

3 Cohen MM. Asymmetry: molecular, biologic, embryopathic, and clinical perspectives. *American Journal of Medical Genetics*. *Part A* 2001; **101**: 292–314.

4 Cohen MM, Kreiborg S. A clinical study of the craniofacial features in Apert syndrome. *International Journal of Oral and Maxillofacial Surgery* 1996; **25**: 45–53.

5 Kreiborg S, Cohen MM. The oral manifestations of Apert syndrome. *Journal of Craniofacial Genetics and Developmental Biology* 1992; **12**: 41–48.

6 Sonnenberg EM, Catalanotto FA. Apert's syndrome: report of case. *ASDC Journal of Dentistry for Children* 1977, 39–42.

7 Goodman RM, Gorlin RJ. *Atlas of the Face in Genetic Disorders*. Saint Louis, MD: Mosby Company, 1977: 80–81.

8 Ferraro NF. Dental, orthodontic and oral/maxillofacial evaluation and treatment in Apert syndrome. *Clinics in Plastic Surgery* 1991; **18**: 291–307.

9 Bricker SL, Lanlgais RP, Craig S. *Oral Diagnosis, Oral Medicine and Treatment Planning*, 2nd edn. Philadephia: Lea & Febiger, 1994: 370–371.

10 Roger EA, Robert JV. Analgesic concerns in glucose-6-phosphate dehydrogenase-deficient dental patients: myth or reality? *Military Medicine* 1991; **156**: 681–684.

11 Stokman J, Lubin B, Oski F. Aspirin-induced hemolysis: the role of concomitant oxidant (H_2O_2) challenge. *Pediatric Research* 1978; **12**: 927–931.

12 Scully C, Cawson RA. *Medical Problems in Dentistry*, 4nd edn. Oxford: Butterworth-Heineman, 1998: 120–121.

13 Peterson JS, Pruzansky S. Palatal anomalies in the syndromes of Apert and Crouzon. *Cleft Palate Journal* 1974; **11**: 394–403.

14 Solomon ML, Medenica M, Pruzansky S, Kreiborg S. Apert syndrome and palatal mucopolysaccharides. *Teratology* 1973; **8**: 287–292.

15 Farkas LG. Ear morphology in Treacher Collin's , Apert's and Crouzon's, syndromes. *Archives of Otorhinolaryngology* 1978; **220**: 153–157.

16 Gorlin RJ, Cohen MM, Levin LS. *Syndromes of the Head and Neck*, 3rd edn. New York: Oxford University Press, 1990.

17 Kaloust S, Ishıı K, Vargervık K. Dental development in Apert syndrome. *Cleft Palate Journal* 1997; **34**: 117–121.

18 Thesleff I, Vaahtokarı A, Partanen AM. Regulation of organogenesis. Common molecular mechanisms regulating the development of teeth and other organs. *International Journal of Developmental Biology* 1995; **1**: 35–50.

19 Cohen S, Weber W. Pharmacogenetics. *Pediatric Clinics of North America* 1972; **19**: 21–31.

20 Glader BE. Evaluation of the hemolytic role of aspirin in glucose-6-phosphate dehydrogenase deficiency. *Journal of Pediatrics* 1976; **89**: 1027–1028.

21 Beutler E. Current concepts: glucose-6-phosphate dehydrogenase deficiency. *The New England Journal of Medicine* 1991; **324**: 169–173.