Multiple developmental dental anomalies and hypermobility type Ehlers-Danlos syndrome

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Concurrent existence of multiple developmental dental anomalies: hypodontia of permanent mandibular incisors, dentin dysplasia, transmigration, root dilaceration, ectopic eruption and delayed eruption combined with systemic abnormalities including joint hyperlaxity and skin hyperextensibility aided in diagnosis of a sporadic case of hypermobility type of Ehlers-Danlos syndrome in a Jordanian Arab male. In dental practice the presence of multiple developmental dental anomalies expressing simultaneous defects in different stages of tooth development should raise suspicion of possible of manifestation of an underlying systemic abnormality.
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INTRODUCTION

Ehlers-Danlos syndrome (EDS) is a relatively rare group of heritable connective tissue disorders with a clinical and genetic heterogeneity characterized mainly by articular hypermobility, skin extensibility, and tissue fragility.[1,2] EDS is caused by disordered fibrillar collagen metabolism due to deficiency of collagen-processing enzymes, dominant-negative effects of mutant -chains, and haploinsufficiency.[1]

According to Villefranche classification, six major types of the syndrome have been distinguished based on clinical, biochemical and molecular differences[2] of which the classical and hypermobility types are the most common.[1] Hypermobility type (formerly EDS type III) of Ehlers-Danlos syndrome (HT-EDS), which is transmitted as an autosomal dominant trait and accounts for 10% of EDS cases,[3] is characterized by generalized joint hypermobility and variable hyperextensibility and softness of skin.[2,4] To date the genetic basis of HT-EDS have not been identified although haploinsufficiency of tenascin-X, an extracellular matrix protein, have been found to be associated with HT-EDS in some patients.[5] Joint hypermobility is usually assessed using the Beighton hypermobility scoring system, in which points were given for each of the following characteristics: (1) passive dorsiflexion of the fifth metacarpophalangeal joint beyond 90 degrees, one point for each hand; (2) passive apposition of the thumb to the volar aspect of the ipsilateral forearm, one point for each hand; (3) elbow hyperextension beyond 10 degrees, one point for each elbow; (4) knee hyperextension beyond 10 degrees, one point for each knee and (5) forward trunk flexion with knees fully extended allowing the palms to rest flat on the floor, one point. A score of 5/9 or greater makes a diagnosis of joint hypermobility.[2,6]

Other abnormalities of HT-EDS include recurrent joint dislocations especially the shoulder, patella, and temporomandibular joints,[3,7] cardiac abnormalities,[8,9] aortic root dilation,[10] chronic musculoskeletal pain,[7] and peripheral neuropathy.[11]

In this report we describe a sporadic case of this rare inherited disorder associated with unusual dental and systemic manifestations.

CASE REPORT

A 15-year-old Jordanian Arab boy (born on December 17th, 1986) presented to the Pediatric Dental Clinic at Prince Rashid Bin AL-Hassan Hospital in March 2002 after being referred by his general dental practitioner for assessment of mandibular hypodontia. The family history revealed that he was the eighth of ten siblings; he had an older sister who died from Burkitt's lymphoma at age of seven. The parents appeared healthy with a history of consanguineous marriage. None of the family members had any clinical deformity. The subject had been born after uncomplicated full term pregnancy with a weight of 3000 gr. His mother gave no history of exposure to radiation or taking medication during pregnancy. He had a history of recurrent epistaxis without known cause. The patient and the parent denied any history of orofacial trauma during childhood, recurrent dislocations or chronic joint pain.

Physical examination revealed that the patient had a proportionate short stature, with a height of 156 cm (3rd percentile) and a weight of 55.5 Kg (50th percentile), broad nasal bridge, unilateral right amblyopic strabismus (Figure 1), delayed puberty, hypotonia, pes planus, marked generalized joint hypermobility involving small and large joints with a Beighton score of 9 out of 9 (Figure 2). His skeletal age was 11 years and 6 months. The skin appeared normal with moderate extensibility and no evidence of bruising or dystrophic scars could be seen. Later during the follow-up sessions left inguinal hernia developed.

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Psychometrics assessed on the Wechsler Intelligence Scale for Children demonstrated a verbal IQ of 56, a performance scale IQ of 77, and a full scale IQ of 63+5. His full IQ scale was achieved with a significant 21 point difference between verbal and performance abilities in favor to the latter. He was functioning below his age level and classified on the range of low average on the performance IQ, though he was ranged on the level of mild mental retardation regarding his verbal and full IQ.

Endocrinological evaluation revealed partial deficiency of serum follicle-stimulating hormone (FSH), serum luteinizing hormone (LH), and free testosterone. Provocative growth hormone assays, thyroid function tests, liver function tests, cortisol level, complete blood count, electrolytes, coagulation tests and urinalysis were within normal limits.

Echocardiogram showed a bicuspid aortic valve with aortic regurgitation. Renal and thyroid ultrasonography, brain MRI and angiography were within normal limits.

Intraoral examination showed that seven permanent teeth did not erupt – the mandibular incisors, mandibular left second premolar, and maxillary second molars. Three mandibular teeth were partially erupted – the right second premolar and second molar, and the left canine ectopically partially erupting in the midline. Of the primary dentition, the mandibular left canine was retained. The patient gave no history of tooth extraction or traumatic loss. The crowns of teeth were of normal color, size and form without noticeable mobility. Caries activity was low and one tooth was restored. The first permanent molars were in class III malocclusion during centric occlusion and intraoral soft tissues appeared normal except for migratory glossitis (Figure 3, A and B).

Panoramic radiography showed the absence of the permanent mandibular incisors, pulp stones in all of permanent teeth, stunt roots mainly in the molars, dilaceration of the roots of permanent mandibular canines, and alveolar crest bone loss in the mandibular posterior areas. The mandibular primary canine did not show any radiographic pathology (Figure 4). Panoramic radiographs of the parents and the other siblings did not show any radiographic abnormality of the dentition. At 2-year follow-up radiographic examination showed internal resorption of the root of the primary canine with progressive pulpal calcification involving all the permanent teeth (Figure 5).

Replacement androgen therapy was administered for six months which improved his overall height, weight and pubertal stage. The primary canine was extracted under infiltration local anesthesia after preoperative antibiotic cover of 2.0 g of amoxicillin administered orally one hour before the surgical procedure, and hemostasis was insured one hour postoperatively using bone wax compressive pack.

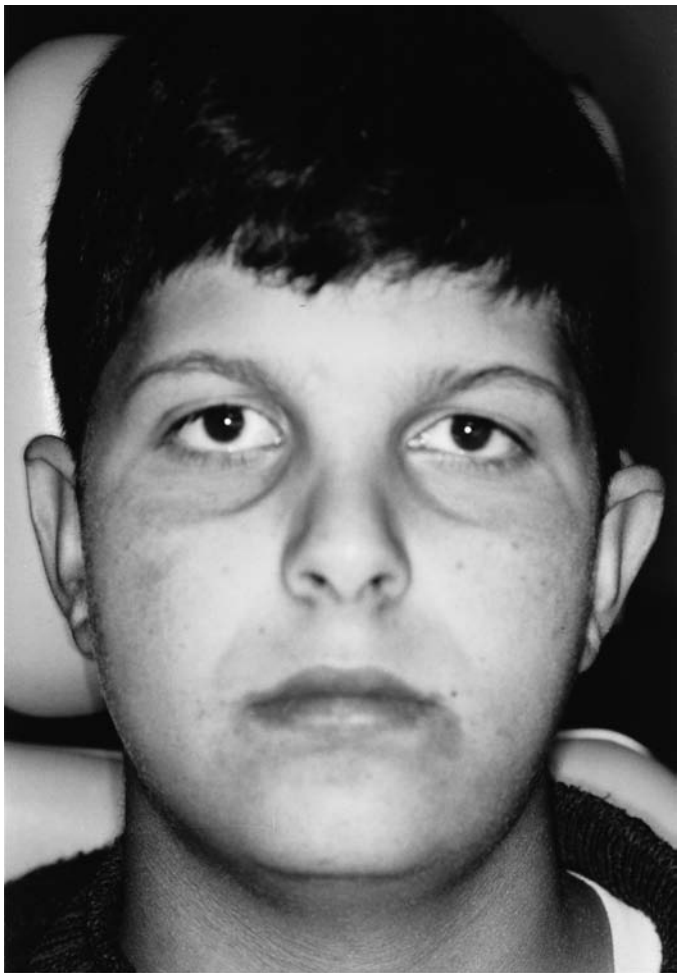

Figure 1. Frontal facial view of the affected proband.

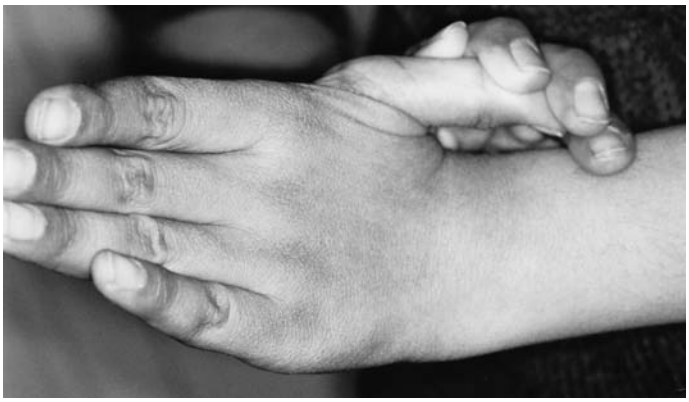

Figure 2. Dorsiflexion of patient's thumb demonstrating joint hypermobility evident at the metacarpophalangeal joint.

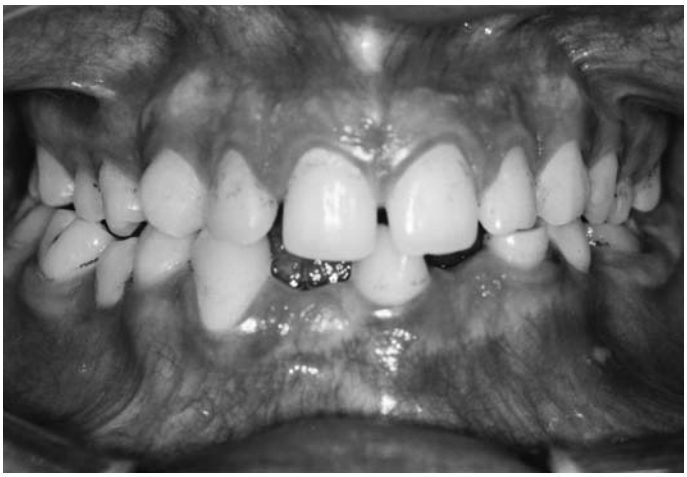

Figure 3A. Frontal intraoral view of both maxillary and mandibular dentitions with missing mandibular permanent incisors and ectopic eruption of the permanent left canine in the midline.

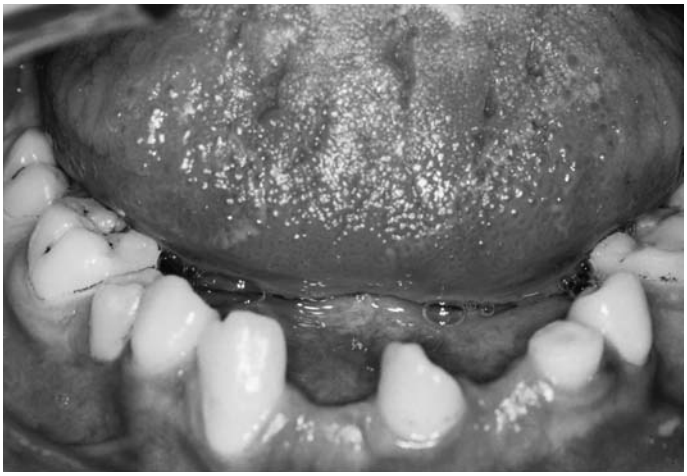

Figure 3B. Mandibular view showing also delayed eruption of the second premolars and retained mandibular left primary canine.

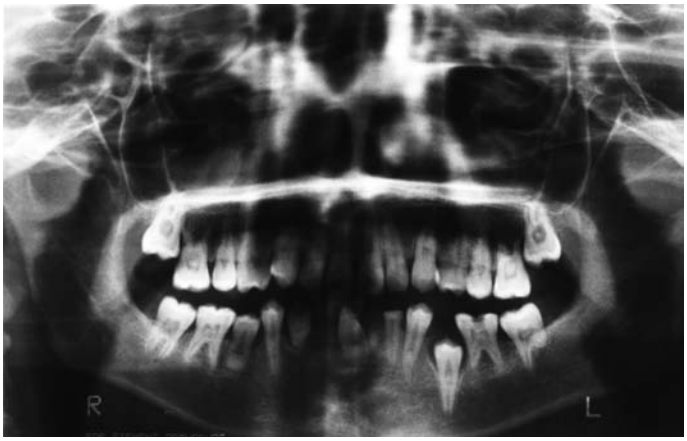

Figure 4. Panoramic radiograph at initial presentation showing congenital absence of mandibular permanent anterior teeth, transmigrant mandibular canine, stunt and tapered roots. Note presence of pulp stones.

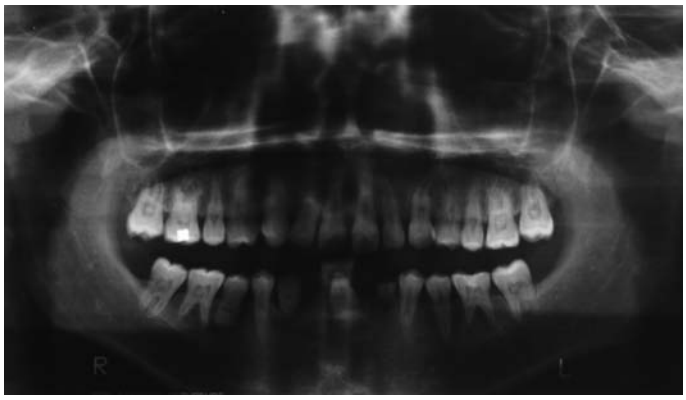

Figure 5. Panoramic radiograph at two year follow-up with pulp stones obliterating pulp chambers in nearly all teeth.

Three months later an overdenture removable partial denture to replace missing lower incisors was constructed taking advantage of the midline canine for support. Meticulous multi-disciplinary dental review visits were implemented to include the following:

- Plaque control and oral hygiene instructions
- Diet control and advice

Table 1. Oral features reported in patients with hypermobility type of Ehlers-Danlos syndrome

Dental
Hypodontia[12,*]
Retained primary teeth[12,*]
Supernumerary teeth[13]
Transmigration*
Ectopic eruption*
Delayed eruption*
Slender roots[14,*]
Dentin dysplasia*
Pulp calcification/stones[15,*]
Root dilaceration*
Periodontal
Aggressive periodontitis[14]
Horizontal and vertical bone resorption[14,*]
Mucosal
Absent inferior labial and lingual frenula[16]
Abnormal oral mucosal reflectance[17]
Mucosal fragility[15]
Tongue
Tongue hypermobility (Gorlin's sign)[12,16]
Palate
High arched palate[18]
TMJ
Recurrent subluxation and dislocation[2,12,15,16]
TMJ dysfunction[15,19]

- Periodic application of topical fluoride varnish (2.26% F) Duraphat® (Colgate Oral Phrmaceuticals, USA)
- Taking care in minimizing the length of procedures that require prolonged mouth opening as the risk of temporomandibular dis location is increased, and avoiding tissue injury as the risk of mucosal fragility, delayed wound healing and susceptibility to bacterial endocarditis is quite high.

DISCUSSION:

The diagnosis of EDS is based mainly on clinical manifestations with major and minor diagnostic criteria defined for each of the six subgroups.[2] Heterogeneity between different types of EDS occurs which complicates the diagnosis and makes accurate diagnosis of a specific type imperative.[1,2] In HT-EDS the clinical picture is dominated by marked large and small joint hypermobility, minimal or marked skin hyperextensibility, little scarring or bruising, and limited skin splitting.[2,7] Our patient had two major diagnostic criteria, joint hypermobility and skin hyperextensibility, with high diagnostic specificity for HT-EDS. Other manifestations, which are minor diagnostic criteria with low diagnostic specificity, such as recurrent joint dislocations, chronic joint/limb pain and positive family history were absent. He had a history of recurrent epistaxis which suggests bleeding tendency despite normal coagulation studies, and lacked the presence of atrophic scars which suggests the diagnosis

Table 1. Comparison of clinical and radiographic findings between different types of dentin dysplasia and the present case

	DD-I *	*DD-II* *	*Present case*
Clinical Features			
Primary teeth amber, translucent	+	+ +	-
Secondary teeth discolored	-	-	-
Discoloration in both dentitions	-	-	-
Loose teeth	+ +	-	-
Rapid attrition of crowns	-	-	-
Fragile roots	+	-	0
Radiographic Features			
Ovoid crowns	-	-	-
Short tapering roots	+ +	-	+
Obliteration of pulp cavities			
Before eruption	+ +	-	-
After eruption	-	+	+
Horizontal line at DEJ	+ +	-	+
(crescent-shaped pulp chamber)			
Apical extension of pulp chamber	-	-	+
Multiple apical radiolucencies	+ +	-	-
Thistle-tube shape to pulp chamber	-	+	+
Reduced x-ray contrast of dentin	+ +	-	-
Pulp stones in pulp chamber	-	+ +	+

* Modified form reference 38

DD-I, type I dentin dysplasia; *DD-II*, type II dentin dysplasia; DEJ, dentinoenamel junction; + +, typically evident in all teeth; +, variable in frequency or severity; -, absent; o, not determined.

of the classical type. The patient best fits HT-EDS although he had short stature, mental retardation, and hypogonadotropic hypogonadism which are not features of HT-EDS. He had multiple developmental dental anomalies affecting different stages of tooth development which include disturbances in the number of teeth causing hypodontia, the form of teeth causing root dilaceration, the structure of teeth causing dentin dysplasia, and the eruption of teeth causing delayed eruption, transmigration, ectopic eruption, and abnormal root development.

Oral manifestations of HT-EDS are variable and not constant. This may be due to the overlapping between different types of EDS in some cases. Table 1 lists the oral features reported in patients with HT-EDS with temporomandibular joint problems being almost a constant clinical finding.[2,12-19]

Agenesis of mandibular incisors is rare with racial variation, being low in the Western population with a prevalence rate of 0.23% and 0.08% for the lower central and lateral incisor region, respectively, and higher in the Asian population with a prevalence rate of 0.51% and 1.14% for the lower central and lateral incisors, respectively.[20] Mandibular incisor agenesis can be seen as an isolated trait, and more frequent or a constant finding in syndromic contexts including type I Oral-facial-digital syndrome, Ellis-van Creveld syndrome, Coffin-Lowry syndrome, Hypoglossia-hypodactylia syndrome, and Rieger syndrome.[21] Hypodontia occurring in different types of EDS have been previously reported but without apparent pattern of hypodontia.[12,22]

Dentin dysplasia (DD) is a rare disturbance of dentin formation resulting in abnormal pulp morphology and defective root formation.[23] DD can occur in association with systemic disorders including calcinosis universalis,[24] tumoral calcinosis,[25] Singleton-Merten syndrome,[26,27] Trichoonychodental syndrome,[28] Branchio-skeleto-genital syndrome,[29] pycnodysostosis,[30] Ehlers-Danlos syndrome,[31] dysosteosclerosis,[32] Seckel syndrome,[33] and sclerotic bones with skeletal anomalies.[34] Dysplastic dentin, stunt roots, pulp stones and pulp obliteration have been previously reported in the classical (formerly EDS type I and II) and dermatosparaxis (formerly EDS type VIIC) types of EDS.[22,31,35,36] Dysplastic changes of the dentin-pulp complex is part of the spectrum of the defects that could occur in dental tissues of patients with EDS. These defects mainly affect radicular dentin causing reduction number of dentinal tubules, increase of intertubular dentin, and development of vascular inclusions and giant channels. Scalloping of the amelodentinal junction, fibrous degeneration and diffuse pulpal calcification with development of numerous pulp stones have been described.[31,37]

Shields *et al.*[38] classified two major types of DD, type I (DD-I) and type II (DD-II), based on clinical, radiographic and histological differences. Table 2 summarizes the differences between the major types and the present case. It is apparent that this case combines features of both DD-I and DD-II clinically and radiographically.

Transmigration of mandibular canines is a rare phenomenon with the left canine being affected more than the right canine. Eruption of transmigrated canine is even more rare.[39] Hypodontia, excess space, overretained mandibular primary canine, tumors, cysts and odontomes might be associated with this anomaly. The etiology and mechanism of transmigration is still not clear although a number of factors have been suggested.[39,40] In the present case agenesis of the

mandibular incisors might have favored the retention of the primary left canine and caused absence of correct path of eruption and led the permanent left canine to migrate and erupt ectopically in the midline even with absent and abnormal root development.

In EDS the defect of collagen metabolism is reflected in different tissues of the body including the orofacial region, and dentists treating patients with manifestations of EDS should be aware of possibility of complications that might compromise their treatment plan which include bleeding tendency, cardiovascular abnormalities, oral mucosal fragility, delayed wound healing, predisposition to periodontal disease, temporomandibular joint problems, orthodontic problems and endodontic problems related to tooth fragility, abnormal root and canal morphology and pulp stones.

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