Clin Oral Invest (2007) 11:183–187
DOI 10.1007/s00784-006-0092-x

REVIEW

Ehlers-Danlos Syndrome (EDS) type IV. Review of the literature

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Received: 21 June 2006 / Accepted: 4 December 2006 / Published online: 13 January 2007

Abstract Ehlers-Danlos syndrome (EDS) is a heterogeneous group of connective tissue heritable disorders. EDS type IV is a rare form that presents typical clinical signs, such as easy bruising and haematomas at sites of trauma, skin manifestations (translucent skin with visible veins), and joint hyperlaxity. To illustrate the dermatological features and describe an aggressive periodontitis, a symptom not yet reported in this EDS type, we present a case of a 23-year-old young man. This patient has been suffering from bruised skin, haematomas, and varicose veins in his legs. These lesions, typical of EDS type IV, were associated with trauma followed by slow and difficult cicatrization. Teeth loss and clinical attachment loss in all the remaining teeth, a symptom compatible with a severe destruction of the periodontal support, was reported after orthodontic treatment. The treatment is limited to control the disease and teeth loss. Considering this new clinical symptom associated with EDS type IV, we suggest that the use of orthodontic apparatus should be carefully considered in such patients.

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Keywords Ehlers-Danlos syndrome · Diagnosis · Oral anomalies · Periodontitis · Early tooth loss

Introduction

Ehlers-Danlos syndrome (EDS) [19] is a rare and heterogeneous group of connective tissue heritable disorders characterized by joint hypermobility, skin hyperextensibility, cardiac valvular defects, and tissue fragility [7, 8, 27, 29]. There are eight major different types of EDS classified according to their symptoms, phenotypes, and signs. The clinical manifestations of each type are different. However, classical types (I–III) frequently present only the general manifestations of the syndrome, whereas in all other types (IV–VIII), there is a wide range of variation [18, 20] (see Table 1). The reported prevalence for EDS, considering all subtypes together, is 1 out of 5,000 births [29], being the diagnosis of this syndrome often difficult and mainly based on clinical criteria and family history [11, 29].

The EDS type IV is a rare form and presents the typical clinical signs also present in all other subtypes. Moreover, the main EDS type IV (named vascular type) characteristics are easy bruising and haematomas at sites of trauma, skin manifestations (translucent skin with visible veins), and joint hyperlaxity [17, 23]. This pathology was associated with mutations in the *COL3A1* gene, which encodes type III procollagen, a structural component of internal organs and blood vessels [11, 14]. Patients with type IV EDS are at risk for gastrointestinal, uterine, and arterial rupture, and death for these reasons has been reported [23, 26, 30]. The most common causes of death in individuals affected by EDS type IV are rupture of abdominal aorta [21], colon perforation, and cerebral bleed [4]. However, blood vessels

Table 1 Clinical characteristics that determines the diagnoses and type of EDS

Type	Main clinical characteristics
I and II (classic)	Marked skin hyperextensibility, with widened atrophic scars and joint hypermobility Molluscoid pseudo tumors (calcified hematomas) and periodontitis has been reported
III (hypermobility type)	Joint hypermobility is the dominant clinical manifestation. The hyperextensibility and/or smooth velvety skin as well as bruising tendencies in the hypermobility type are present but variable in severity. Periodontitis has been reported
IV (vascular type)	The skin is usually thin and translucent with veins being seen through the skin. The facial characteristics are large eyes, thin nose, lobeless ears, short stature, and thin scalp hair. Also evident is a decrease in subcutaneous tissue, particularly, in the face and extremities. Easy bruising manifests as spontaneous ecchymoses, frequently recurring in the same areas. Arterial/intestinal/uterine fragility or rupture are common
V	The current EDS type V (X-linked) has been described in a single family. It is a rare variant and the molecular basis remains unknown
VI (kyphoscoliosis type)	Generalized joint laxity and severe muscle hypotonia (weak muscle tone) and scoliosis at birth are seen in this type of EDS. Tissue fragility, including atrophic scars, easy bruising and marfanoid habitus (Marfan-like features); micro cornea (abnormally small cornea); and radiologically considerable osteopenia (diminished amount of bone tissue) can be seen
VII A and B (arthrochalasia type)	Congenital hip dislocation, generalized joint hypermobility with recurrent subluxations, skin hyperextensibility with easy bruising, tissue fragility including atrophic scars; muscle hypotonia; kyphoscoliosis and radiologically mild osteopenia are seen in individuals with this type of EDS
VII C (dermatosparaxis type)	Severe skin fragility and substantial bruising. Wound healing is not impaired, and the scars are not atrophic. The skin texture is soft and doughy. The redundancy of facial skin results in an appearance resembling cutis laxa. Large hernias (umbilical, inguinal) may also be seen The oral findings are alterations on the teeth and severe periodontitis
VIII	The current EDS type VIII is similar to the classical type except that it also presents periodontal friability. This is a rare type of EDS. The existence of this syndrome as an autonomous entity is uncertain

Modified from Ehlers-Danlos National Foundation (available in http://www.ednf.org/mambo/index.php)

fragility and the death rate are highly variable even considering affected individuals from the same family [4].

There are few reports on orofacial abnormalities in EDS type IV [9, 13]. Dental alterations are only reported in EDS types VII and VIII [6]. Conversely, severe clinical attachment loss had already been reported in EDS classical types (I–III) and EDS type VIII [14, 18, 22].

The aim of the present study is to review the clinical findings presented by individuals affected by EDS type IV and to describe the occurrence of clinical and oral manifestations in a patient with a phenotype of EDS type IV.

Case report

The clinical examination of a 23-year-old white young man, with a major complaint of skin fragility on the legs and teeth loss, showed several regions of bruised skin, haematomas, and varicose veins in the legs. The patient's skin was thin and fragile, with deep scars and evident veins on hands and feet. These lesions had been present since childhood, and the patient reported that they were associated with trauma followed by slow and difficult cicatrization.

The patient has a thin face with remarkably large eyes, thin nose, lobeless ears, and fine scalp hair (Fig. 1). A chemical evaluation of the hair composition was performed before the patient's participation in the present investigation, aiming to determine any alterations. A higher concentration of aluminium (7.5 μg/g), silver (0.2 μg/g), and calcium (30 μg/g) as compared to reference values (up to 7 μg/g, 0.12 μg/g, and 750 μg/g, respectively) were observed. Conversely, lower concentrations of lithium (<0.004 μg/g), cobalt (0.005 μg/g), and sulphur (42300 μg/g) as compared to reference values (from 0.007 to 0.023 μg/g, from 0.013 to 0.035 μg/g, and from 44,500 to 52,000 μg/g, respectively) were observed. Nevertheless, the clinical meanings of these findings have not been described so far.

The examination of joint mobility was based on the following movements: (a) passive apposition of thumbs to the flexor aspect of the forearms; (b) passive hyperextension of the fingers, parallel to the extensor aspect of the forearms; (c) active hyperextension of the elbows >10° beyond 180°; (d) active hyperextension of the knees >10° beyond 180°; (e) ability to place palms on the floor with knees extended [13]. The joint mobility was assessed using the Beighton's point scale [3], where a score equal to 5 or higher defines hypermobility [4]. The patient was scored at level 5 in the Beighton scale, mainly due to his fingers mobility.

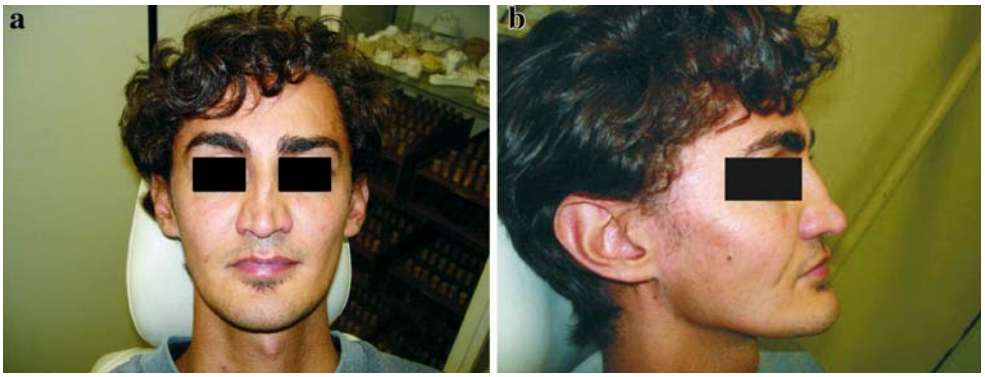

Fig. 1 Patient's face frontal (**a**) and lateral (**b**) view, with large eyes, thin nose, lobeless ears, and thin scalp hair

Haematological parameters, such as time of coagulation (9 min—reference value 2 to 12 min), protrombine time (1.08 rni—reference value 1 to 1.25 rni), KTTP (36 s—reference value up to 45 s), and bleeding time (4 min—reference value 1 to 7 min), were normal at the time of examination, as well as the patient's height (1.78 m) and weight (69 kg). The exception was the Hess test (Rumple–Leede test) that issued 20 marks in the patient's arm when the normal score is up to five marks, thus showing the vascular fragility of the patient. The patient reported no history of use of any systemic medication and a previous forearm skin biopsy that revealed reduced thickness of the epithelium and connective tissue. Collagen production type III assay was performed in skin cultured fibroblasts from the same biopsy. The analyses were performed in the Genetics Laboratory of the Federal University of Rio Grande do Sul by metabolic labelling with ^{14}C-proline followed by pepsin digestion and polyacrylamide gel electrophoresis [17]. Both intracellular and extracellular fractions were analysed, and the evaluation was performed qualitatively and quantitatively. The result showed an amount of only 40% type III collagen in relation to the laboratory control group. The qualitative analysis showed protein with normal molecular height, and there was no indication of intracellular accumulation.

It was possible to partially reconstitute the patient's family history identifying an affected grandfather with a history of haemorrhagic lesions on the body and early tooth loss. Nevertheless, although EDS is considered to present an autosomal dominant inheritance pattern, considering the little family information available, it was not possible to conclusively ascertain the genetic pattern of inheritance in this family.

The intraoral examination identified absence of numerous teeth, possibly related to syndromes (no. 25, 26, 28, 46, 45, 44, 43, 33, 34, 35, 36, and 37). Few restorations and absence of caries activity were also observed. A full mouth periodontal examination and radiographs were performed. An extensive clinical attachment and alveolar bone loss was observed in all remaining teeth, compatible with a severe destruction of the periodontal support. On the other hand, no clinical findings, such as supragingival plaque, dental calculus, periodontal probing depth, and bleeding on probing, could explain such a severe support apparatus destruction (Fig. 2).

According to the patient's report and radiograph examinations, tooth loss was progressive and accelerated after 2 years of orthodontic treatment (Figs. 3 and 4).

All other oral features were normal, and the movements of the temporomandibular joints were in normal dimensions although the patient reported pain and noise during masticatory movements.

Discussion

As EDS diagnosis is based predominantly on clinical findings, the features described in this case are compatible with an EDS type IV phenotype [1, 26]. Nine subtypes of EDS have been identified, with type IV being associated with sudden death due to rupture of the bowel, uterus, or major blood vessels. In a review [3], major and minor criteria for type IV EDS diagnosis were established. Our patient fulfilled several major criteria, such as a thin and

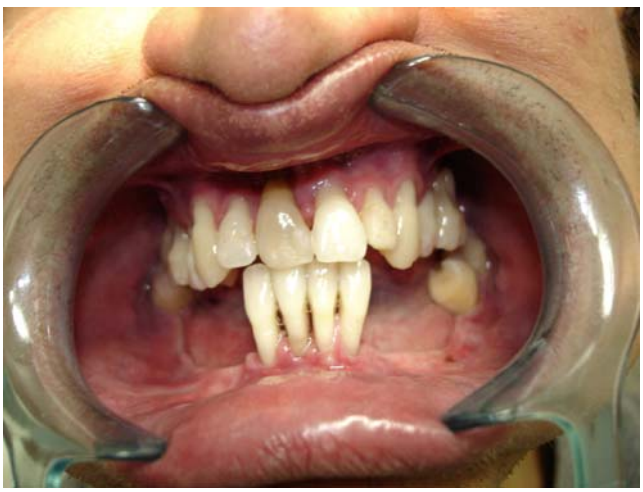

Fig. 2 Current oral status of the patient with loss of teeth 33 to 36 and 43 to 46. Note the extensive gingival contraction both in the superior and inferior teeth

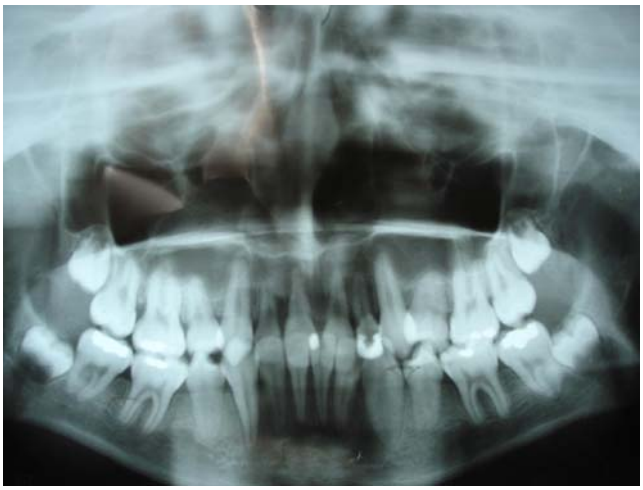

Fig. 3 Panoramic radiography showing the patient's oral status before the use of an orthodontic device. A single radiolucid area can be observed, located at the superior incisors as well as remodelling of the bone alveolar crest on several teeth

translucent skin, facial characteristics, including large eyes, thin nose, and lobeless ears, a short stature, and thin scalp hair (Fig. 1). Spontaneous ecchymoses, frequently recurring in the same areas due to skin and/or vascular fragility or rupture, were also observed. Within the minor criteria for diagnosis, we could point out the occurrence of gingival recession (Fig. 2). The vascular lesions in the legs—a highly susceptible region for trauma—and the veins, seen by transparency on the hands dorsum and feet of our patient, are typical of this EDS type (see Table 1). Other features described for EDS type IV are joint hyperlaxity and gastrointestinal and arterial rupture, but these were not present in the patient [17, 23]. It is important to point out that this high variability in clinical features and symptoms are due to the incomplete penetrance and variable expressivity of this syndrome. This variability probably reflects the variable amount of type III collagen synthesized in affected individuals, what seems to be inversely proportional to the risk of spontaneous rupture of blood vessels [4]. The type III collagen is a main structural component of internal organs and blood vessels [11, 14], and a disfunction in its deposition results in a decreased collagen fibril diameter found in the walls of almost all the vessels in patients with EDS IV. This feature and a decrease on elastin fibers can contribute to a low resistance in the blood vessels in patients with EDS IV [5, 10].

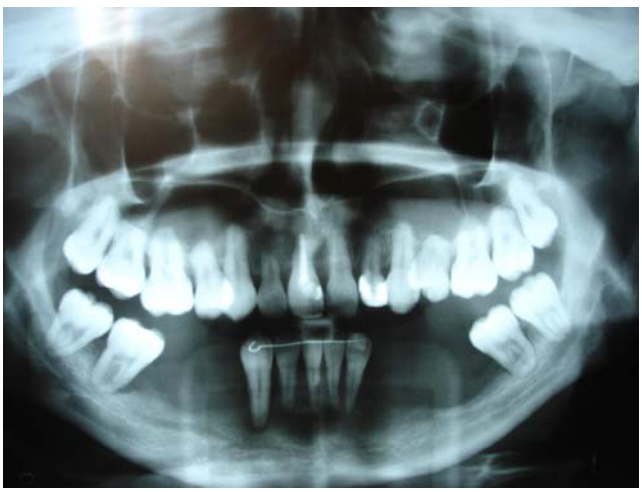

Fig. 4 Panoramic radiography showing the patient's oral status with a 2-year orthodontic treatment. The loss of teeth 33 to 36 and 44 to 46 is evident

Oral manifestations are commonly described in only EDS types VII and VIII [6, 14, 15, 22]. Few cases of patients with EDS type IV were reported with early periodontitis [9, 12, 13] Thus, excluding the cases of early periodontitis, this is the first report of oral signs in a patient with EDS type IV. Considering the patient's records, the deciduous dentition did not show signs of early onset of periodontal destruction. With the exception of a low degree of micrognathia associated with deficiencies on the patient's maxillae, no other dental abnormalities were observed at that time. The micrognathia determined the use of fixed appliances. It seems that the periodontal destruction was initiated and exacerbated by such fixed appliances. This consequence was reported by a group of researchers [15] but just in patients classified under the type VIII syndrome. Nonetheless, the magnitude of this interference cannot be measured, only suggested. High levels of root resorption were noted, and its pattern could be observed in the extracted/lost teeth.

On the other hand, periodontal maintenance treatment did not result in the control of the periodontal attachment loss and root resorption. It seems that a well-known anti-infective periodontal therapy [2, 18, 24, 25] could not refrain this periodontal destructive tendency even in patients with high levels of oral hygiene. Thus, as previously pointed out [16], genetic factors, the presence of type IV EDS, may modify the individual susceptibility to periodontal support tissue loss.

As EDS seems to be caused by a defect in the collagen biosynthesis [28] or in biosynthesis of the enzymes involved in the post-translational modification of collagen [31], we speculate that the exacerbated tooth loss observed along 6 years, since the beginning of orthodontic therapy, was due to the combination of two related factors: (a) a collagen fragility of the periodontal ligament in association with orthodontic forces and (b) the bone remodelling and its potential to determine root resorption. Although, as described previously, early periodontitis was reported for some EDS type IV patients, this is the first report of aggressive periodontitis in Ehlers-Danlos type IV.

We can conclude that high levels of oral hygiene are not sufficient to control the clinical attachment loss. Considering

the association of EDS type IV and such a destructive process, a profound investigation should be carried out to understand the mechanisms behind this periodontal destructive pattern. So far, little information is available on this syndrome and its oral signals and symptoms. In this sense, both familial and personal medical histories should be reinforced based on the assumption that early diagnosis can be helpful in deciding the ideal therapy for each individual.

Conclusions

Considering that EDS patients present collagen fragility, which can interfere with bone remodelling, and considering the existence of phenotypic overlap among different Ehlers-Danlos syndrome types, the use of orthodontic apparatus should be carefully considered in such patients.

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