A young adult male was referred for orthodontic recurrence with unesthetic secondary migrations. He was also treated for severely disabling joint pain in a type-III Ehlers-Danlos syndrome.

He had been treated in childhood using multiple braces, with no particular precaution.

There was no history of trauma.

Clinically, he showed asymmetric class II division 2 malocclusion (total on the left, with almost ideal relations on the right), with anterior supra-occlusion, and exo-occlusion of 1 maxillary premolar associated with 90° rotation (Fig. 1).

Figure 1
a) AP intra-oral view in occlusion. b) Asymmetric occlusion. c) Vestibular version of 22 with diastema and secondary migration. Note asymmetric egression of the mandibular incisors. d) Right class I) Left complete class II molar, rotation and exo-occlusion of 24.
There was little mandibular crowding, with asymmetric egression of the incisors. Overhang was asymmetrically increased, with vestibular version of 21 and diastemas. There were no signs of inflammation or deposit, but retraction of the interdental papillas on either side of the maxillary canines and mesially to 46.

**RADIOGRAPHY FILE**

The radiography file comprised long-cone alveolar assessment of the anterior arcade and lateral teleradiography in occlusion (Fig. 2), revealing:

- Skeletally, 1 class II retromandibulism, partially compensated for by vestibular version of the mandibular incisors and by a doubled mandibular edge, implicated in the dental asymmetry, without intra-osseous or joint abnormalities;

- Dentally, total obliteration of the canal lumen in 11 (with attempted radio-opaque obturation), and partial obliteration in 34 and 44, in the apical region, and generalized horizontal alveolysis affecting a third of the root height. Severe root resorption in 11, and slight apical resorption in 12 and 21. There was similar mandibular alveolysis, with homogenous radio-opaque corono-radicular obturation in 41.

*Figure 2
a) Partial long-cone assessment. b) Lateral teleradiography in occlusion.*
Ehlers-Danlos syndrome (EDS) is a heterogeneous group of genetic diseases involving the connective tissue. First described by two dermatologists, Dr Edvard Ehlers followed by Dr Henri Alexandre Danlos, EDS is a rare disease (1/5,000 to 1/10,000 births), although prevalence may be greatly underestimated\(^1,2,10\). Expression is highly variable, clinically and genetically, as the cause is a defect in the synthesis of collagen, a complex protein found in almost all tissues.

EDS is characterized by a combination of mutations in genes coding for collagenic fibril proteins, or enzymes involved in post-transcriptional modification, inducing increased connective tissue elasticity or “elastorrhexis”. According to subtype and individual characteristics, EDS is classified as minor, with minimal functional impact, to severe, where it may be life-threatening. The skin, joints, muscles and tendons may be involved, but also the vascular and visceral walls.

The Villefranche classification\(^3\) distinguishes at least 6 types, phenotypically:

- **Classical EDS**, the most frequent, formerly types I and II on the Berlin classification, involves hyperextensibility and fragility of the skin, which tears under even slight impact; generalized joint hyperlaxity, and delayed healing, with frequent hematoma in the absence of coagulation disorder. These patients show numerous papyraceous (“cigarette-paper”) scars, exemplifying the fragility of the skin. There may also be dental involvement, with loss of periodontal attachment. Prevalence is 1/30,000, implicating type-V collagen defect.
- **Hypermobile EDS**, formerly type III on the Berlin classification, is fairly frequent and shows slighter skin fragility but severer joint involvement, with frequent dislocation or subluxation and chronic musculoskeletal pain. Pain management is the priority. Early periodontitis was reported in 1 case\(^12\), associated with anaerobic bacteria and a very strong tendency for attachment loss.
- **Vascular EDS**, formerly type IV, is the most serious form, involving extreme fragility in vascular and visceral walls, especially in the gastrointestinal tract, uterus, liver and spleen, with elevated risk of perforation or tear. Victims are very thin, with reduced subcutaneous tissue of the skin and extremities. Certain facial features have been associated with complete forms: translucid skin, with visible veins, large eyes, thin nose, lobeless ears, and fine hair\(^1,2\). A specific deficit in type-III collagen, the main component of vascular walls and internal organs, has been implicated. This form shows similarities to type VIII. Prevalence is 1/50,000.
- **Cyphoscoliotic EDS**, formerly type VI A, associates severe early childhood scoliosis, severe muscle hypotonia, ocular involvement (abnormal cornea, risk of retinal detachment) and osteopenia. It derives from an abnormality of the lysyl hydroxylase enzyme, involved in collagen synthesis. It has certain similarities to Marfan’s syndrome, another rare
genetic disease of the connective tissue (due to mutation of the fibrillin-1 gene (FBN1)).

- **EDS with arthrochalasis**, formerly types VII A and B, is associated with congenital dislocation of the hip.
- **EDS with dermatosparaxis**, formerly type VII C, is very rare, with predominantly cutaneous involvement, mimicking cutis laxa, without atrophic scarring or impaired healing.

Other types: type VIII may be associated with severe periodontal involvement (early aggressive periodontitis). Early periodontitis is diagnosed in case of severe destruction of the periodontal attachment, with recessions and tooth loss before the age of 35 years.

**MANAGEMENT, AND POSSIBLE DELAY OF ORTHODONTIC TREATMENT**

**Definitive diagnosis and complementary examinations**

Diagnosis of EDS is clinical, as specific genetic, biological or histologic tests are lacking. Joint imaging is non-contributive, usually appearing normal.

Patients should be referred to a reference center for exploration and differential diagnosis, ruling out benign articular hyperlaxity, Marfan’s syndrome, osteogenesis imperfecta (brittle bone disease) and Silverman syndrome (child abuse). The description of EDS signs, classification and clinical guidelines are updated on dedicated rare diseases websites: OMIM™ (Online Mendelian Inheritance in Man), the international database of Johns Hopkins University, or the French-language Orphanet® site.

Clinical signs are highly variable, due to incomplete penetrance and variable expressivity of the implicated mutations. There are 3 possible types of transmission: autosomal dominant (the most frequent), autosomal recessive and, more rarely, X-linked autosomal recessive. Some cases may involve de-novo mutation subsequently becoming transmissible.

**Articular risk**

EDS entails elevated risk of subluxation or complete joint dislocation due to tendon and ligament hyperlaxity. Reduction may in turn cause intra-articular hemorrhage. Physiotherapy should therefore be as gentle as possible and surgery should be avoided.

Rehabilitation can be effective if well-conducted, avoiding any movement that might aggravate the risk of dislocation while strengthening the stabilizer muscles.

At dental level, there is a risk of dislocating the temporomandibular joints during extraction.

**Surgical risk**

Despite the above, certain general surgical procedures are inevitable: e.g., for arterial wall lesions, which are not specific to so-called “vascular” forms.

For example, classic EDS involves a risk of mitral or tricuspid valve
prolapse, requiring valve replacement; cardiac valve abnormality requires prophylactic antibiotic therapy for infectious endocarditis. There are written guidelines concerning anesthesia and suture (risk of detachment) and the healing phase in general, which is often defective: fine sutures are recommended (non-resorbable, left for a long time) and tension should be low.

Failure of local anesthesia has been reported in type III EDS. In case of dental extraction, the risk of bleeding and delayed healing is elevated. A plate or acrylic splint can be used to compress the affected area postsurgically, to facilitate hemostasis.

Endodontic risk

Apart from root abnormalities (short, deformed or lacerated root), spontaneous canal obliteration has been reported, jeopardizing endodontic treatment. This may be due to calcareous degeneration of pulp or to pulp-stones.

Periodontal risk

Severe and especially early periodontitis has been reported in EDS, mainly in types VII and VIII, where antigens acting against type-I collagen were detected in some cases, but also in classic and vascular forms.

In one proven case of vascular (type IV) EDS in a 23 year-old patient, radiography showed aggressive periodontal destruction following multibrace orthodontic treatment. Analysis found slight radicular resorption but above all severe alveolysis without plaque deposit, which periodontal treatment failed to stabilize. The patient thus lost all his mandibular premolars and first molars; one incisor was necrotic.

In another case, of type-III (hypermobile) EDS, early periodontitis was reported in a 17 year-old patient, who responded positively to periodontal treatment, with enhanced attachment and increased alveolar height at 18 months. A 10 year-old boy with type-III EDS was successfully treated by Norton and Assael, without pulp, root or periodontal complications; the patient showed class-III dentomaxillary disharmony, with maxillary canine ectopia and 80% supra-occlusion, resolved within 1 year.

Apart from root abnormalities (short, deformed or lacerated root), spontaneous canal obliteration has been reported, jeopardizing endodontic treatment. This may be due to calcareous degeneration of pulp or to pulp-stones.

Figure 3

a) Splint on thermoformed set-up, multi-brace mandibular device. b) Soft resin on threatening hooks.
For Norton and Assael², the risk/benefit ratio of orthodontic treatment in EDS needs careful assessment; orthodontic devices should be simplified and adapted, so as to provide light force and limit the risk of mucosal damage. The authors explain that collagen defect in EDS may greatly increase desmodontal stress for a given moment/force ratio in comparison to that found in healthy subjects. The risk of desmodontal microhemorrhage and dental mobility increases with activation.

In the particular case of Norton and Assael’s patient, a compromise was struck, conserving unilateral class II relations, seeking occlusal balance after leveling. Orthognathic surgery was initially indicated but ruled out in the light of all the attendant risks and absence of masticatory or respiratory disorder. Although orthodontic displacements were limited, the patient was more fully informed of the risk of pulp necrosis and possible aggravation of periodontitis.

Figure 4
a) AP view of end of orthodontic treatment. b) Overhang. c) Leveling and free-edge coronoplasty. Note marks of articulating paper to avoid local hyperpressure.

Figure 5
Check on glue contention allowing use of soft picks.

Figure 6
Retroalveolar views. a) Superior. b) Inferior.

Adaptation of orthodontic treatment
PAINFUL HYPERLAXITY (EHLERS-DANLOS SYNDROME)

Given the fragility of the resorbed incisors and loss of attachment, only flexible braces, produced by progressive set-ups, were used for the superior arcade (Fig. 3a). Mandibular leveling used round hyperelastic nickel-titanium wires with flat metal braces, in view of the supra-occlusion (Integra™, Rocky Mountain Orthodontics, Fig. 3b). Soft resin for provisional obturation (Telio CS Inlay®, Ivoclar Vivadent) was used on hooks or rough relief threatening the lip, and only elastomeric ligatures were employed.

Treatment was completed in 5 months; movements were obtained relatively quickly, despite sessions at 6-week intervals (Fig. 4).

The contention wires were adapted passively using an indirect technique and glued to the loaded composite, checking that there were passages for soft picks; this also contributed to patient education for plaque control (Fig. 5). Absence of hyperpressure in occlusion was checked using articulating paper. The patient was supplied with supplementary nocturnal contention splints, as contention needs to be prolonged or indeed permanent in these cases.1,7

In hypermobile EDS, as was the case for Norton and Assael’s patient, muscle and joint pain is intense and heightened by weight-bearing, leading to frequent changes of position and stretching. To avoid the discomfort of the seated position – and possible incomprehension on the part of others in the waiting room – appointments were made at the beginning of the day. Sessions were short and, for better comfort, used a chair with shape-memory seat (Tempur™).

End-of-follow-up radiographs, taken by the patient’s dentist (Figs. 6a and b), showed no periodontal or radicular deterioration. Even so, long-term periodontal, endodontic and occlusal maintenance is mandatory. Prognosis being unsure for certain dental or organs, implants are likely to be needed in the medium to long term. Implantation seems not to be contraindicated in EDS; indeed, in the case series reported by Jensen and Storhaug7, post-implantation bone defect was minimal over 2 to 12 years’ surveillance, and no implants were lost.

CONCLUSION

Ehlers-Danlos syndrome is not a progressive disease but rather a “constitutional state” of tissue fragility. The various subtypes as described in the literature are not clearly distinct entities; certain features may be superimposed, such as periodontal involvement, which is not restricted to types VIII and III. Orthodontic treatment in EDS incurs risks of endodontic, periodontal and articular complications.

Conflict of interest: The authors declare no conflicts of interest.
REFERENCES


Links:
https://www.orpha.net/data/patho/Pro/en/Ehlers_Danlos_En.pdf
http://www.afsed.com/
http://www.ednf.org/mambo/index.php

Recommended reading: