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Periodontal Ehlers–Danlos syndrome associated with type III and I collagen deficiencies

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Conflicts of interest

None declared.

Summary

In 1997, Ehlers–Danlos syndrome type VIII (EDS-VIII) was excluded from the diagnostic categories as there were insufficient data regarding the clinical features and the precise underlying molecular basis. However, a recent review of published cases shows that EDS-VIII has distinctive clinical features, which would suggest that it should be considered as a separate entity in future nosological classifications. The underlying molecular defect in EDS-VIII is unknown. A reduction of collagen type III was reported in a single case, but no consistent biochemical or structural changes are detectable. We report a patient with EDS-VIII who showed a reduction in the collagen type I and type III synthesis rates. Type I and type III procollagen and collagen synthesis and secretion rates were investigated in cultured fibroblasts and compared with five healthy controls and three patients with EDS type IV whose fibroblasts were cultured in parallel.

Ehlers–Danlos syndrome (EDS) is a clinically and genetically heterogeneous group of connective tissue disorders caused by collagen defects. Until recently, EDS was divided into as many as 11 different subtypes (types I–XI), according to clinical phenotype.[1] In 1997, in view of recent advances in the understanding of the biosynthesis of collagen, a consensus conference was held and a revised nosology was proposed. Several previously described but exceedingly rare subtypes of EDS, including type V (X-linked variant), type VIII (periodontal type) and type X (fibronectin type) were excluded from the diagnostic categories as there were insufficient data regarding the clinical features and the precise underlying molecular basis.[2]

We report the case of a 10-year-old girl with EDS-VIII (periodontal type) to draw attention to this rare condition and to discuss its clinical and molecular features.

Case report

A 10-year-old girl was referred for clinical evaluation because of pretibial ecchymotic lesions and a tendency to bruising on mild trauma. Her parents also mentioned that her wound healing was defective and led to atrophic scars. In addition, the patient reported a history of severe periodontal disease with bleeding after tooth brushing and minor trauma since early childhood. She was the eldest child of a couple with no consanguinity and no relevant clinical disorders. The patient had a 7-year-old sister who was in perfect health. The only relevant clinical history of the patient was a traumatic fracture of her radius and ulna 2 years previously.

Dermatological examination revealed purple-brown atrophic plaques covering the pretibial areas and mimicking necrobiosis lipoidica (Fig. 1). Two 'cigarette paper' scars were present on the right elbow and knee, respectively. Her skin was thin and translucent with a visible venous pattern (Fig. 2). She had only mild cutaneous hyperelasticity, and minimal articular hypermobility limited to the digits. The patient scored 4/9 points on the Beighton scale (a score of ≥ 5/9 defines hypermobility). This score was obtained by passive dorsiflexion of the little fingers beyond 90° (2 points) and passive apposition of the thumbs to the flexor aspect of the forearm (2 points).[3] On oral examination, both the attached and marginal gingivae were swollen and demonstrated recession. In addition, the alveolar mucosa was very thin and translucent. On musculoskeletal examination, a slight asymmetry in the shape of the back was observed. On general examination, the patient exhibited a marfanoid habitus and a triangular face, short philtrum, long nose and large prominent eyes (Fig. 3).

The only relevant ophthalmological finding was the visibility of the peripheral corneal nerves. Laboratory studies disclosed normal values for total blood count, coagulation test, renal and liver function tests, erythrocyte sedimentation rate and urinalysis. In addition, spine and serial bone X-ray, chest X-ray, abdominal and cardiac echography and thoracic, abdominal, pelvic and cerebral computed tomography scans were all normal.

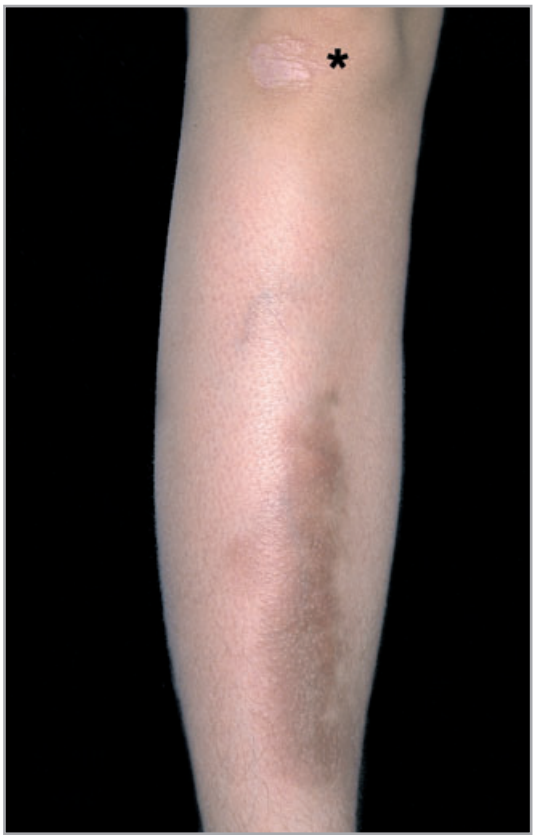

Fig 1. Brownish atrophic pretibial plaques. Asterisk indicates a 'cigarette paper' scar on the patient's knee.

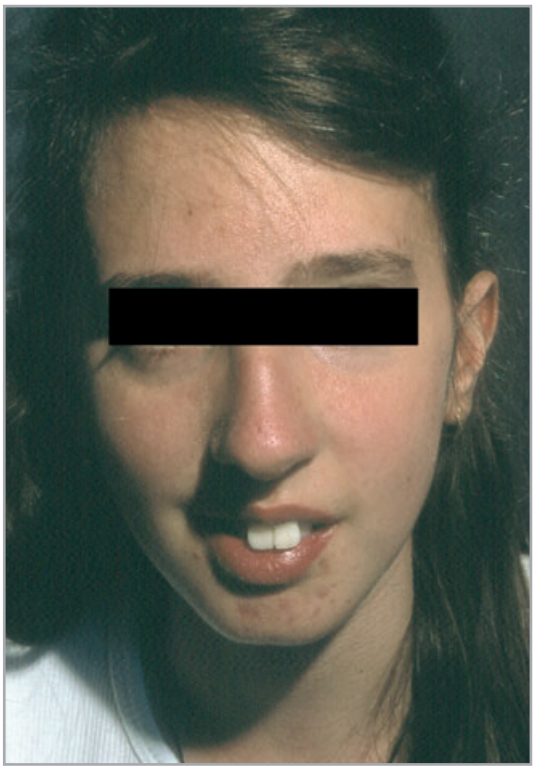

Fig 3. Photograph of the face of the proband, demonstrating triangular facies, prominent eyes, long nose and short-appearing philtrum.

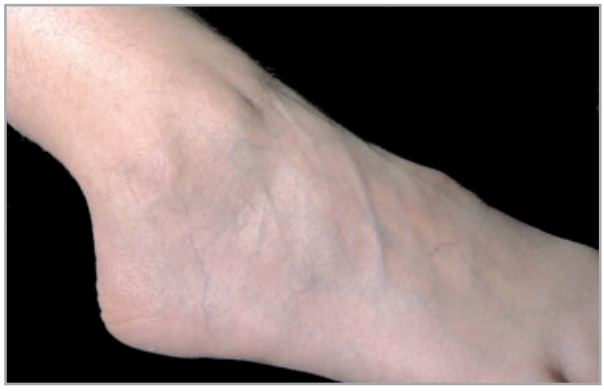

Fig 2. Thin and translucent skin with a visible venous pattern on dorsal aspect of the foot.

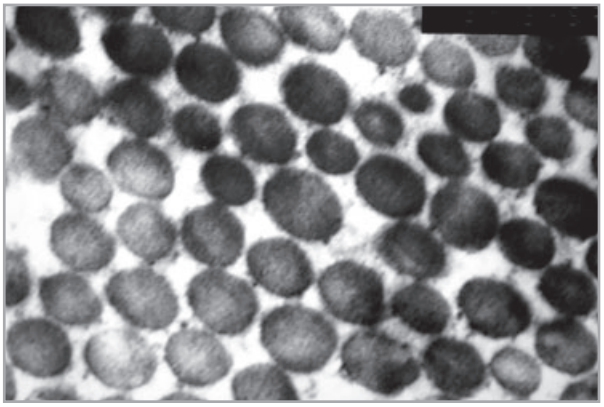

Fig 4. Electron micrograph of cross-section of collagen fibres showing the presence of collagen fibrils of variable sizes and/or irregular shape.

Histological examination of a biopsy taken from the dorsum of her foot showed a marked thinning of the reticular dermis. On electron microscopy examination, collagen fibrils of variable diameters were seen (Fig. 4). The presence of clinical signs, which can be associated with the EDS-IV phenotype, led us to investigate collagen metabolism in particular in this patient. Type I and type III procollagen and collagen synthesis and secretion rates were investigated in cultured fibroblasts and compared with five healthy controls and three patients with EDS type IV whose fibroblasts were cultured in parallel. The normal control fibroblast cell lines were obtained from organ donors who had been involved in road traffic accidents (skin donors, age range 7–16 years) whereas EDS-IV cell lines were obtained from our tissue bank (three patients – two males and one female – with a definite diagnosis of EDS-IV). Results are summarized in Table 1.

At the age of 16, our patient still has all her teeth and has managed to reduce the gingival retraction by means of

Table 1 Synthesis of collagen in fibroblast culture. In comparison with age-matched, control dermal fibroblasts, analysis of the carboxyterminal and aminoterminal procollagen propeptides shows a reduction in the type I and type III collagen synthesis rates of 31% and 61%, respectively. In addition, type I collagen synthesis rate is 46% and 40% lower than that of controls with Ehlers–Danlos syndrome acrogeric type IV [EDS-IV(a)] and EDS ecchymotic type IV [EDS-IV(e)], respectively. Type III collagen synthesis rate is 85% less than in the control with EDS IV(a) and 55% more than in the control with EDS-IV(e). In comparison with normal controls, EDS-IV(a) shows a markedly low type III collagen secretion rate whereas EDS-IV(e) shows a pronounced low type III collagen production rate. On the other hand, no alterations in type I collagen secretion or synthesis rates are observed in either EDS-IV cases or normal controls

	Control (n = 5)	EDS-IV(a)[a] (n = 1)	EDS-IV(e)[a] (n = 2)	Proband
Incorporation of proline (IC) (DPM per 10^6 cells mL^{-1})[b]	$6 \times 10^4 \pm 15\,000$	$1{\cdot}4 \times 10^5 \pm 17\,500$	$3{\cdot}1 \times 10^4 \pm 16\,200$	$3{\cdot}9 \times 10^4 \pm 14\,300$
Incorporation of proline (SC) (DPM per 10^6 cells mL^{-1})	$11 \times 10^3 \pm 3350$	$1{\cdot}9 \times 10^3 \pm 338$	$1{\cdot}6 \times 10^3 \pm 460$	$3{\cdot}3 \times 10^3 \pm 512$
Collagen I synthesis (IC) (ng mL^{-1} per Eq 10^6 cells)[c]	236 ± 48	301 ± 15	270 ± 42	163 ± 12
Collagen I secretion (SC) (ng mL^{-1} per Eq 10^6 cells)	85 ± 19	79 ± 6	101 ± 37	43 ± 7
Collagen III synthesis (IC) (ng mL^{-1} per Eq 10^6 cells)	$27{\cdot}2 \pm 10{\cdot}3$	$72{\cdot}1 \pm 3{\cdot}3$	$6{\cdot}9 \pm 3{\cdot}2$	$10{\cdot}7 \pm 1{\cdot}6$
Collagen III secretion (SC) (ng mL^{-1} per Eq 10^6 cells)	$5{\cdot}6 \pm 2{\cdot}1$	$< 0{\cdot}5$	$1{\cdot}4 \pm 0{\cdot}7$	$2{\cdot}2 \pm 1{\cdot}1$

IC, intracellular; SC, supernatant of the culture medium; DPM, disintegration per min.

[a]According to Pope *et al.*, we define as acrogeric EDS IV those cell lines with intracellular retention and no secretion of type III collagen and ecchymotic EDS IV as those cell lines with diminished amount of normally secreted collagen production that is not retained intracellularly.[11,12]

[b]The fibroblast cultures were made in F10 medium, without serum and with ascorbic acid supplement (50 μg mL^{-1}) and fibroblastic growth factor (50 μg mL^{-1}). The cells from the healthy and pathological controls and the proband were recovered from the initial cultures when the confluent phase was reached and resuspended in fresh F10 medium. Then they were seeded in 24-well tissue culture plates at a rate of 1 mL of medium per well, and maintained thus for 24 h for incorporation of proline and 48 h for synthesis and secretion of collagen. The cultures from healthy controls were seeded three times and those of the pathological controls and the proband six times. The results shown in the table are the means ± SD of the mean values in the healthy controls and EDS-IV(e) and the mean ± SD of the values measured in each culture in the cases of EDS-IV(a) and the proband.

[c]Radioimmunoassay equipment from Farmos Diagnostica® (Oulunsalo, Finland) was used for measurement of type I collagen (carboxyterminal propeptide) and type III collagen (aminoterminal propeptide).

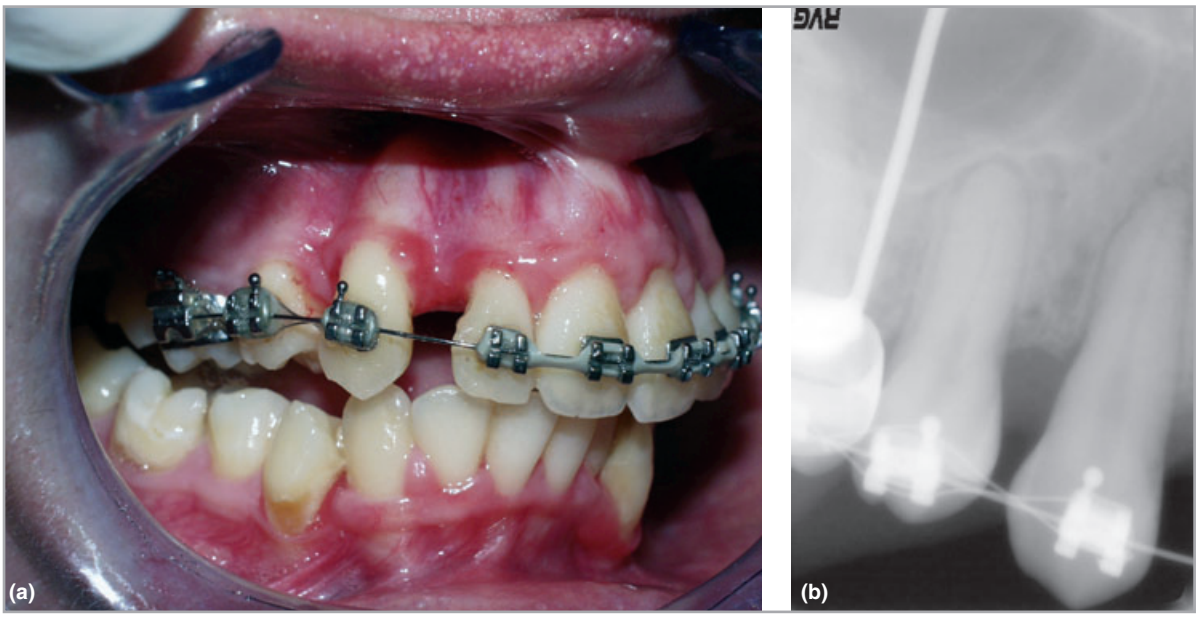

Fig 5. (a) Variable gingival recession on the right side at the age of 16. (b) Alveolar bone loss around the upper right canine.

Table 2 Comparison of periodontitis-type Ehlers–Danlos syndrome (EDS), vascular-type EDS, classical-type EDS, Marfan syndrome and the proband

	Periodontal type EDS (VIII)	Vascular type EDS (IV)	Classical type EDS (I)	Marfan syndrome	Proband
Inheritance	AD	AD	AD	AD	–
Molecular defect	Unknown[a]	*COL3A1* mutations	*COL5A1* and *COL5A2* mutations	Fibrillin-1 and type II *TGFB* receptor mutations	Reduction in the type III collagen synthesis
Joint hypermobility	+ Limited to the fingers	+ Limited to the fingers	+ + Generalized	+ Generalized	+ Limited to the fingers
Cutaneous hyperelasticity	–	–	+ +	–	–
Easy bruising	+ +	+ +	+	–	+ +
Atrophic scarring	+ +	+ +	+ +	–	+ +
Translucent skin	+	+ +	+ +	–	+
Ophthalmological anomalies[19]	+/–	+/–	+/–	+ +	+
Corneal anomalies, subluxation of the lens, scleral fragility, blue sclerae, marked myopia, vitreous haemorrhages and retinal detachment				Ectopia lentis Myopia	Visibility of the peripheral corneal nerves
Oral manifestations[17]	+ +	+/–	+/–	–	+ +
Periodontitis, mucosal fragility, recurrent temporomandibular joint dislocations, abnormal pulp shape and pulp stones	Periodontitis	Periodontitis[20]			Periodontitis
Marfanoid body habitus	+ +	+/–	–	+ +	+
Facial findings	Triangular face Short philtrum Long nose Large, prominent eyes	Pinched, thin nose Thin lips Prematurely aged appearance Lobeless ears	–	–	+ +
Additional features	None[b]	Arterial, intestinal and uterine rupture	Molluscoid pseudotumours	Mitral valve prolapse Aortic dissection	None
Histological examination	+	+	+	–	+
H&E: thin reticular dermis and collagen fibrils reduced in number or thickness					
Electron microscopy: collagen fibrils of variable sizes and/or irregular shape					

AD, autosomal dominant; H&E, haematoxylin and eosin
+ +, major clinical feature; +, minor clinical feature; +/–, occasional feature
[a]A reduction of collagen type III was reported in a single case.[13]
[b]There is only a single report of duodenal rupture in a middle-aged man with EDS-VIII.[21]

meticulous oral hygiene and very conservative orthodontic treatment. However, exploration of the oral soft tissues still shows there to be a thin alveolar mucosa, with reduced attached gingiva on some areas, insufficient on the first upper premolars and absent on the upper and lower canines and first left premolar teeth (Fig. 5a). Dental X-rays showed a reduction of alveolar bone of approximately 30% (Fig. 5b).

Discussion

EDS-VIII (OMIM 130080) is an exceedingly rare autosomal dominant disorder first described by McKusick in 1972 in a family with skin fragility and abnormal scarring together with severe periodontal disease which led to early loss of teeth.[4] Since that time, 45 additional cases have been reported. According to the 1997 Villefranche Consensus Meeting, these

patients should remain unclassified and be included under the 'other' category due to the lack of a clear description of the clinical features and the precise molecular basis.[2]

However, a review of the published cases shows that EDS-VIII has distinctive clinical features, which would suggest that it should be included as a separate entity in future nosological classifications. Recently, Moore *et al.*,[5] in an excellent review, described the most characteristic clinical findings of this rare condition. In order of frequency, the main clinical findings in EDS-VIII are: severe periodontal disease, skin fragility, minimal skin hyperextensibility, minimal–moderate joint mobility often limited to the fingers, a strikingly marfanoid habitus and a characteristic facies. The periodontal disease starts in infancy and may lead to a premature loss of teeth in the third decade of life. The cutaneous fragility is also a major feature of EDS-VIII. The main clinical characteristic is the presence of brownish atrophic pretibial plaques, which resembles necrobiosis lipoidica diabeticorum. The phenotype of these patients is also typical with a marfanoid habitus and a triangular facies, with prominent eyes and a long nose (Table 2).

In general, periodontitis is characterized by the irreversible destruction of periodontal tissue (periodontal ligament and alveolar bone) and is currently classified as either chronic, aggressive, or as a sign of underlying systemic disease.[6] The periodontal ligament is mainly made up of type I collagen (80%) and to a lesser extent of type III collagen (20%).[7] It is therefore easy to understand how defects in the collagen mesh affect periodontal tissue in EDS.

Several authors have emphasized the marked clinical overlap between vascular EDS (type IV) and EDS-VIII (Table 2).[8] Vascular EDS results from mutations in the gene for type III procollagen (*COL3A1*).[9,10] Although there is a consensus classification that unifies the denomination of all the subtypes of what was formerly known as EDS-IV in vascular EDS, there is a variable spectrum of clinical manifestations of this entity with a heterogeneous molecular and pathogenic basis.[11,12] The underlying molecular defect in EDS-VIII is unknown but it is possible that there could be allelic variants of this syndrome with different types of mutations as it occurs in vascular type EDS.

A reduction of collagen type III was reported in a single case,[13] but no consistent biochemical or structural changes are detectable.[5,8,14] In our case, we observed a significant reduction in the type III collagen synthesis rate with no apparent reduction in the secretory capacity since the proportion of collagen synthesized/secreted by the patient's fibroblasts is much the same as that of fibroblasts of healthy controls. The same may be said of type I collagen, although its significance is more difficult to assess as the reduction in rate of collagen synthesis is only 31%. Because type III collagen is crucial for type I collagen fibrillogenesis,[15] abnormal levels of type I collagen found in our case could be related to a type III collagen deficiency. It should be emphasized that the type I and type III collagens synthesis and secretion rates of the patient's fibroblasts show a different profile from that of controls with EDS-IV (Table 1). These data support the hypothesis that EDS-VIII is a different pathological process from vascular EDS.

Recently, Rahman *et al.* mapped the gene causing EDS-VIII in three large Swedish families to chromosome 12p13.[16] This is the first evidence for the existence of EDS-VIII as a separate genetic entity. However, to our knowledge, chromosome 12p13 does not contain genes involved in biosynthesis, secretion or formation of collagen fibrils.

Currently, there is no treatment available for any of the EDS subtypes. In EDS-VIII the most important aspect is prevention of trauma to the skin and meticulous care of surgical scars. Early recognition and treatment of periodontal disease may considerably improve the long-term prognosis. The basis of treatment of periodontal disease is meticulous oral hygiene and suitable orthodontic treatments. However, as the integrity of collagen is essential in order to support the tensile force created by orthodontic apparatus, there should be careful vigilance of these patients as such apparatus may lead to acceleration of the alveolar reabsorption.[17,18]

In conclusion, EDS-VIII is a disorder which is well-defined from the clinical aspect, and should probably be reconsidered for inclusion as a distinct entity in future nosological classifications.

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