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The Natural History, Including Orofacial Features of Three Patients With Ehlers-Danlos Syndrome, Dermatosparaxis Type (EDS Type VIIC)

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Abstract

Ehlers-Danlos syndrome (EDS) dermatosparaxis type (type VIIC) and the related disease of cattle dermatosparaxis, are recessively inherited connective tissue disorders, caused by a deficient activity of procollagen I N-proteinase, the enzyme that excises the N-terminal propeptide in procollagen type I, type II, and type III. Although well documented in cattle, to date only seven human cases have been recorded, most of them aged under 2 years. We document the natural history of three patients with EDS dermatosparaxis type, two of whom have been reported before the age of 2 years, and one new patient. The phenotype of the patients, and especially the facial resemblance, is striking, making this a clinically recognizable condition. The most consistent anomalies during the first years of life are premature rupture of the membranes, extreme skin fragility and easy bruising, large fontanels, blue sclerae, puffy eyelids, micrognathia, umbilical hernia, and short fingers. Joint hypermobility becomes more important with age. The children are at risk for rupture of internal organs due to soft tissue fragility, as is illustrated by different internal events in two of the three patients described here. Orofacial features include micrognathia, a frontal open bite, and gingival hyperplasia with varying degrees of hyperkeratosis. The deciduous dentition shows abnormal morphology of the molars, obliteration of the tooth pulp, and severe enamel attrition. The permanent dentition shows agenesis and microdontia of several teeth. Tooth discoloration, dysplastic roots, and tooth pulp obliteration are present in a restricted number of permanent teeth.

Keywords : human dermatosparaxis ; Ehlers-Danlos syndrome type VIIC ; Ehlers-Danlos syndrome ; dermatosparaxis type ; diagnosis ; natural history ; clinical variability ; prognosis ; skin fragility ; type I collagen ; procollagen I N-proteinase ; *ADAMTS2* gene

INTRODUCTION

The Ehlers-Danlos syndromes (EDS) comprise a heterogeneous group of inherited connective tissue disorders characterized by altered mechanical properties of skin, joints, blood vessels, and ligaments, causing skin extensibility, tissue fragility, and articular hypermobility [Steinmann, 2002]. The most recent classification recognizes six subtypes, based on clinical, genetic, and biochemical characteristics [Beighton et al., 1998].

EDS dermatosparaxis type or EDS VIIC (MIM 225410), and the related animal disease dermatosparaxis, are recessively inherited connective tissue disorders, caused by a deficient activity of procollagen I N-proteinase, the enzyme that excises the N-terminal propeptide in procollagen type I, type II, and type III. As a consequence, there is accumulation of pN-procollagen (collagen that still contains the N- but not the C-propeptide) [Nusgens et al., 1992], resulting in polymerization of abnormal collagen fibers that appear thin, irregular, branched and "hieroglyphic" in cross-section [Pierard and Lapiere, 1976]. The clinical picture is characterized by premature rupture of the membranes, extreme skin fragility and laxity, easy bruising, large fontanels, characteristic face, puffy eyelids, blue sclerae, micrognathia, umbilical hernia, short fingers, and short stature [Fujimoto et al., 1997].

To date only seven human cases of EDS dermatosparaxis type have been recorded, most of them being aged under 2 years [Nusgens et al., 1992; Smith et al., 1992; Wertelecki et al., 1992; Petty et al., 1993; Reardon et al.,

1995; Fujimoto et al., 1997; Pasch et al., 2000]. There is only one published case reporting on the natural history of the disorder in a 15-year-old girl [Reardon et al., 1995]. We document here the natural history and some unusual features of two earlier reported patients [Nusgens et al., 1992; Pasch et al., 2000] as well as of one new patient in order to illustrate the evolution of this disease in childhood and early puberty.

CLINICAL REPORTS

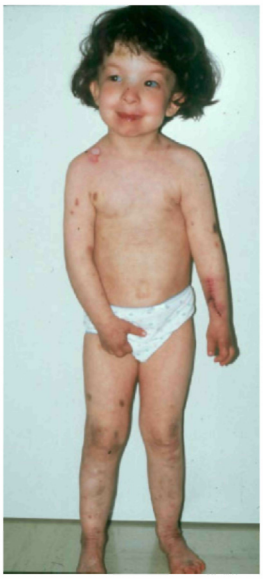
Patient 1

The patient (Fig. 1) is the only daughter of healthy nonconsanguineous Caucasian parents. She was born prematurely at 29½ weeks due to premature rupture of the membranes. At birth she had a large umbilical hernia. At 3½ months of age she was evaluated for small stature, dysmorphic facies, and lack of ossification of the cranial bones. Her weight was 32 kg (10th centile), height was 134 cm (<3th centile), and head circumference was 51 cm (25th centile). At the age of 12 months, occipital fracture with massive hematoma occurred following a minor trauma. She had easy bruising, blue sclerae, and a soft, velvety and hyperextensible skin. Suturing of wounds was very difficult due to the extreme skin fragility. The diagnosis of EDS dermatosparaxis type was made on clinical grounds at the age of 2 years and confirmed by transmission electron microscopy of the dermis, which showed the characteristic hieroglyphic pattern of the collagen fibrils, and by biochemical analysis, displaying reduced pNI-procollagen processing [Nusgens et al., 1992].

Between the age of 2 and 12 years she encountered multiple problems as a result of her extreme tissue fragility. At the age of 5% years she had a spontaneous bladder rupture following an episode of urinary infection and retention. Ultrasound examination revealed the presence of bladder diverticulae. Recurrent urinary infections, due to post-mictional residue, continue to be a problem. At the age of 9 years she underwent a surgical intervention for hemorrhoids associated with complaints of severe constipation. During postoperative vomiting, the diaphragm ruptured, complicated by a para-esopagheal hernia and incarceration of the stomach. Upon reduction, a voluminous hematoma in the wall of the stomach occurred. Postoperatively she suffered from atelectasis and pleural serohemorrhagic effusion of the left lung.

At age 12 years (Figs. 4A and 5A), marked skin fragility and easy bruising still predominate the clinical picture. The skin tears easily after minor trauma, and wound healing, although initially without extensive scar formation, eventually leads to the formation of several widened atrophic scars all over her body (Fig. 7A). Her hands and feet are very short with excessive skin folds on fingers and ankles (Fig. 6A). She bruises very easily and healing of hematomas is slow. All tests of coagulation and platelet count are normal. Clinical findings at time of investigation are summarized in Table I.

Fig. 1. *Patient 1 at approximately 3 years showing characteristic facial appearance, short stature, and short limbs. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]*



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Patient 2

This 7-year-old boy is the second child of healthy non-consanguineous Caucasian parents. Because his mother had four spontaneous abortions, chromosome analysis was performed in the parents and showed no abnormalities. He was born after 38 weeks of gestation by caesarian section because of his large size (3,900 g = 90th centile). Birth length was 49 cm (25th centile). During birth the short umbilical cord (18 cm) ruptured very easily. Post-partum appearance was characterized by generalized edema and gave the face a coarse appearance with swollen eyelids which could not be opened initially (Fig. 2A). Additionally, a short forehead with hypertrichosis, absent supra-orbital ridge, broad nasal root with wide nares, smooth philtrum, large mouth with thin upper lip, and micrognathia were noted. The gingiva was hypertrophic with irregular cystic swellings (Fig. 2B). The large size of the fontanels and the wide cranial sutures were striking. Arms and legs were short with short stubby hands with sausage-like fingers and toes. There was bilateral camptodactyly of the third and fourth finger. An operation for the camptodactyly was not successful. A large umbilical hernia was present after birth but became smaller gradually. After the edema had resolved sagging skinfolds appeared under his jaws suggesting cutis laxa. Large sagging cheeks and blepharochalasis with small slitlike eyefissures gave his face a characteristic appearance (Fig. 2C). His hands had a progeric appearance because of the many fine creases of the skin (Fig. 2D). Two large submucosal herniations behind the lower lip hindered oral hygiene and were excised without problems (Fig. 2E). Additionally, the strongly protruding lower lip was surgically corrected. The diagnosis of dermatosparaxis was made at the age of 15 months based on the clinical findings, and was confirmed by electron microscopic analysis of a skin biopsy, showing the pathognomic hieroglyphic pattern of the collagen fibres (Fig. 3). Psychomotor development was normal. As he became more active it was noted that he sustains bruises easily and has a fragile skin that tears easily but heals with normal scars. The skin was very soft and only slowly fell back into position after stretching. Unusual joint hypermobility became apparent during childhood. At age 7 years he was short (Figs. 4B and 5B), with very short hands and feet (Fig. 6B,C), and a very soft and fragile skin which bruises easily (Fig. 7B). Clinical findings at time of investigation are summarized in Table I.

Fig. 2. *A: Patient 2 at birth showing a short forehead with hypertrichosis, swollen eyelids, micrognathia, umbilical hernia, and short arms and legs with sausage-like fingers and toes. B: Patient 2 at 16 days showing the hypertrophic gingiva with irregular cystic swellings. C: Patient 2 at 3 years. Striking facial appearance with short forehead and hypertrichosis, puffy eyelids and blepharochalasis causing small slitlike eyefissures, large sagging cheeks, micrognathia and protruding lower lip. D: Patient 2 at 3 years. Note the progeric appearance of the hands, with many fine creases, and camptodactyly of the 3rd and 4th finger. E: Patient 2 at 3 years. Large submucosal herniation of the lip. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]*

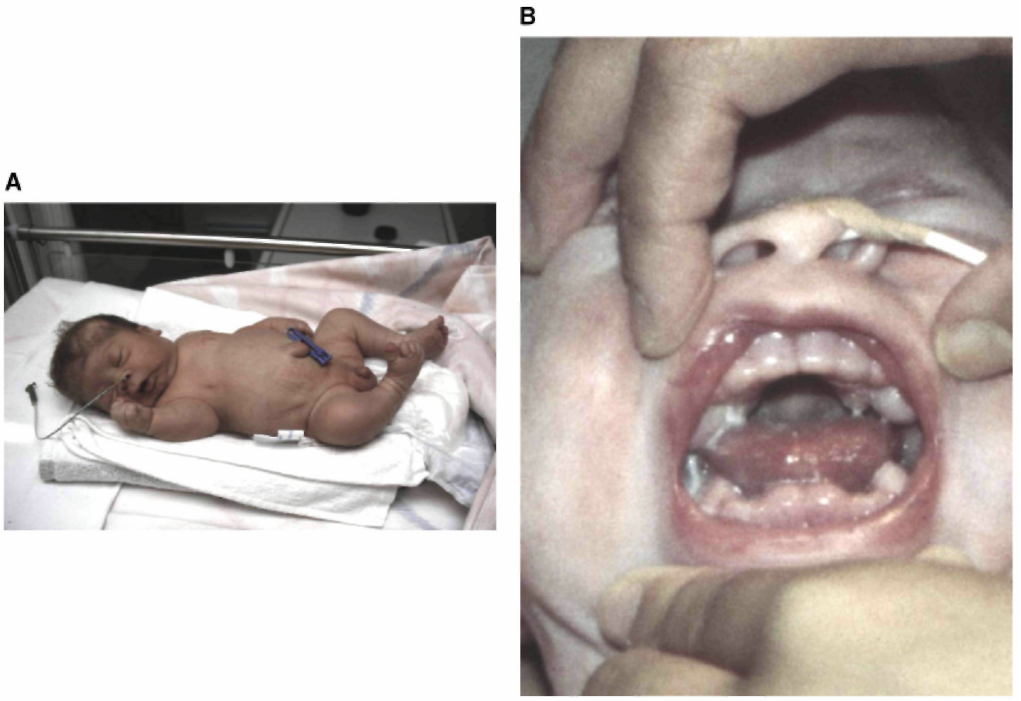

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Fig. 2. *(Continued)*

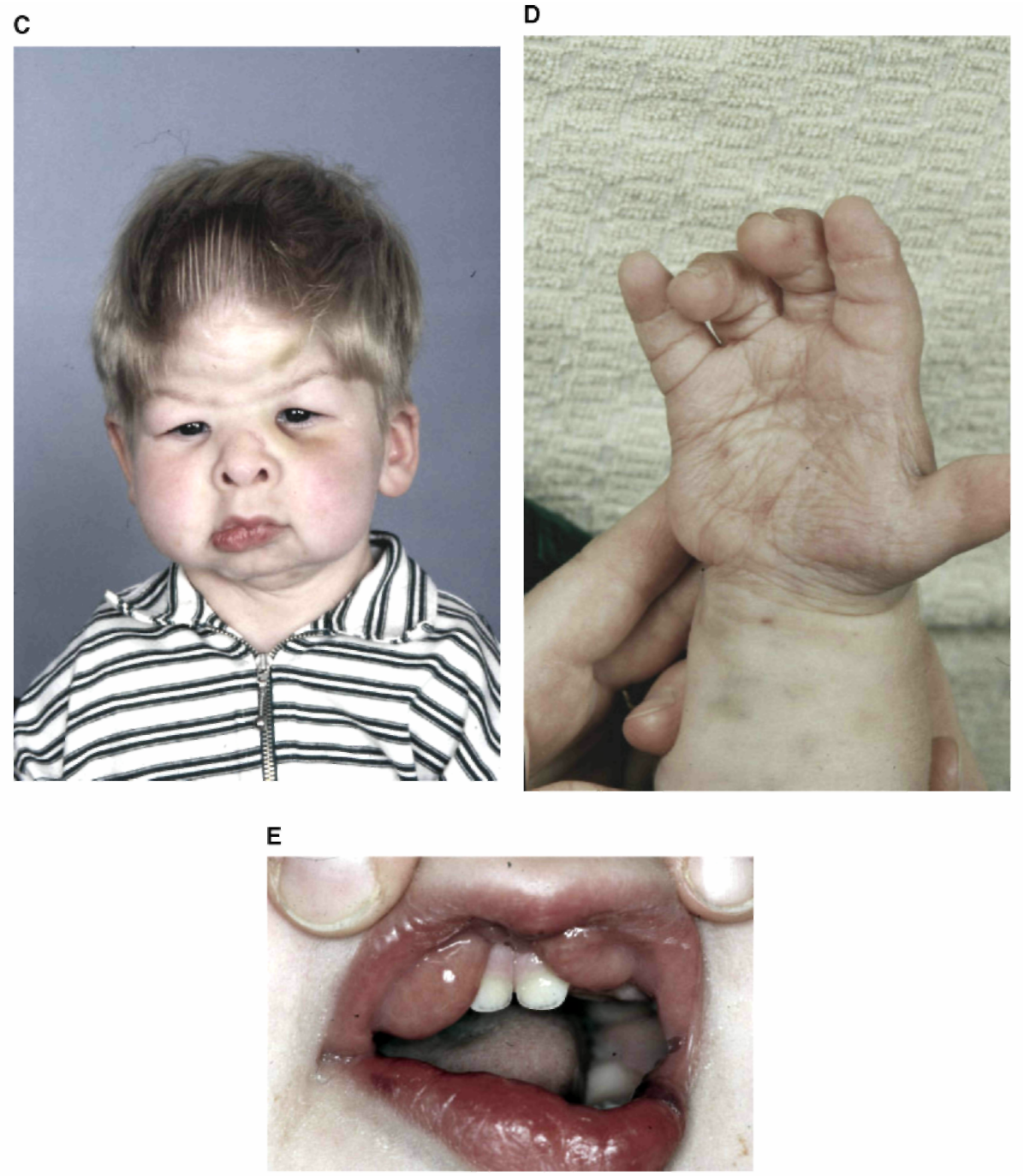
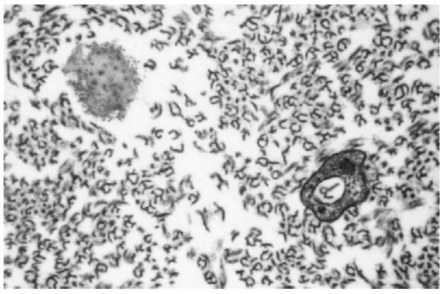


Fig. 3. *Transmission electron microscopy of the dermis of patient 2. The transverse section of bundles of collagen polymers illustrates the hieroglyphic pattern of the individual fibrils.*



Patient 3

This 5-year-old boy is the second child of healthy non-consanguineous Caucasian parents. He was born after 34 weeks of gestation by caesarian section because of breech presentation and polyhydramnion. At birth a very large anterior fontanel (3×3 cm) and excessive wrinkling of the skin over hands and feet were the only evident abnormalities. In the following months a psychomotor retardation developed along with increasing bulging of the anterior fontanel, puffy eyelids, umbilical hernia, and a strong bleeding tendency. His skin was soft, thin and very fragile, with frequent hematomas and mild joint hypermobility. Between the age of 6 and 10 months, an ophthalmologic examination, urinary screening for organic acids, visual evoked potentials and electro-encephalography, were performed with normal results. Cerebral MRI scan showed an Arnold-Chiari-malformation and turricephaly. The karyotype was normal.

At age 22 months a skin biopsy was done because of increasing clinical signs of fragile connective tissue. Electron microscopy showed the typical hieroglyphic pattern of collagen fibrils, disclosing the diagnosis of EDS dermatosparaxis type.

The boy's main problems at age 5 years were easy bruisability, especially of the buccal mucosa, and severe skin fragility (Figs. 4C and 5C). Joint hypermobility became more apparent as the boy grew up. At 5½years of age he developed an acute abdomen as a consequence of a ruptured bladder diverticulum with urinary ascites. Subsequent surgery was complicated by the fragility of the tissue and during the following days a urinary fistula developed due to insufficiency of the sutures. Urinary ascites regressed spontaneously without further need for intervention. Clinical findings at time of investigation are summarized in Table I.

TABLE I. *Summary of Clinical Features in Four Patients With EDS Dermatosparaxis Type*

	Patient 1	Patient 2	Patient 3	Reardon et al. [1995]
Gender	Female	Male	Male	Female
Age (years)	12	7	5	15
Height (cm)	134 (<3rd centile)	115 (3rd centile)	101 (<3rd centile)	<3rd centile
Weight (kg)	32 (10th centile)	25 (25th centile)	14.5 (3rd centile)	3rd centile
OFC (cm)	51 (25th centile)	52.5 (>50th centile)	50 (25th centile)	10th centile
Facial characteristics				
Micrognathia	+++	+++	++	+
Blue-grey sclerae	+	+	+	+
Epicanthic folds	+	+	+	+
Downslanting palpebral fissures	+	+	+	+
Puffy eyelids	+	++	-	-
Skin				
Soft and doughy skin	+++	+++	+++	+++
Redundant skin	+++	+++	+	+++
Cigarette paperscars	+++	-	-	+++
Skeletal manifestations				
Joint hypermobility	Mild	Moderate	Moderate	Severe
Short hands and feet	+++	+++	++	+++
Delayed closure of fontanels	Present	Present	Present	Present
Other features				
Umbilical hernia	Treated by surgery	Mild	Complete regression	Treated by surgery
Easy bruising	+++	+++	++	+++
Transparent veins	+	+++	+	?
Echocardiography	Normal	Normal	Normal	?
Eye abnormalities	Astigmatism	Astigmatism, Idiopathic nystagmus	Astigmatism, hyperopia, strabism	Myopia
Internal complications				
	At 5½ years: spontaneous bladder rupture At 9 years: rupture of diaphragm and para-esophageal hernia	/	At 5½ years: spontaneous bladder rupture	At 15 years: unilateral eventration of diaphragm on X-ray

Orofacial Features

Table II summarizes the orodental findings at the time of investigation of our three patients at 12, 7, and 5 years of age. Micrognathia, gingival hyperplasia with varying degrees of hyperkeratosis, and a frontal open bite dominate the oral clinical image in all of the patients. The temporomandibular joints display moderate to severe capsular laxity, resulting in incoordination during mandibular excursions and recurrent subluxations. The oldest patient (patient 1) presents severe restriction of mouth opening as a result of succesive microtrauma of the temporomandibular ligaments [De Coster et al., 2003]. The deciduous dentition of patients 2 and 3 shows abnormal morphology of the molars, obliteration of the tooth pulps, and a strong susceptibility to enamel attrition. The permanent dentition shows agenesis of one maxillary canine, two mandibular premolars and one mandibular molar in patient 1, agenesis of two mandibular incisors and two mandibular premolars in patient 2, and microdontia of two maxillary incisors in both patients 1 and 2. In the permanent dentition of patient 1, most permanent teeth have a light, opalescent discoloration. The mandibular incisors have short, dysplastic roots and tooth pulp obliteration is present in most erupted teeth (Fig. 8A, B).

TABLE II. *Orofacial Features at Time of Investigation*

	Patient 1	Patient 2	Patient 3
Oral features			
Micrognathia	+	+	+
Gingival hyperplasia/ hyperkeratosis	+++	++	++
Gingival bleeding	+++	+++	+++
Mobility of temporo-mandibular joints	History of increased capsular laxity—restricted mouth opening	Increased capsular laxity	Increased capsular laxity
Dental features			
Hypodontia	Agenesia 4 permanent teeth	Agenesia 4 permanent teeth	/
Irregular occlusal morphology	-	Deciduous molars	Deciduous molars
Enamel attrition	/	Deciduous dentition	Deciduous dentition (generalized)
Tooth discoloration	Localized	Localized (permanent dentition)	/
Tooth pulp obliteration	Localized	/	/

MOLECULAR RESULTS

Mutations in the gene encoding procollagen I N-proteinase or *ADAMTS2* were identified in all three patients described here.

In patient 1 a homozygous nonsense-mutation in exon 16 was identified [Colige et al., 1999]. In patient 2, a genomic homozygous deletion starting in intron 2 and ending in intron 5 causes in-frame skipping of exons 3 to 5 in the mRNA and results in the synthesis of an enzyme lacking the end of the prodomain and the beginning of the metalloproteinase domain [Colige et al., 2004]. In proband 3, compound heterozygosity was detected with a genomic 5.9 Kbp deletion starting in intron 13 and ending in intron 16 and replacement with a TCC triplet of unknown origin. This mutation was inherited from the father. The mutation affecting the maternal allele was out-of-frame skipping of exon 3, with the creation of a premature termination codon. On the protein level this results in the synthesis of an enzyme lacking most of the spacer region [Colige et al., 2004].

DISCUSSION

Dermatosparaxis, an autosomal recessive disorder first identified in cattle and subsequently in sheep [Helle and Nes, 1972] and cats [Holbrook et al., 1980], is characterized primarily by extreme fragility of the skin and early death. The corresponding phenotype in humans was first recognized in 1992 in three patients, one of them being the first patient described in this report (patient 1). Here, we report the clinical and orofacial features in three unrelated patients with EDS dermatosparaxis type. Only seven patients with EDS dermatosparaxis type have been reported so far, most of them aged under 2 years. There is only one report of an adolescent with this disorder [Reardon et al., 1995]. Major problems at age 15 years in this girl (Fig. 4D) were easy bruising, skin fragility with easy tearing of the skin and extensive scar formation, and joint hyperextensibility.

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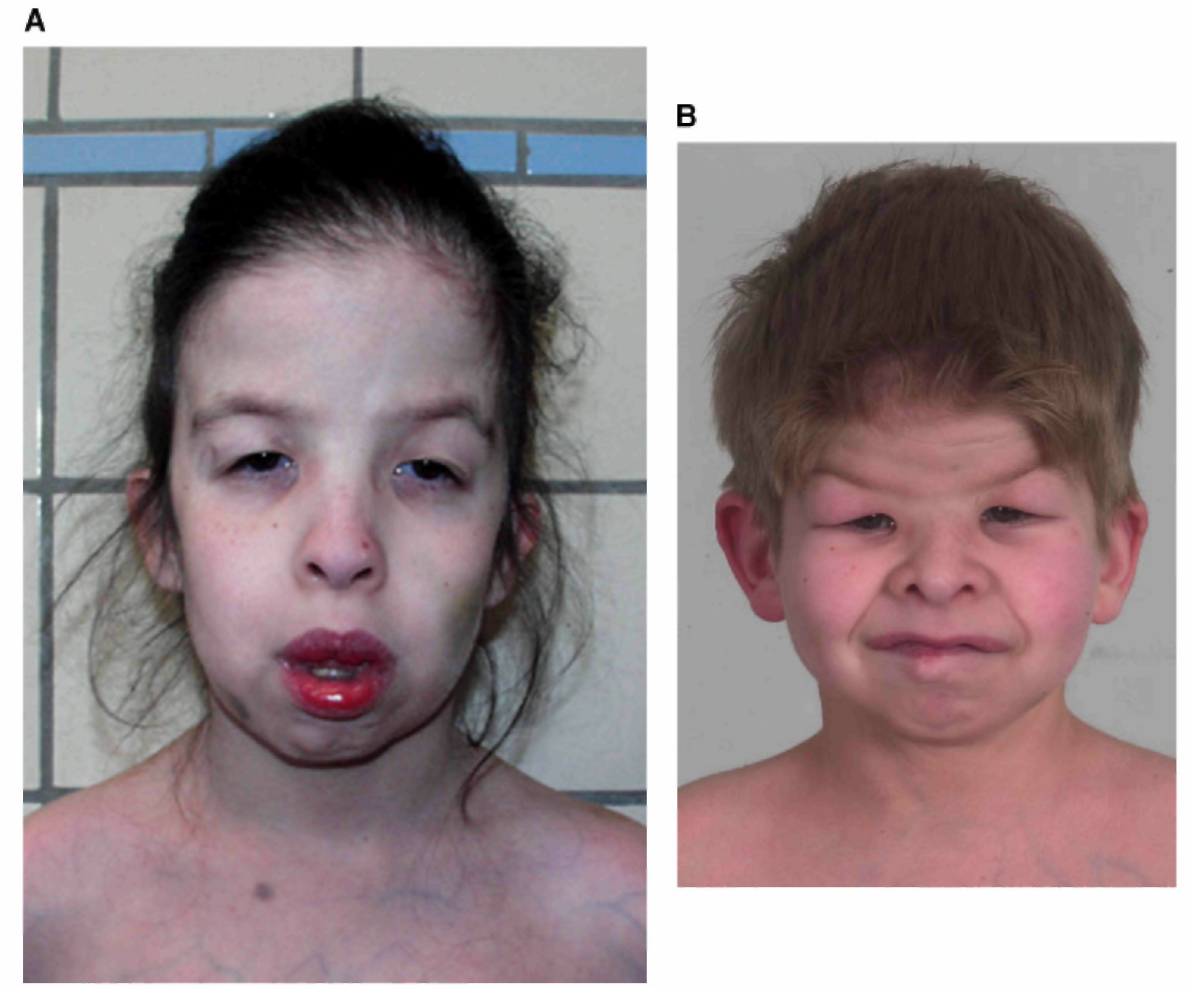
The phenotype in all reported patients with EDS dermatosparaxis type, including the three children reported here, is strikingly similar, although there is some variability in severity of the clinical features. The most consistent anomalies are large fontanels, blue sclerae, puffy eyelids, micrognathia, umbilical hernia, short fingers, redundant lax skin, which is extremely fragile, and easy bruising. All patients except two (patient 2 and 3 in the present report) were born after premature rupture of the membranes. Facial resemblance in the four patients older than 4 years of age (the present three patients and the patient reported by Reardon et al. [1995]) is obvious, characterized by epicanthic folds, blue sclerae, down-slanting palpebral fissures, prominent lips and excessive buccal mucosa (Fig. 4A-D). All children have short stature and short hands (Figs. 5A-C and 6). The main problems of all 4 children are the increased bruisability and the severe fragility of the skin. Wound healing is not delayed and initial scar formation is only minimal. In the older patients, however, more typical atrophic scarring with pigmentation is seen, probably due to repeated skin tearing, bruising and secondary infections.

Fig. 4. *Illustration of facial resemblance between patients 1 at 12 years (A), patient 2 at 7 years (B), patient 3 at 5 years (C), and the patient reported by Reardon et al. [1995] at 15 years (with permission) (D). Note epicanthic folds, downslanting palpebral fissures, blepharochalasis, micrognathia, sagging cheeks. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]*



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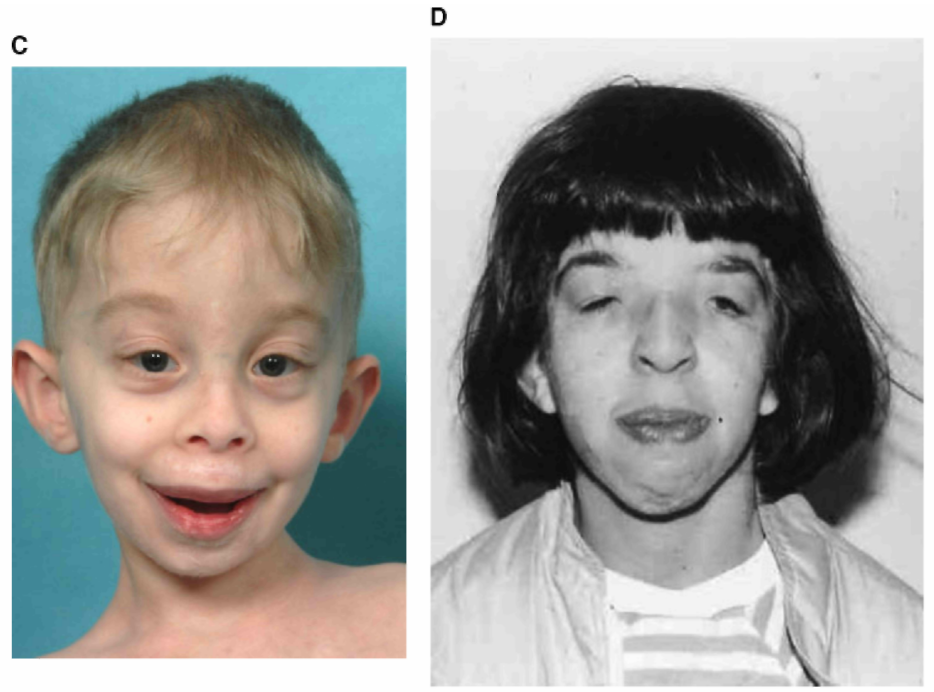

Fig. 5. *A: Patient 1 at 12 years; B: Patient 2 at 7 years; C: Patient 3 at 5 years. Note short stature and short limbs in the three patients. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]*

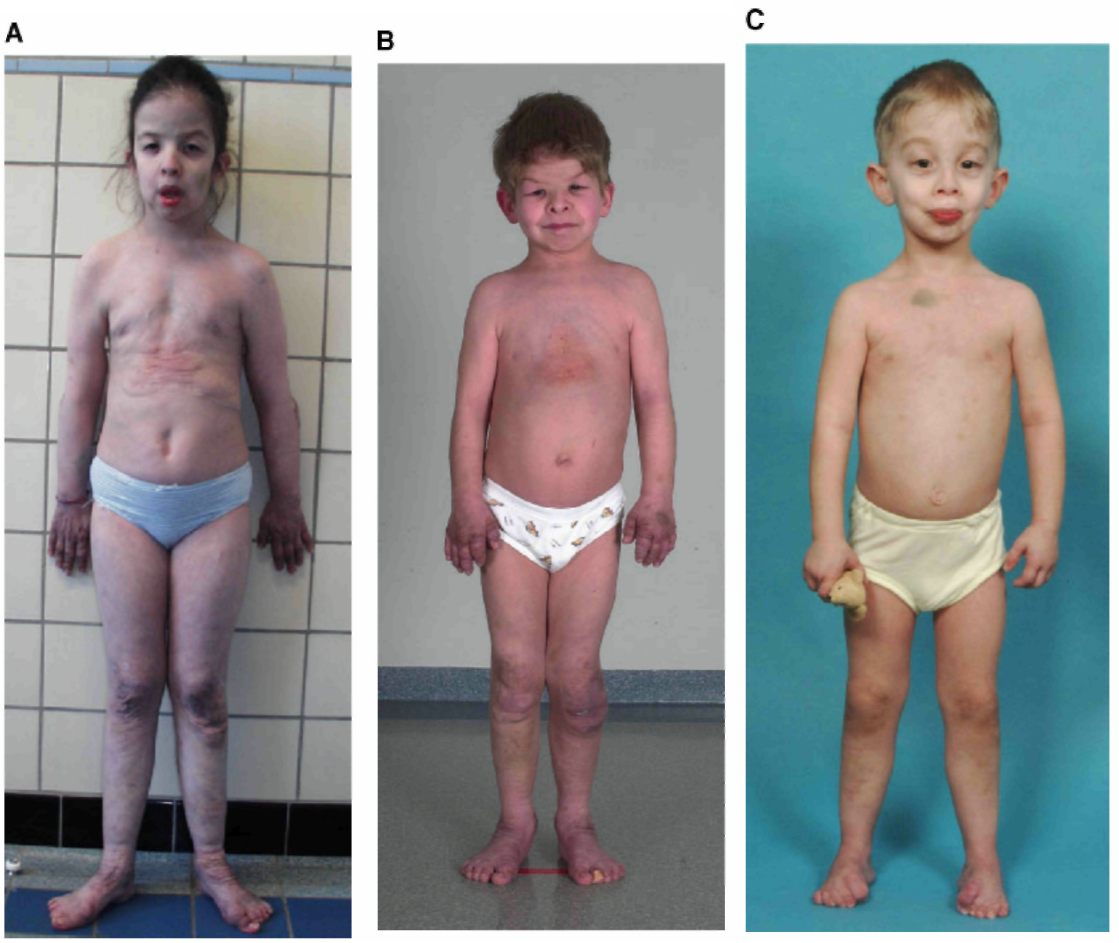

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Fig. 6. *A: Patient 1; B, C: Patient 2. Note short hands and feet with sausage-like fingers and excess skin folds on fingers and around ankles, reminiscent of "fallen socks." [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]*

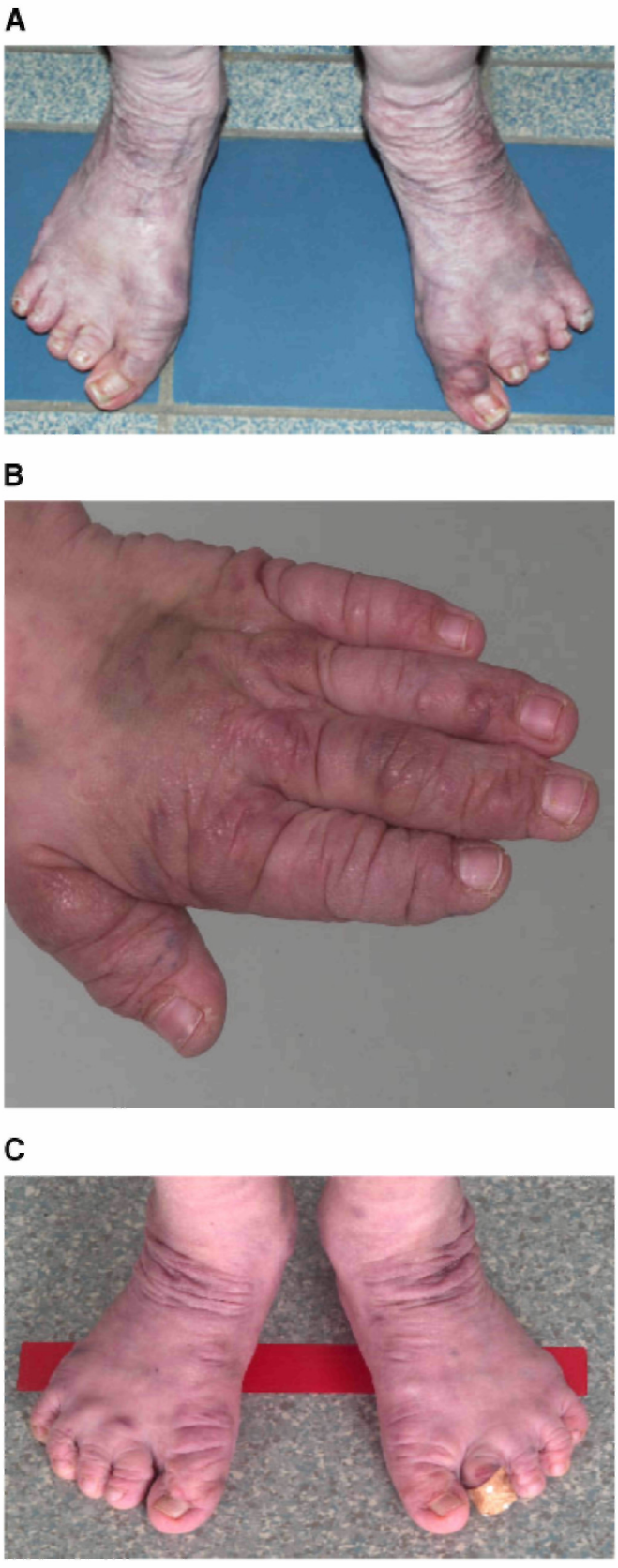

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Fig. 7. *A: Patient 1 at 12 years. Note excessive bruising around the elbow, and abnormal wound healing with distended and hyperpigmented scars on the elbow. B: Patient 2 at 7 years. Note excess skin and sagging of the skin on the knees. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]*

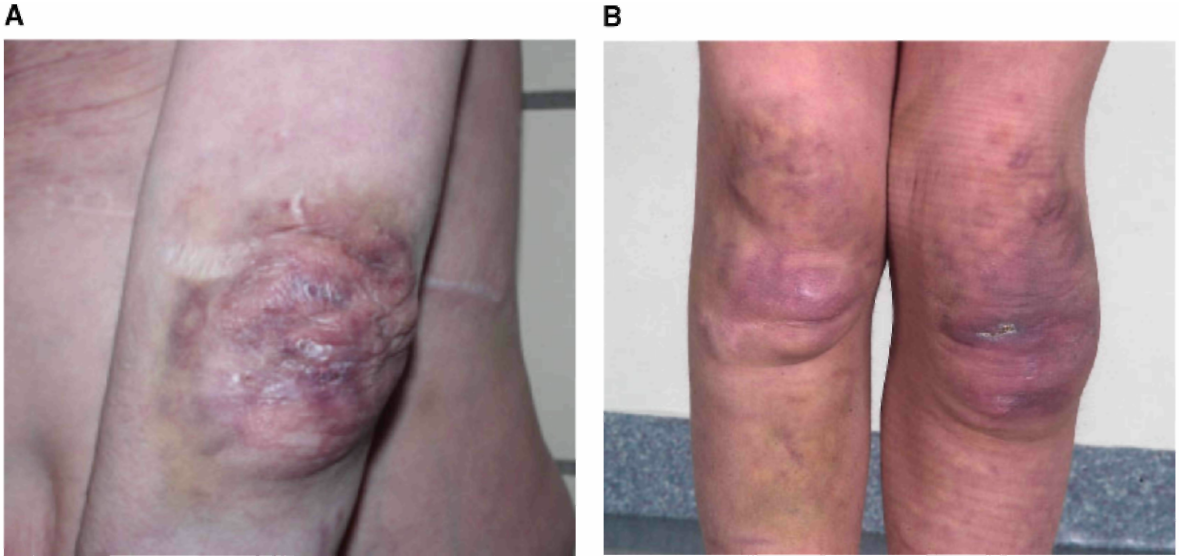
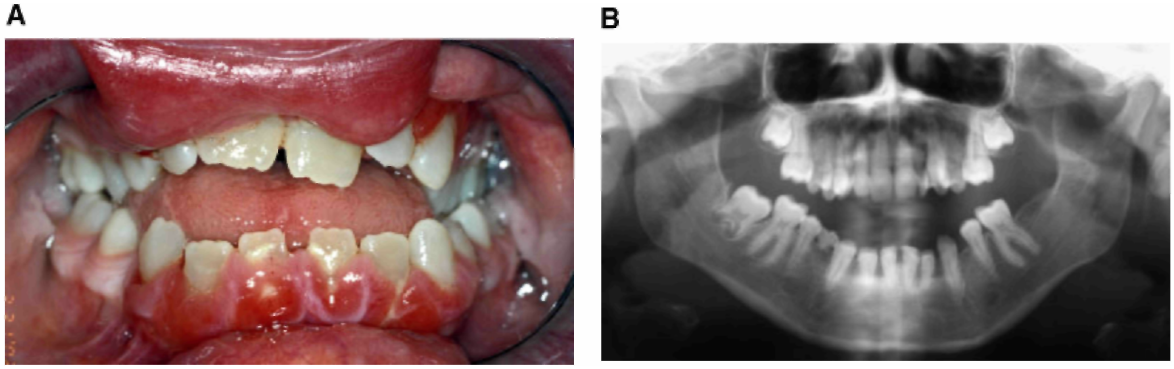


Fig. 8. *A: Patient 1 at 12 years. Oral cavity showing prolapse of lips and discolored permanent teeth. B: Radiograph showing tooth agenesis and dysplastic roots. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]*



Despite the striking similarities, there is some variation in severity of the different clinical symptoms among the patients presented here. Facial dysmorphism, as well as the loose, redundant skin with multiple skin folds on hands and around the ankles, is less obvious in patient 3 than in patient 1 and 2, both at birth and at older age (Figs. 4C and 5C). Joint hypermobility, although not obvious during the first years of life, has become obvious during childhood in patient 2 and 3. Only patient 1 did not have significant joint hypermobility at the age of 12 years. It is noteworthy that in the patient reported by Reardon et al. [1995], joint hypermobility became one of the major clinical features. Fragility of internal tissues can cause major complications like the bladder ruptures in patient 1 and 3.

In EDS dermatosparaxis type different orofacial structures primarily consisting of type Tcollagen, such as the craniofacial skeleton, mucosa, teeth and temporomandibular joints [Gage et al., 1995], may be affected. Evidence of dentin defects, presenting with opalescent discoloration, pre- and post-eruptive pulp calcification and dysplastic roots, may be seen in some permanent teeth. These findings are not consistent with dentinogenesis imperfecta as seen in some types osteogenesis imperfecta [Schwartz and Tsipouras, 1984; Lukinmaa et al., 1987a,b], but are probably more correctly classified as localized dentin defects [Ranta et al., 1993]. Osteogenesis imperfecta and EDS dermatosparaxis type are both characterized by abnormal type Tcollagen synthesis and

secretion, and may therefore produce widespread or localized low mineralized dentin, which primarily contains type I-collagen. The presence of dentin defects, however, basically similar to those seen in osteogenesis imperfecta, but present only in part of the permanent dentition of patients with EDS dermatosparaxis type, is a unique finding within the spectrum of dentin pathologies.

EDS dermatosparaxis type is readily distinguishable from other types of EDS. In classic EDS (EDS type I and II) (OMIM 130000 & 130010), the skin also has a soft and velvety texture, and is very fragile with formation of atrophic scars. The skin is however hyperextensible, which means that it snaps back easily upon release, in contrast to the dermatosparaxis-skin, which is lax and sagging. The other features, such as the dysmorphic facies, blue sclerae, short stature, help to differentiate clinically between the two types. EDS kyphoscoliosis type (EDS type VI) (OMIM 225400), is also an autosomal recessive condition but is distinguished by a marfanoid habitus, by a milder degree of skin fragility, and often by the presence of scleral fragility. EDS dermatosparaxis type is distinct from EDS arthrochalasis type (EDS type VIIA, and VIIB) (OMIM 130060), which is characterized by congenital hip dislocation, severe joint hypermobility, and recurrent joint dislocations. The pathognomonic hieroglyphic pattern of collagen fibrils on electron microscopic examination (Fig. 3) rapidly distinguishes EDS dermatosparaxis type from other forms of EDS. Also cutis laxa (OMIM 219100) may be confused clinically with this condition, but EM examination of the skin rapidly distinguishes the two disorders.

Procollagen I N-proteinase (ADAMTS2) is an enzyme belonging to an expanding family of zinc metalloproteinases found in vertebrates and invertebrates [Colige et al., 1997]. In all patients reported with EDS dermatosparaxis type, the causal mutations in *ADAMTS2* were detected. No genotype-phenotype correlations can be observed so far. The severe phenotype in patients 1 and 2 can probably be explained by loss of functionally crucial domains, such as the thrombospondin type I repeats (patient 1) or the pro- and the metalloproteinase domain (patient 2). Although the phenotypic abnormalities in patient 3 are milder than in other patients, loss of the spacer domain also leads to ineffective function of the procollagen I N-proteinase with important clinical consequences, as is reflected by the bladder rupture and urinary ascites.

In 2001 an *ADAMTS2* knock-out mouse was reported by Li et al. [2001]. A striking observation in the knock-out mice was that the phenotype became more severe with age. Homozygous mice were grossly normal at birth, and only by 1-2 months of age they developed thin skin that tore after gentle handling. Electron microscopy of collagen fibrils in skin of 2-days-old mice was normal, whereas the typical hieroglyphic pattern was only visible by 2 months of age. Age-dependent changes in dermatosparactic cattle were not reported so far, probably because the large skin lacerations and subsequent infections lead to premature death in most of the cases. In the patients reported here tearing of the skin becomes more important as they grow up and become more active. Joint hypermobility increases with age in most of these patients, and during childhood the patients are at risk for complications of internal tissue fragility. All these symptoms taken together, clinical severity seems to increase with age in human dermatospar-axis.

An unexpected finding in *ADAMTS2* double null mice was sterility and reduced spermatogenesis. Other animals with defects in *ADAMTS2* generally do not survive until the reproductive age, and so far there are no reports of adult human EDS VIIC patients. The female patient reported by Reardon et al. [1995] had a normal menarche at the age of 13 years; our patients are still in the prepubertal stage. It will be interesting to learn whether the sterility is also seen in human males with defects in *ADAMTS2*.

One of the striking features in all patients with EDS dermatosparaxis type is the increased bruising tendency, with the formation of large hematomas after minor trauma and in well-protected areas. Easy bruising is a common feature in vascular EDS (EDS type IV) (MIM 130050), a subtype of EDS that is caused by autosomal dominant mutations in the *COL3A1* gene. Type III collagen is one of the major constituents of the blood vessel wall, the hollow organs of the gastrointestinal tract and the uterus. Recently, it was shown that ADAMTS2 not only cleaves procollagen type I and type II, but also procollagen type III N-propeptides [Wang et al., 2003]. This finding may explain the easy bruising phenotype, since inefficient cleavage of type III procollagen may lead to capillary fragility. Although not reported so far, further follow-up will be needed to see whether these patients are at risk for rupture of the major arteries, the bowel or the uterus. In the mean time invasive interventions such as angiography or catheterization should be avoided or, if necessary, performed with the utmost care.

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