

# Ehlers-Danlos syndrome: type VI A – kyphoscoliosis; a case report

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Ehlers-Danlos syndrome (EDS) is a clinically heterogeneous group of inherited disorders with ten different types, all involving a genetic defect in collagen and connective-tissue synthesis and structure that affect the skin, joints, and blood vessels. EDS type VIA, a very rare kyphoscoliotic type, is autosomal recessive and clinically characterized by soft extensible skin, laxity of joints and kyphoscoliosis. We present a case of an adult male patient complaining of recurrent acne over the chin, axilla and pyoderma in the groin region since he was 14 years of age. Past medical history was positive for recurrent pyoderma which healed with scarring, bleeding tendency, double vision and backache. On examination, the patient had hyperextensible skin, joint hypermobility, kyphoscoliosis, easy bruising, and scleral fragility. Urinary analysis revealed a decrease in the hydroxylysyl-pyridinoline to lysyl-pyridinoline ratio indicative of EDS type VIA with a severely reduced Lysyl Hydroxylase (LH) activity in the skin fibroblast culture.

**Keywords:** collagen disorder, Ehlers-Danlos syndrome, genetic disorder, kyphoscoliosis

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## INTRODUCTION

Ehlers-Danlos syndrome is named after two doctors, Edvard Ehlers of Denmark, and Henri-Alexandre Danlos of France, who identified it at the turn of the 20th century<sup>1</sup>. It is also known as "*Cutis Hyperplastica*" and is an inherited disorder estimated to occur in 1 in 5000 live births worldwide<sup>2</sup>. There are more than ten types but six major types of Ehlers-Danlos syndrome are known which vary in their prevalence dramatically<sup>3</sup>. Type III – the hyperextensibility type - is the most common. Type VI – Kyphoscoliosis - is very rare, less than 60 cases have been reported to date. EDS type VIA, the kyphoscoliotic type, is autosomal recessive and clinically characterized by soft extensible skin that is subject to easy bruising, laxity of joints and kyphoscoliosis. We report a case of type VI – Kyphoscoliosis - Ehlers-Danlos syndrome and briefly review the literature.

## CASE REPORT

A 35-year-old male was visited in the skin outpatient department with chief complaints of recurrent acne over the chin, axilla and pyoderma in the groin region since he was 14 years of age. His past medical history was positive for recurrent pyoderma which healed with scarring, episodes of spontaneous bleeding, double vision and backache.

The patient had severe acne with scarring (Figure 1), multiple pyoderma, hidradenitis suppurativa over the axilla and the groin region and marked skin hyperextensibility (Figure 2), especially over the elbow region. Marked general joint hypermobility without joint dislocations was also present (Figure 3) with a mildly progressive profound kyphoscoliosis (Figure 4). Ophthalmic examination revealed widely separated eyes with a shallow anterior chamber and associated glaucoma.



Figure 1. Grade IV acne with scarring



Figure 2. Hyperextensible skin over the elbow region

In addition, episodes of easy bruising were seen as several hyperpigmented cicatrices on both lower limbs.

Skin biopsy revealed elongated elastic fibres. (Figure 5) Urinalysis sent for examination was positive for an abnormal pattern of lysyl pyridinoline and hydroxylysylpyridinoline crosslinks. The ratio of deoxypyridinoline and pyridinoline crosslinks in the urine, measured by high-performance liquid chromatography (HPLC), was reported 5.8. Assay of lysyl hydroxylase enzyme activity in skin fibroblasts culture showed a markedly decreased activity. On DNA analysis, a mutation at LH 1 or PLOD 1 ("procollagen-lysine 1, 2-oxoglutarate 5-dioxygenase 1") gene on chromosome 1p36.3-p36.2 was reported. Regarding to these clinical and laboratory data the diagnosis of Ehlers-Danlos syndrome: type VI A was made.



Figure 3. Hyperextensible joints.

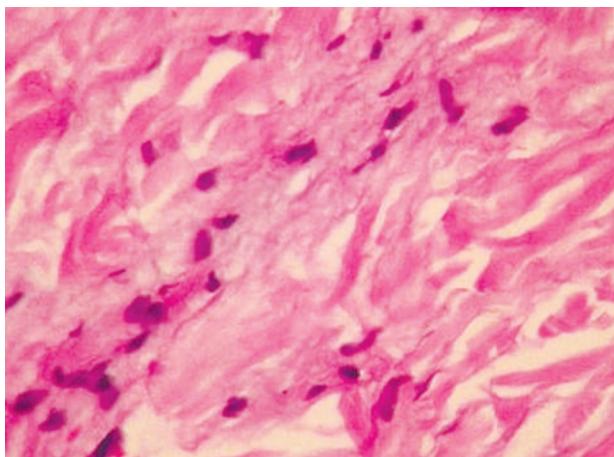
## DISCUSSION

Ehlers-Danlos Type VI – kyphoscoliosis is the most common autosomal recessive form of EDS. As such, the disorders are present at birth; however, symptoms may not be noticeable until later in life. It equally affects all races but whites are reported to be affected more. No sex predilection is seen. The clinical hallmarks of EDS VIa are severe neonatal muscular hypotonia and mildly progressive profound kyphoscoliosis with lax joints, fragile hyperextensible skin and generalized connective tissue weakness <sup>4,5</sup>.

The patient in the current study was suggested to have EDS VIA on the basis of his clinical characteristics. We confirmed this diagnosis by the measurement of the severely reduced LH activity in the cultures of skin fibroblasts and identified the causative mutation in the LH1 gene by mutational analysis. At least 20 different mutations have been identified in the Lysyl Hydroxylase1 (LH1) gene on chromosome 1p36.3-p36.2. The official name of this gene is PLOD 1 "procollagen-lysine 1, 2-oxoglutarate 5-dioxygenase 1." that contributes to enzyme lysyl hydroxylase deficiency and the clinical characteristics of EDS VI <sup>6</sup>. Two of these mutations, a large duplication of exons 10-16, arising from a homologous recombination of intronic Alu sequences, and a nonsense mutation, Y511X, in exon 14 of the LH1 gene, have been identified in five or more unrelated patients <sup>7</sup>. Both mutations appear to have originated from a single ancestral gene. Alternative processing pathways involving



**Figure 4.** X-rays showing kyphoscoliosis



**Figure 5.** Section shows elongated elastic fibers (H & E $\times$ 400)

alternate splicing and mRNA degradation, which reduce the effect of the mutant allele and restore partial activity of the enzyme, have been identified<sup>7</sup>. Lysyl hydroxylase is a collagen modifying enzyme that hydroxylates specific lysine residues in the collagen molecule to form hydroxylysines. Homozygosity or compound heterozygosity for one or more mutant alleles coding for the enzyme results in its deficiency<sup>7</sup>.

Diagnosis can be made by different methods. The biochemical test that is performed for diagnosis is high performance liquid chromatography (HPLC) analysis of the urine, which allows the simultaneous quantitation of pyridinoline and deoxypyridinoline. In patients with EDS VI, the excretion of deoxypyridinoline is markedly

increased. As a result, the deoxypyridinoline/pyridinoline ratio is also markedly increased (from 0.2 in normal controls to 4-6 in patients with EDS VI) and allows for the diagnosis. Detection of hydroxylysylpyridinoline by HPLC excreted in the urine is both sensitive and specific<sup>8</sup>.

Another way to diagnose EDS VI is to perform enzyme assay. The activity of the enzyme PLOD1 can be measured in cultured fibroblasts. In individuals with the kyphoscoliotic form of EDS, enzyme activity is below 25% of normal. Biochemical testing and enzyme assay are clinically available but both are unable to detect the carrier state. Sequence analysis of all exons and flanking intronic sequences can be done for this purpose. Duplication can be confirmed in genomic DNA by PCR using duplication-specific primers<sup>7,8</sup>.

In summary, we identified clinical characteristics of EDS VIA in a patient and his genetic and laboratory findings also favored the diagnosis of type VI EDS at the same time, which is a very rare case. In addition, the age of presentation was later than the usual age of presentation which is an unusual for patients with EDS VIA.

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