Ehlers-Danlos Syndrome Type V

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Introduction

The Ehlers-Danlos Syndromes (EDS) are a genetically, biochemically and clinically diverse group of heritable connective tissue disorders having joint laxity and dermal features in common. Prior classifications of EDS have included upto eleven disorders. Table 1 provides the currently accepted classification. Many patients with features of EDS do not fit readily into one of the well-defined subtypes. Some cases have been reported from India [1-3]. EDS Type V described here is a rare variety. There is only one single large, well-documented family with EDS type V [4]. The diagnosis is clinical.

Case Report

On 25 July 2001 a 4 year old son of a serving Army soldier was brought to the skin OPD by his mother with complaints of easy bruisability, delayed wound healing, excessive scar formation at injury sites since 1 year of age. This second born male child was delivered vaginally at home after 8.5

months gestation. Gestation period and delivery were normal. There was no history of any drug intake by mother during pregnancy. Child was apparently asymptomatic till about 1 year of age when he started having presenting complaints. There was no history of seizures/mental retardation/delayed milestones/prolonged bleeding from wounds or body orifices. There was no history of passing high colour or orangish red urine. There was no history of repeated bony fractures. Personal/family history revealed that the child was born out of non-consanguineous marriage. No family history of similar complaints was present in parents, grandparents, other relatives, siblings (2 sisters - 6 years and 2 years). No history of maternal abortions was elicited. General physical and systemic examination revealed no abnormality. The child was normal in growth and intelligence. All relevant investigations including blood coagulation profile were normal. Skin biopsy revealed wavy collagen fibrils in dermis. Dermatological examination revealed velvety, hyperelastic skin with normal recovery time, easy bruisability, multiple hypertrophic scars/cigarette paper scars at previous wound sites over forehead and limbs, molluscoid pseudotumours

Table 1

Classification of Ehlers Danlos Syndrome

Type	Clinical features	Inheritance	Biochemical defects
I (Gravis)	Soft, hyperextensible skin; easy bruising; thin, atrophic scars; hypermobile joints; varicose veins; premature birth	AD	Mutations in pro X1 (V) or pro X2 (V) chains of type V collagen
II (Mitis)	Similar to EDS type I but less severe	AD	Same as EDS I
III (Familial hypermobility)	Soft skin; large and small joint hypermobility	AD	Not known
IV (Arterial (ecchymotic))	Thin, translucent skin with visible veins, easy bruising; absence of skin and joint extensibility; arterial, bowel, and uterine rupture	AD	Mutations in COL3 A1; abnormal type III collagen synthesis, secretion or structure
V (X-linked)	Similar to EDS type II	XRL	Not known
VI (Ocular)	Soft skin muscle hypotonia; scoliosis; joint laxity; hyper-extensible skin	AR	Lysyl hydroxylase deficiency; mutations in PLOD gene
VII (Arthrochalasis multiplex congenita)	Soft skin with normal scarring, congenital hip dislocation, severe joint hyper-mobility	AD/AR	Structural defect at the aminoterminal cleavage site pro X 2 Amino terminal protease deficiency
VIII (Periodontal)	Hyperelastic, fragile, skin, moderate joint hyper mobility, severe periodontitis	AD	Reduced type III collagen
IX	Hernias, bladder diverticulae, mild skin laxity, skeletal defects	?	Increased copper incorporation and lysyl-oxidase deficiency
X	Similar to EDS type II, with abnormal clotting studies	AR	Proposed defect in fibronectin

Fig. 1 : Excessive scarring over forehead from previous wounds, widely spaced eyes, broad nasal bridge and hyperelastic skin is clearly seen

over both shins. Widely spaced eyes, broad nasal bridge, hyperextensible joints and muscle hypotonia were present (Figs 1 & 2). Hair/mucosa/nails/eyes/oral cavity/dentition - was normal. Limb span : body segment ratio was normal. A clinical diagnosis of Ehlers-Danlos Syndrome Type V, X-linked recessive (XLR) was made based upon the following findings - parents and relatives not affected, 2 sisters not affected, broad nasal bridge, hyperelastic velvety skin with normal recovery time, easy bruisability, multiple hypertrophic cigarette paper scars at previous wound sites, hyperextensible joints, muscle hypotonia and molluscoid pseudotumours over shins.

Parents were advised to protect the child from trauma/physical abuse and tablet Vit C- 500 mg twice daily for 6 weeks was given.

Discussion

Virtually all forms of EDS consisting of a group of inherited disorders of collagen tissue are the result of mutations that code for fibrillar collagen genes or for enzymes that catalyze the intracellular or extracellular post translational modifications [5]. The basic abnormality is deficient collagen biosynthesis, apparently of type I and type III. Most of the clinical manifestations are secondary to involvement of skin, joints, cardiovascular system, gastrointestinal tract and eyes. Its severity ranges from mild to lethal. EDS may be inherited as an autosomal dominant (AD), autosomal recessive (AR) or XLR trait. Biochemical defects have been identified in some. Histological examination reveals scanty, whorled and disorderly dermal collagen. Elastic tissue is usually but not invariably increased. Pseudotumours consisting of fat and mucoid material cuffed by fibrous capsule are present, these may be

Fig. 2 : Hyperextensible thumb

calcified. Similar changes are observed in bone collagen. An abnormal bleeding tendency in EDS is attributed to defects in platelets. However, no such platelet abnormality was detected in this case.

In EDS type V, the exact biochemical defect is not known. EDS type V is a rare X-linked disorder characterised by mild skin hyperelasticity, abnormal scarring, and joint hyperextensibility. Female carriers are asymptomatic. It clinically resembles EDS type II except that the latter disorder has AD inheritance. Features observed in this case included characteristic velvety hyperextensible skin which when released returned quickly to its normal position, easy bruisability, delayed wound healing leaving atrophic scars and molluscoid pseudotumours, widely spaced eyes and broad nasal bridge, hypermobile joints and muscle hypotonia.

EDS has to be differentiated from cutis laxa, where the skin is lax and hangs in folds. Cutis laxa, pseudoxanthoma elasticum, osteogenesis imperfecta, renal tubular acidosis, medullary sponge kidney, osteolysis of terminal phalynx and Marfan's syndrome have been associated with EDS type 1 [6]. However no such association was seen in this case. EDS-II, V & VI may respond to oral ascorbic acid (1 gm/day) [7]. Plastic surgery may be performed for cosmetic benefit. Physical and mental development and life expectancy is normal in EDS type V as opposed to some of the other types of EDS [6]. Marriage counselling may help in reducing the incidence.

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Answer to Radiological Quiz

RADIOLOGICAL DIAGNOSIS : OSTEOPETROSIS CONGENITA

The figure reveals 'bone within bone' which is vertical in femoral shafts and arcuate beneath the iliac crests. These are characteristic features of osteopetrosis. It is an autosomal recessive disorder. This means that both parents carry the gene for this disease to develop in their children. The parents carry a "silent" gene, they do not develop the disease and don't know that they carry the gene [1]. It presents in one of the three forms : osteopetrosis congenita, marble bone disease and osteopetrosis tarda. Osteopetrosis tarda, the benign form, presents in adulthood, while the other two more malignant variants present in infancy and childhood.

Osteopetrosis congenita is a rare congenital disorder. It occurs because of defect in osteoclasts, which are necessary for the formation of bone marrow. As the osteoclasts don't work correctly, the cavity for bone marrow does not form. Few blood cells form because of absence of bone marrow. Other blood-forming organs, particularly the spleen and liver, take over blood production and become greatly enlarged. Failure of normal osteoclastic bone resorption results in dense, deformed sclerotic bones [1] that show typical and diagnostic patterns on radiograph. Bones look solid on radiograph, but are actually brittle.

Osteopetrosis congenita presents in infancy and is associated with failure to thrive and growth retardation [1]. This form of osteopetrosis is very severe and usually results in death by the age of 2 years. Proptosis, blindness, deafness and hydrocephalus occur in these patients as bone encroaches on the cranial foramina. A critical feature of osteopetrosis congenita is severe bone marrow failure, resulting in pancytopenia, extramedullary haematopoiesis resulting in hepatosplenomegaly and hypersplenism which cannot compensate for bone marrow failure. Thrombocytopenia, leukoerythroblastic anaemia and elevated serum acid and alkaline phosphatase levels are also usually present. Hypocalcemia may or may not be present. Death from osteopetrosis congenita occurs as a result of severe anaemia, bleeding and / or infection [1]. In rare instances, patients survive into adulthood. In osteopetrosis tarda, the benign adult form, patients are asymptomatic and have good long-term survival rates because bone marrow failure rarely occurs [1].

The presence of 'bone within a bone' differentiates osteopetrosis from the other sclerosing dysplasias. The 'bone within a bone' may be vertical in long bone shafts and digits, transverse at the metaphysis. In vertebral body an appearance like 'rugger jersey' spine may be seen due to the inserted shadow of the earlier denser body. Neural foramina are encroached upon and blindness results.

Progressive loss of vision occurs in osteopetrosis as a result of encroachment of neural foramina and can be prevented by optic nerve decompression in the form of unroofing the optic canal and drilling away bone on both sidewalls of the optic nerve in the early stage of visual deterioration [2]. When managing patients with osteopetrosis the importance of careful and regular assessment of visual function should be stressed.

The only cure that exists for osteopetrosis is bone marrow transplant. Review of pathophysiology, management and the role of bone marrow transplantation shows that infants transplanted with marrow from an HLA-identical sibling or unrelated volunteer donor have an actuarial five - year survival with a functioning graft of 50-70%, while those transplanted with a T-cell-depleted mismatched marrow have a very poor survival of only about 10% [3]. Patients must receive a bone marrow transplant early enough in life so that complications of osteopetrosis can be reversed or prevented altogether [4]. Bone marrow transplant in infantile osteopetrosis may be followed by reversal of optic canal stenosis and preservation of vision [5].

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