Open angle glaucoma in a case of Type IV Ehler Danlos syndrome: A rarely reported association

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A 26-year-old male presented to us with defective vision in the left eye. He had best corrected visual acuity (BCVA) of hand movement (HM) in right eye and 6/9 in left eye. He had ptosis with ectropion in both eyes and relative afferent pupillary defect (RAPD) in right eye. Intraocular pressure (IOP) was 46 and 44 mmHg in right and left eye, respectively. Fundus showed glaucomatous optic atrophy (GOA) in right eye and cup disc ratio (CDR) of 0.75 with bipolar rim thinning in left eye. Systemic examination showed hyperextensible skin and joints, acrogeria, hypodontia, high arched palate, and varicose veins. He gave history of easy bruising and tendency to fall and history of intestinal rupture 5 years ago for which he had undergone

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surgery. He was diagnosed as a case of Type IV Ehler-Danlos syndrome (EDS) with open angle glaucoma. He underwent trabeculectomy in both eyes. This is a rare case that shows glaucoma in a patient of EDS Type IV. Very few such cases have been reported in literature.

Key words: Acrogeria, easy bruising, Ehler-Danlos syndrome, glaucoma, hyper extensible joints, trabeculectomy

Ehler -Danlos syndrome Type IV (EDS Type IV) results from mutations in the COL3A1 gene, which encodes chains of type III procollagen. Patients with EDS Type IV have typical features like thin translucent skin with a tendency for easy bruising, typical facial appearance, acrogeria, hypermobility of joints, and arterial, intestinal, or uterine fragility or rupture. Glaucoma is a seldom reported finding in a case of EDS Type IV. We report a case of advanced glaucoma in a patient with typical features of EDS Type IV.

Case Report

A 26-year-old male presented with the complaint of defective vision in the left eye. He was a known myope on refractive correction since childhood. He noticed dimness of vision in the right eye seven years ago, which has gradually progressed [Figs. 1 and 2]. His best corrected visual acuity (BCVA) was hand movement (HM) in the right eye and 6/60, improving to 6/9 with -4.00 diopter sphere and -0.25 diopter cylinder at 180°(-4.00/-0.25 × 180) in the left eye. Lid examination showed ptosis and ectropion in both eyes [Figs. 3a and b]. Fornices showed congestion with papillae in both eyes. Right eye anterior segment examination showed a relative afferent pupillary defect (RAPD). Left eye examination was normal. Intraocular pressure (IOP) in the right and left eyes were 46 and 42 mmHg, respectively. Gonioscopy showed open angles in both eyes [Grade IV Shaffer's in all quadrants]. Fundus examination showed glaucomatous optic atrophy (GOA) in right eye and a cup disc ratio of 0.75 with bipolar rim thinning with pallor of the neuroretinal rim in the left eye [Fig 4a and b]. Central corneal thickness (CCT) was 588 µ and 576 µ in right and left eye, respectively. Visual field of left eye was not reliable in spite of repeat tests, due to high false negative errors.

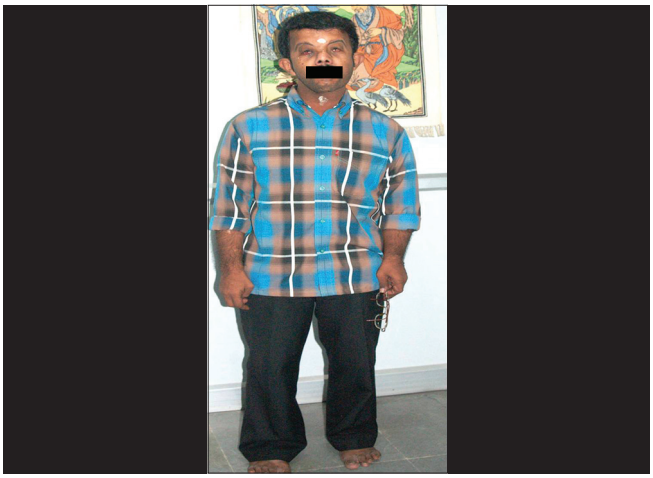

Figure 1: Photograph of the patient showing typical facial appearance, acrogeria and skeletal abnormalities along with ptosis and ectropion

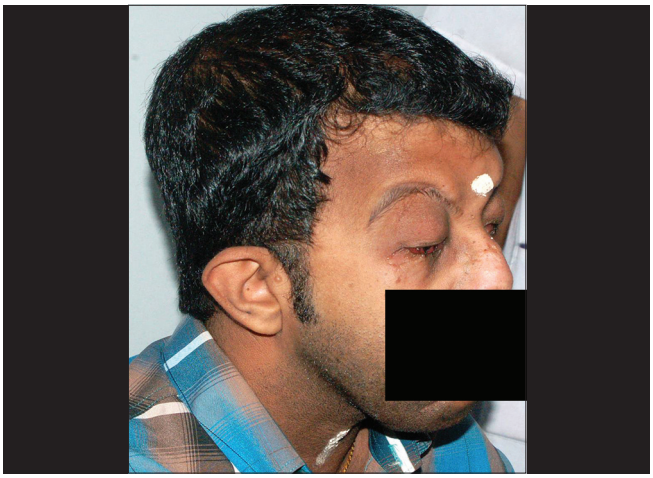

Figure 2: Photograph of side profile of the face showing typical facial appearance, micrognathia, beaked nose, lobeless ear with ptosis and ectropion

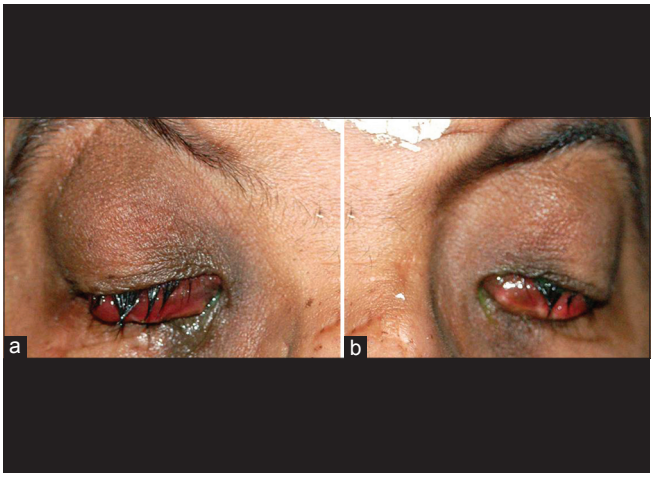

Figure 3 : (a) Photograph of the right eye showing ptosis with ectropion (b) Photograph of the left eye showing ptosis with ectropion

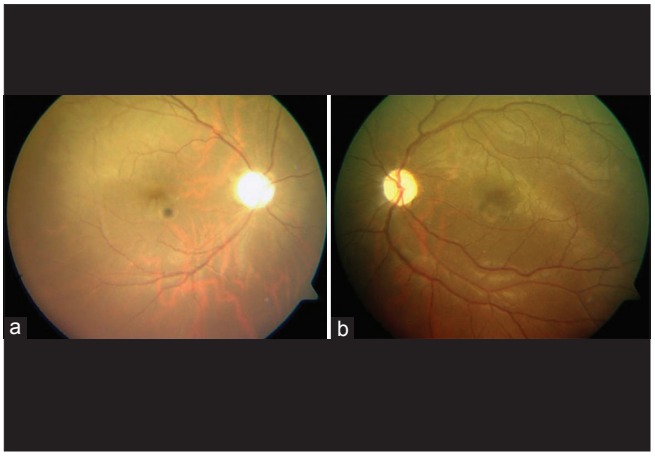

Figure 4 : (a) Fundus photograph of the right eye showing Glaucomatous Optic Atrophy (b) Fundus photograph of the left eye showing a cup disc ratio of 0.75 with bipolar thinning with pallor of the neuro-retinal rim

Systemic examination showed hyperextensible skin and joints. Hypermobility of the finger joints was present since childhood, and he had a tendency for skin-splitting. Acrogeria-an aged appearance in the extremities, particularly the hands-was apparent. He provided a history of easy bruising and tendency to fall easily, with two episodes of shoulder dislocation in the past. There was no family history of EDS. He had a hematoma in his right leg at presentation along with varicose veins in both legs. He had hypodontia, high arched palate, and history of delayed eruption of teeth. He also had skeletal abnormalities [Figs. 5-7]. He provided a history of having an intestinal rupture 5 years ago for which he had undergone surgery. These features were suggestive of EDS Type IV.

A diagnosis of open angle glaucoma in a case of EDS Type IV was made. He was referred to a rheumatologist. A decision to perform a trabeculectomy in the left eye first was made and done followed by a palliative trabeculectomy in the right eye [Figs. 8a and b]. Ectropion correction by horizontal lid tightening and lower-lid retractor reinsertion was done for both eyes. At the last follow up (3 years after trabeculectomy in the right eye) IOP was 14 and 12 mmHg in the right and left eye, respectively.

Discussion

EDS is a clinically and genetically heterogeneous connective tissue disorder affecting as many as 1 in 5,000 individuals.[1] EDS is characterized by abnormal collagen synthesis, affecting skin, ligaments, joints, blood vessels, and other organs. Following the identification of specific mutations in the genes the EDS classification scheme was condensed into six distinct clinical syndromes.[2] Each subtype is based on the severity of clinical symptoms, pattern of inheritance, and the underlying genetic defect [Table 1]. All these gene mutations for specific subtypes of EDS involve the synthesis of collagen, collagen-modifying proteins or enzymes, and tenascin-X.[3]

EDS Type IV is generally inherited in an autosomal dominant (AD) fashion, but autosomal recessive (AR) inheritance has also been reported. It is a very serious vascular disorder and not just a skin disease. Major complications of EDS

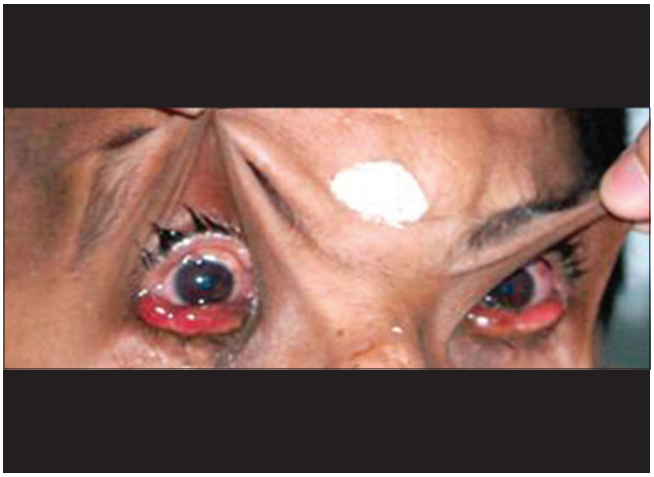

Figure 5: Photograph showing redundant skin of the upper lids which is hyperextensible

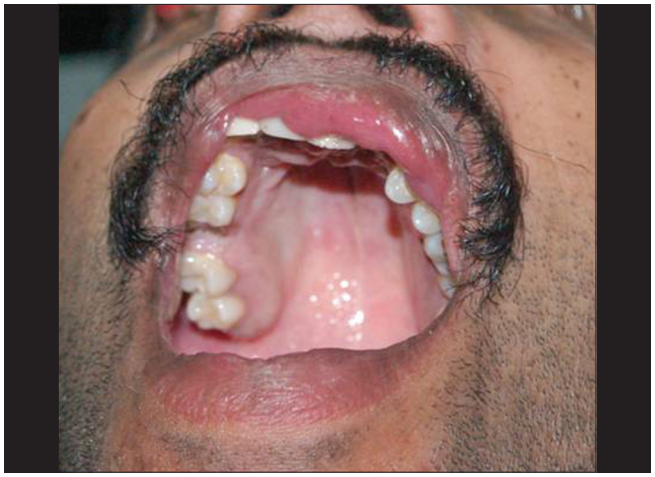

Figure 6: Photograph showing hypodontia along with high arched palate

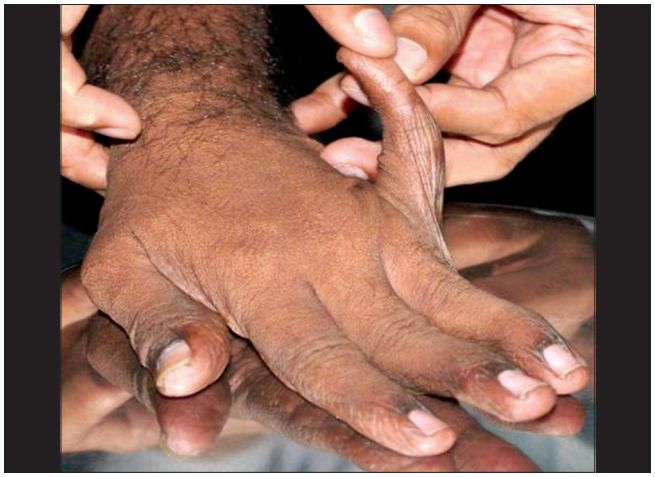

Figure 7: Photograph of the left hand of the patient distinctly showing Acrogeria which is an aged appearance to the extremities, particularly the hands along with hypermobility of the finger joints

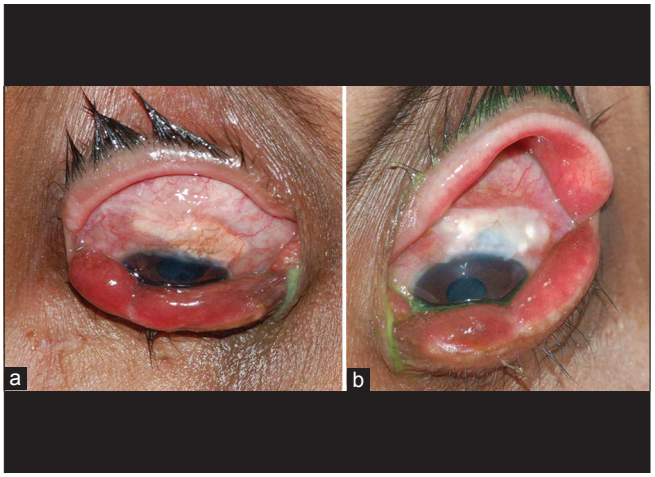

Figure 8 : (a) Photograph of the right eye post palliative Trabeculectomy showing a diffuse bleb (b) Photograph of the left eye post Trabeculectomy showing a thin walled avascular bleb

Table 1: The type, protein affected, inheritance pattern, and diagnostic criteria for Ehlers-Danlos syndrome

Type	Protein	Inheritance	Diagnostic criteria
Classic (type I/II)	Type V procollagen	AD	Major: Hyperextensible skin, widened atrophic scarring, and joint hypermobility. Minor: Easy bruising, smooth/velvety skin, molluscoid pseudotumors, subcutaneous spheroids, hypotonia, complications of joint hypermobility, surgical complications, and positive family history
Hypermobility (type III)	Unknown	AD	Major: Generalized joint hypermobility, and mild skin involvement Minor: Recurring joint dislocations, chronic joint pain, and positive family history
Vascular (type IV)	Type III procollagen	AD	Major: Excessive bruising, thin and translucent skin, arterial/intestinal/uterine fragility or rupture, and characteristic facial appearance. Minor: Acrogeria, early onset varicose veins, hypermobility of small joints, tendon and muscle rupture, arteriovenous or carotid cavernous sinus fistula, pneumo (hemo) thorax, positive family history, and sudden death in close relative
Kyphoscoliotic (type VI)	Lysyl hydroxylase 1	AR	Major: Severe muscular hypotonia at birth, generalized joint laxity, kyphoscoliosis at birth, sclera fragility, and rupture of the globe. Minor: Tissue fragility, easy bruising, arterial rupture, marfanoid habitus, microcornea, osteopenia, and family history
Arthrochalasis (type VIIA/VIIB)	Type 1 procollagen	AD	Major: Severe generalized joint hypermobility with recurrent subluxations, and congenital bilateral hip dislocation Minor: Skin hyperextensibility, tissue fragility, easy bruising, muscular hypotonia, kyphoscoliosis, mild osteopenia, and occasional fractures
Dermatosparaxis (type VIIC)	Procollagen-N-proteinase	AR	Major: Severe skin fragility, sagging, redundant skin, excessive bruising Minor: Soft, doughy skin texture and premature rupture of membranes

AD = Autosomal dominant, AR = Autosomal recessive

Type IV are arterial, bowel, and uterine rupture. Reduced life expectancy is not generally a feature of EDS, with the exception of this vascular form (EDS Type IV). Median life expectancy for patients with EDS Type IV is 50 years because medium-sized arteries, the GI tract, and other organs tend to spontaneously rupture. Morbidity in EDS Type IV is due to dislocations, pain, or both from chronic joint laxity as well as aberrant scarring and wound healing from abnormal tensile strength of the skin. Various skeletal abnormalities described in EDS Type IV include micrognathia, club foot, congenital dislocation of hip, pectus excavatum, acroosteolysis, and joint contractures.[4] Our patient was referred to a rheumatologist for his systemic problems and was confirmed to be a patient of EDS Type IV.

Major ocular complications are very infrequent in EDS. These patients have been commonly reported to have redundant skin on the upper eyelids, ease of eversion of the upper lid (Metenier's sign), and widely-spaced eyes. Other features like epicanthic folds and blueness of the sclera, strabismus, and myopia are less frequently encountered.[5] Keratoconus, ectopia lentis, postoperative dehiscence of cataract wounds, and bilateral corneal lacerations as a result of minor trauma have been observed. Blue sclera, microcornea, and glaucoma were observed in a patient reported by Durham.[6]

There have been very few reports of grave ocular complications in EDS Type IV patients and very few authors have reported association of glaucoma with EDS Type IV. Pollack *et al*., reported a case of recurrent carotid cavernous fistula (CCF) with secondary glaucoma and cerebral aneurysm in a case of EDS Type IV.[7] Akar *et al*., reported a rare case of EDS Type IV with open angle glaucoma and skeletal abnormalities.[8] Thus, although ocular abnormalities have been reported in some patients with EDS (including EDS Type IV), the association of glaucoma in a case of EDS Type IV has very rarely been reported in literature.

EDS Type IV patients have a Type III procollagen defect.[9] The features of EDS Type IV results from mutations in the COL3A1 gene, which encodes the chains of type III procollagen. COL3A1 cause variable clinical phenotypes including acrogeria and vascular rupture.[10] The corneoscleral and uveal trabecular meshwork is composed of Type I, II, and IV collagen, while the Juxtacanalicular Meshwork (JCM) has Types I, III, IV, V, and VI collagen. The Schlemms canal also has Type III collagen. Since EDS Type IV has the defect in the Type III procollagen, these patients have a propensity to develop an open angle glaucoma although very few cases have been reported in literature. The management of glaucoma in EDS Type IV has not been specified. Our patient had GOA in the right eye and advanced cupping in the left eye; therefore, we opted for surgical intervention.

This case report presents the extremely rare association of glaucoma in a case of EDS Type IV. The theories of pathogenesis and possible relationship between the syndrome and a defect in the ocular collagen have been established. Ophthalmologists should be aware of the ocular manifestations, hazards in clinical management, and possible significance of this syndrome in the study of the pathogenesis of glaucoma.

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