Ruptura de globo ocular y síndrome de Ehlers-Danlos VI

Eye globe rupture and Ehlers-Danlos VI syndrome

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Abstract

Introduction: Ehlers-Danlos syndrome (EDS) comprises a clinically and genetically heterogeneous group of inheritable disorders of the connective tissue. Classification recognizes six main subtypes. ED type VI or kyphoscoliotic type (ED-VI) is a rare autosomal recessive inherited disease characterized by severe neonatal muscular hypotonia, kyphoscoliosis, joint hypermobility, skin fragility, osteopenia, arterial rupture, microcornea and scleral fragility with increased risk of eyeball rupture. This is a case report of eyeball rupture in a patient with ED-VI. **Case report:** A 13-year-old male consulted due to decreased visual acuity after mild trauma in the right eye. Ophthalmic examination showed in right eye a visual acuity of light perception with no color discrimination, hypotonic eye, hyposphagma and 360° chemosis, clear cornea with a horizontal diameter of 9.8 mm, 70% hyphema and other structures were not evaluable. Left eye had a visual acuity of 20/60, a corneal horizontal diameter of 9.8 mm and lightly blue-gray sclera, without other abnormalities. Systemic evaluation demonstrated smooth and hyperelastic skin, scoliosis, atrophic scars and joint hypermobility. **Conclusions:** In every patient with eyeball rupture associated with mild trauma, we must consider the diagnosis of EDS. It is necessary to have a complete medical record and systemic evaluation.

Key words: Ehlers-Danlos. Kyphoscoliosis. Eye globe rupture. Microcornea. Joint hypermobility.

Resumen

Introducción: El síndrome de Ehlers-Danlos (ED) comprende un grupo heterogéneo de enfermedades hereditarias del tejido conectivo; se reconocen 6 variedades principales. El tipo VI o variedad xifoescoliotica (ED-VI) es una variante rara, con modo de herencia autosómico recesivo, caracterizada clínicamente por hipotonía muscular neonatal, xifoescoliosis progresiva, hiperlaxitud articular, piel frágil e hiperelástica, osteopenia, ruptura de arterias, microcórnea y fragilidad de esclera, con riesgo de ruptura del globo ocular. El objetivo del reporte es la presentación de un paciente con síndrome de ED-VI identificado por la ruptura del globo ocular posterior a un trauma leve. **Caso clínico:** Paciente masculino de 13 años que acude por disminución de la agudeza visual de 12 h de evolución posterior a trauma leve en ojo derecho. A la exploración se encontró: agudeza visual de percepción de luz que no discrimina color, hipotonía, hiposfagma y quemosis de 360°, córnea transparente de 9.8 mm, cámara anterior estrecha, hipema 70%, otras estructuras no eran valorables; el ultrasonido modo B demostró pérdida de la continuidad escleral; en ojo izquierdo la agudeza visual era de 20/60, córnea de 9.8 mm, esclera de tonalidad azul-grisácea, otras estructuras sin alteraciones. En la cirugía se describió esclera delgada y friable, así como músculos friables. En la valoración sistémica se encontró: piel hiperelástica, escoliosis toracolumbar,

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cicatrización atrófica e hiperlaxitud articular. **Conclusiones:** En todo paciente con ruptura del globo ocular asociado a trauma leve debe considerarse la posibilidad del síndrome de ED, por lo que será conveniente contar con historia clínica y valoración sistémica.

Palabras clave: Ehlers-Danlos. Xifoescoliosis. Ruptura de globo ocular. Microcórnea. Hiperlaxitud articular.

Introduction

Ehlers-Danlos syndrome (ED) comprises a heterogeneous group of connective tissue hereditary diseases with variable manifestations in the skin, ligaments, joints, blood vessels and some internal organs¹. In general, the different clinical forms are the result of gene mutations that encode for collagen fibers or the enzymes involved in their synthesis¹. Because of this, all the tissues and organs of the body have an alteration of the strength and structure of the extracellular matrix. According to the Villefranche classification, there are six main types based on the clinical phenotype, hereditary pattern and on the biochemical or molecular defect^{1,2}. In addition, new variants have been described and, occasionally, the phenotypes overlap, making diagnosis difficult^{1,3}.

ED syndrome type VI (ED-VI) or kyphoscoliotic type is a rare variant (OMIM # 225400), with autosomal recessive inheritance and with an incidence of 1:100,000 live births^{1,3}. Clinically, neonatal muscle hypotonia, delayed motor development, early-onset kyphoscoliosis, joint hypermobility, osteopenia, fragile and hyperelastic skin, ruptured arteries, microcornea, and fragility of the sclera, with risk of eyeball rupture, characterize it. It is caused by mutations in the *PLOD1* gene (procollagen-lysyl, 2-oxoglutarate 5-dioxygenase). The enzyme lysyl-hydroxylase 1 has the function of hydroxylating lysine residues to hydroxylysine: these residues are precursors of collagen cross-linking, an essential mechanism to maintain tension between them⁴.

The objective of this report is to present a clinical case with eyeball rupture after mild trauma in a patient with ED-VI syndrome or kyphoscoliotic type.

Case report

This is a 13-year-old male who goes to the Emergency Department of an ophthalmological hospital due to a decrease in visual acuity 12 hours after ocular trauma. The patient reported a mild trauma: "He was hurt by the finger of a schoolmate." Initial exploration revealed a visual acuity of light perception with no color discrimination, hypoglobus, hypotonia, hyposphagma and 360° chemosis, clear cornea of 9.8 mm in diameter, narrow anterior chamber, 70% hyphema, and the

rest was non-evaluable. Left eye (OS) showed a visual acuity of 20/60, the cornea was 9.8 mm in diameter, the sclera had a blue-grayish color, and the rest of examination was unremarkable. B-mode ultrasonography in OD showed: folds and generalized choroidal thickening and loss of scleral continuity in the temporal and superior sectors (fig. 1). The patient underwent surgery that showed a thin and friable sclera as well as friable muscles; the inferior rectus muscle was not found so a traumatic tear was assumed.

After surgery, an assessment by a geneticist was requested and important background for the clinical history was found. The patient comes from an inbreeding community (less than 2,000 inhabitants) of the State of Mexico, the parents are healthy and not related. He has two healthy siblings and a 21-year-old sister with a diagnosis of heart valve disease. The pregnancy was preterm at 8 months due to an unknown cause. There was a delay in motor development, history of dyslexia, fallen arches, and ankle dislocation at 8 years old and knee ligament rupture at 9 years old. He attends the first year of secondary school with a low school performance.

Systemic findings: the skin was soft, hyperelastic (fig. 2), with pectus excavatum, thoracolumbar scoliosis, diastasis recti; bilateral transverse palmar crease, bilateral absence of medial and distal interphalangeal folds of the 3rd and 4th fingers; atrophic, cigarette paper-like scars on the legs (Fig. 3), patellar hypermobility, fallen transverse arch, hallux valgus and claw toes (from 2nd to 5th toes), bilaterally. Beighton score showed generalized joint hypermobility, with 7 points (fig. 4).

The ocular characteristics consisting of tissue fragility, blue sclera and microcornea, as well as the systemic findings and family history with a sister with valvulopathy, probably associated with connective tissue disease, were compatible with the clinical diagnosis of ED-VI syndrome or kyphoscoliotic type.

Discussion

Severe neonatal hypotonia, progressive kyphoscoliosis, joint hypermobility, scleral fragility and eyeball rupture characterize ED-VI syndrome or kyphoscoliotic

Figure 1. B-mode ultrasound (OD): loss of temporal and superior scleral continuity.

Figure 2. A: Hyperelastic skin in neck B: and knee.

Figure 3. Atrophic scars with "cigarette paper" appearance on the skin of the leg.

type. These alterations are major diagnostic criteria. Other findings called minor criteria are arterial rupture, marfanoid habitus, osteopenia without tendency to pathological fractures, microcornea, tissue fragility with atrophic scarring and positive family history for an autosomal recessive entity^{1,5}.

The severe neonatal hypotonia present in almost all cases causes delays in motor development, abnormal postures and leads to confusion in the diagnosis, mainly with myopathies or early-onset muscular dystrophies⁶. On the other hand, scoliosis can occur from the first months of life and is progressive. This data, coupled with the presence of joint hypermobility and dislocations, may be important for diagnosis, since eyeball rupture is infrequent. It is worth noting that joint hypermobility must be assessed based on the Beighton score (Table 1). In this case a score of 7 was found, which was considered significant for diagnosis^{1,7}.

The initial diagnosis is clinical and confirmed by the urinary determination of the pyridinoline ratio: LP/HP (lysyl-pyridinoline/hydroxylysylpyridinoline), which is found elevated in patients with ED-VI (normal limit is

Figure 4. Hyperelasticity of interphalangeal joints in the index finger.

0.20 ± 0.03 , upper limit in patients with ED-VI is 5.99 ± 1.00). Lysyl-hydroxylase 1 enzyme deficiency in fibroblast cultures should also be evaluated and, finally, a molecular analysis should confirm the presence of *PLOD 1* mutation^{1,4,8}.

Table 1. Beighton score

Assessment	Score
Metacarpophalangeal joint hyperextension >90°	+ 1 right, + 1 left
Wrist hyperextension (thumb can be bent to touch the forearm)	+ 1 right, + 1 left
Elbow hyperextension >10°	+ 1 right, + 1 left
Knee hyperextension >10°	+ 1 right, + 1 left
Hip hyperextension (placing the palms on the floor without flexing the knees)	+ 1
Total	9 points

Beighton score¹ evaluates joint hypermobility, giving a point if the change is unilateral and 2 points if it is bilateral. A score of 5 or greater is significant to establish hypermobility

In this case, the diagnostic suspicion was established on a clinical basis by identifying 4 major criteria: 1) neonatal hypotonia causing delayed motor development, 2) scoliosis, 3) joint hypermobility and 4) scleral fragility causing eyeball rupture after mild trauma, as well as 3 minor criteria: 1) microcornea, 2) tissue fragility with atrophic scarring and 3) positive family history of an autosomal recessive disorder. As we have already pointed out, the clinical feature that highlights ED-VI among all the subtypes of ED are the severe ophthalmological disorders, clearly present in this case; however, eyeball rupture occurs in a minority of patients⁹.

Given the clinical suspicion or when diagnosis is confirmed, it is important to perform an echocardiogram in order to detect cardiovascular alterations, such as aortic dilation or mitral valve prolapse³, and perform studies such as bone densitometry due to the risk of osteopenia⁶.

Among the differential diagnoses to consider are:

- 1) Other types of ED: generally, in all types there is joint hypermobility and abnormal scarring; likewise, there is a risk of scoliosis. However, in type VI scoliosis begins in the first months of life and is progressive. In this case, scoliosis did not manifest early and has not been severe either. Consequently, due to ocular characteristics, subtype VI¹⁻⁴ is considered. There are 2 types of ED with an autosomal recessive inheritance pattern that share several characteristics with ED-VI: ED associated with mutations in *CHST14* (OMIM # 611776), also known as muscle contracture type, in which contractures, arachnodactyly, equinovarus foot deformity, craniofacial, gastrointestinal and urinary tract

alterations are observed; in addition, the urinary LP/HP ratio is normal. This type is difficult to differentiate, since the urinary LP/HP determination could not be made; however, due to the absence of craniofacial alterations in the patient, we consider the kyphoscoliotic or ED-VI type more likely^{1,3,4}. Lastly, ED associated with mutations in *FKBP14* (OMIM # 614557) also has a normal LP/HP ratio and patients present sensorineural hearing loss³.

- 2) Marfan syndrome: although joint hypermobility can be found in this entity, in this case it was not considered a differential diagnosis, given the absence of criteria including lens subluxation, an essential feature for the suspected diagnosis of Marfan syndrome^{9,10}.

- 3) Fragile cornea syndrome, an autosomal recessive entity, characterized by corneal rupture secondary to mild trauma, keratoconus, keratoglobus, blue sclera, hyperelastic skin and joint hypermobility¹⁰. The ocular and systemic characteristics are similar in the two entities; however, eyeball rupture has been described only in ED-VI. In addition, the presence of scoliosis and the history of valvulopathy in one sister correlates more with ED-VI¹¹⁻¹³.

Conclusions

In all patients with eyeball rupture associated with mild trauma, the possibility of ED syndrome should be considered, so clinical history and systemic assessment are highly recommended.

Ophthalmological and systemic findings in a patient with suspected ED syndrome can help establish the specific subtype, which is important for the follow-up and genetic counseling of each case.

The diagnosis of this disease or another underlying entity is important, since it increases the risk of morbidity and mortality of patients.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Conflicts of interest

The authors declare no conflicts of interest.

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