wjpmr, 2021,7(10), 265 – 268.

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Case Report

ISSN 2455-3301

WJPMR

EHLERS-DANLOS SYNDROME: ABOUT A CASE

***S. Kebabi, C. Nasmi, H. Berrani, T. Meskini and N. Mouane**

Pediatric Hepato-Gastroenterology and Nutrition Department Rabat Children's Hospital, Faculty of Medicine and Pharmacy, Mohammed V Rabat University.

***Corresponding Author: S. Kebabi**
Pediatric Hepato-Gastroenterology and Nutrition Department Rabat Children's Hospital, Faculty of Medicine and Pharmacy, Mohammed V Rabat University.

Article Received on 21/07/2021 **Article Revised on 11/08/2021** **Article Accepted on 31/08/2021**

ABSTRACT

A 2-year-old patient has consulted since the age of 4 months for repetitive hemorrhagic syndrome. The history suggests poor healing after injuries and recurrent joint dislocations. Faced with this clinical picture, additional investigations are carried out at the RABAT children's hospital, in the pediatric department 3, which leads to the diagnosis of Ehlers-Danlos syndrome (EDS). This collagen pathology In children, its diagnosis takes on a specific character due to the particular circumstances of the diagnosis, different clinical presentations, consequences on daily life and medical monitoring, and certain ethical aspects related to any approach to genetic investigation in a minor subject. The objective of this work is to discover the SED, to present the main signs of this disease, and also to define some principles for the management of these patients.

KEYWORDS: Ehlers-Danlos / collagen / joint hypermobility / skin extensibility / scars.

INTRODUCTION

Ehlers-Danlos syndrome (EDS) comprises a heterogeneous group of hereditary connective tissue disorders which more or less share a picture comprising skin, joint, vascular and even visceral fragility. It was first described by Tschernogubow in 1891, then by Ehlers in 1901 and Danlos in 1908, but it was not until the 1930s that this syndrome gained the interest of the scientific community.

1. OBSERVATION

This is a 2-year-old boy, from a non- consanguineous marriage, with no particular medical and surgical history, his parents report the appearance of skin wounds for minor trauma (figure 1), difficult healing with the appearance dystrophic scars, the frequent development of skin hematomas (figure 2), and also frequent dislocations in the ankles, knee and elbows during non-traumatic stress.

The clinical examination shows an oval-shaped face with a very slight nasal saddle and protruding ears. There is a discreet bilateral epicanthus giving the eyes an almond shape. The skin is thin, especially on the face and lower limbs. The assessment of laxity shows a Beighton score of 6 out of 9.

- A hemostasis assessment was carried out with assay of the coagulation factors returned to normal,
- A workup of autoimmune and inflammatory disease returned to normal.

An abdominal ultrasound supplemented by a fibroscopy and colonoscopy on the occasion of repetitive digestive bleeding returned to normal.

Faced with this clinical picture and the normality of the additional investigations, a connective tissue abnormality was suspected, a deep skin biopsy with an anatomopathological study was carried out in favor of connective tissue abnormality related to Ehlers-Danlos syndrome. The genetic study is in progress.

Figure 1: Contusion and spontaneously induced hemorrhagic syndrome.

2. DISCUSSION

The SED comprises major manifestations, found in almost all types of SED, and occasional minor manifestations which make it possible to differentiate the different types of SED.[1] There are two classifications

currently used for SED (Tab. I).

a. The Berlin classification, from 1988, which includes 11 types;
b. The Villefranche-sur-Mer classification, from 1997, which includes 6 types.
c. EDS therefore forms a heterogeneous family grouping together several genetic diseases of connective tissue, having in common the following clinical triad.[2–3-4]
d. Skin hyperelasticity, which can be seen by pinching and pulling the skin. After relaxation, the skin returns to its initial position;
e. Articular hyperlaxity which affects all the joints and can lead to recurrent reducible dislocations. In general, it is impressive because of the allowed amplitude, and it is not painful. The evaluation of this phenomenon is carried out using the Beighton scale where a score greater than or equal to 5 out of 9 signs joint hypermobility.
f. Tissue fragility which is found both at the vascular level with the appearance of hematomas during benign trauma and at the cutaneous level with atrophic scars and thin, velvetic skin. Apart from the vascular form of EDS where the large vessels are extremely fragile, this element has no repercussions on the vital prognosis.

Tableau I. Classification des SED de Villefranche *(2)*.

Ancienne classification	Nouvelle nosologie	Clinique	Cause génétique ou moléculaire	Transmission	Fréquence	OMIM
I et II	Classique	– Hyperextensibilité de la peau – Cicatrices atrophiques – Hypermobilité des articulations	Mutation des gènes COL5A1 ou COL5A2	AD	Commune	130000 et 130010
III	Hypermobile	– Hyperextensibilité variable de la peau – Hypermobilité généralisée des articulations – Arthralgies chroniques	?	AD	Commune	130020
IV	Vasculaire	– Peau mince et translucide – Fragilité ou rupture des artères, de l'intestin ou de l'utérus – Aspect caractéristique de la face	Mutation du gène COL3AI	AD	Commune	130050
VI	Cypho-scoliotique	– Articulations lâches – Hypotonie musculaire sévère à la naissance – Scoliose à la naissance – Fragilité de la sclérotique – Rupture du globe oculaire	Déficit en lysyl-hydroxylase	AR	Rare	225400
VIIA et VIIB	Arthro-chalasique	– Hypermobilité sévère des articulations avec subluxations récurrentes – Luxation congénitale bilatérale des hanches	Délétion de l'exon 6 dans COL1A1 ou COL1A2	AD	Rare	130060

COL : collagène ; AD : autosomique dominante ; AR : autosomique récessive ; OMIM : Online Mendelian Inheritance in Man.

Oral and facial abnormalities in EDS are many and varied. Patients may present with specific craniofacial abnormalities in the dermatosparaxis type or a marfanoid facies in the other types.[5] The dentition sometimes includes anomalies of number,[6] but it is especially the anomalies of form which predominate,[7] with more fractured furrows and cusps, often shorter roots, with a more or less marked laceration of which it will be necessary take into account during dental avulsions.

EDS is mainly linked to the appearance of an early termination codon in the gene encoding type V collagen, but it can also be secondary to abnormalities in enzymes involved in collagen biosynthesis.[8,9] Other molecules of the extracellular matrix, such as tenascin X, could be responsible for the appearance of this affection.[10] Since the 2000s, there has been interest in other proteins, such as the zinc transporter SLC39A13,[11] responsible for a new type of ADS. A few cases of abnormalities similar to EDS have been described in children treated with high doses of cysteamine.[12]

Some conditions can be a differential diagnostic problem with EDS, but physical examination alone is enough to distinguish it.[13]

- Marfan syndrome: in this syndrome, a family history of Marfan often exists. The cutaneous involvement is very discreet or nonexistent. The morphotype is evocative (marfanoid type). Joint and ligament hyperstretchability is much more discreet. It is associated with ocular (dislocation of the lens) and vascular (aortic aneurysm) damage. Although it is less common, this syndrome is much more publicized than EDS.
- Cutis laxa, or isolated skin hyper- stretchability: the skin very slowly returns to its initial position after relaxation; it is not fragile and its healing is normal.
- Fibromyalgia: On several occasions, fibromyalgia patients have finally been diagnosed as having "hypermobile" type EDS. The two entities resemble each other by the presence of permanent "diffuse" pain, quite resistant to analgesics, in young women, without any biological or imaging abnormalities, hence the interest of looking for joint hyperstretchability in front of any fibromyalgia picture.
- Benign hypermobility syndrome: this is an isolated joint hypermobility, without functional consequence except the development of arthralgia, often present from childhood. It is extremely common (4 to 13% of the population), predominant in young women and improves with age. It seems to be more common among Africans and populations in the Middle East and Maghreb. An autosomal dominant hereditary component exists in most cases. Some authors consider benign hypermobility syndrome as a mild form of "hypermobile" type of EDS, without pathological consequences.

There is no cure for EDS; however, preventive recommendations exist, common to all forms. These recommendations, although they have not been evaluated on large series of patients with EDS, are based on some logic and some clinical experience, and they are endorsed by most experts in EDS

Management of skin involvement: Children with severe skin fragility should wear pads and bandages on the forehead, chin and knees to avoid lacerations. The wounds should be closed without tension, if possible in 2 layers, and the stitches should be numerous and left long enough to avoid loosening.

Management of vascular involvement: Patients with multiple bruises should be encouraged to avoid contact sports, violent exercise, and drugs that interfere with the mechanisms of hemostasis. Invasive vascular investigations such as coronary angiography are contraindicated because they can lead to vascular rupture. The surgical indications should be reconsidered taking into account the excessive vascular fragility. There is no specific preventive treatment to be administered preoperatively. Ascorbic acid supplementation may decrease vascular fragility in some patients, due to its ability to increase collagen synthesis by fibroblasts in vitro.[14]

Management of musculoskeletal damage: In patients with muscular hypotonia or delayed motor development, a rehabilitation program is essential. Gentle muscle exercises such as swimming are helpful in improving muscle development and coordination. Sports requiring heavy constraints (ballet, gymnastics, contact sports) should be avoided. Scuba diving is prohibited due to the risk of pneumothorax. NSAIDs improve joint pain, but their use may be hampered by their antiplatelet action, which can worsen vascular fragility. The use of paracetamol is preferred. In chronic painful forms, only level II and III analgesics are effective. Depending on the symptoms, Plantar or upper limb orthotics can be used, but with care, to avoid exerting significant pressure on the skin. In severe cases, adapting the environment can be helpful in reducing the risk of injury and falls.

Prevention of unnecessary gestures: The performance of a colonoscopy or an enema is contraindicated, except in an emergency. The indication of endo-uterine procedures must always be discussed again given the fragility of the endometrium; likewise, the insertion of an IUD is contraindicated. Ligament surgery is accompanied by a high risk of failur or recurrence in this type of patient. Spinal manipulations, in particular cervical manipulation, must be prohibited. The attending physician must be made aware of the possible risks of invasive procedures and possible complications after the procedure, due to tissue friability. Finally, psychological and behavioral support or even psychotherapy can be helpful in all types of ADS to help patients cope with their daily lives. Clear information must be transmitted, particularly on the non-progressive nature of the pathology. Patient associations can be beneficial in this pathology.

3. CONCLUSION

This set of genetic pathologies of variable transmission remains poorly understood by the medical profession, despite a much higher frequency than that of other even rarer diseases. Its presumption of benignity must be reconsidered because of the handicap which may result from it. Management by a team with experience of the disease is desirable. Informing the patient and his healthcare team allows treatment in optimal conditions, avoiding therapeutic slippages and limiting functional and aesthetic damage.

REFERENCE

1. Beighton P, De Paepe A, Steinmann B, Tsipouras P, RJ. Wenstrup. Ehlers -Danlos syndromes: revised nosology, Villefranche, 1997. Am J Med Genet, 1998; 77: 31 -7.
2. Callewaert B, Malfait F, Loeys B, De Paepe A. Ehlers -Danlos syndrome and Marfan syndrome. Best Pract Res Clin Rheumatol, 2008; 22: 165 - 89.
3. Hamonet Cl, Boucand MH, Dassouli A, Kponton - Akpabie A, Boulay C, Macé Y, Rigal C, Boulange r A. Contributions of physical medicine and rehabilitation in people with Ehlers -Danlos syndrome. Encycl Méd Chir, Physiotherapy - Physical medicine - Rehabilitation 26 - 478 -A- 10. Elsevier Masson, Paris, 2003.
4. Beylot C, Martin L. Inherited diseases of collag en and elastic tissue. Encycl Méd Chir Dermatologie, 98 -770- A-10. Elsevier Masson, Paris, 2007.
5. Malfait F, De Coster PJ, Hausser I, van Essen AJ, Franck P, Colige A, Nusgens B, Martens L, De Paepe A. The natural history, including orofacial features of three patients with Ehlers - Danlos syndrome, dermatosparaxis type. Am J Med Genet A, 2004; 131: 18 - 28.
6. De Coster PJ, Martens LC, De Paepe A. Oral health in prevalent types of Ehlers -Danlos syndromes. J Oral Pathol Med, 2005; 34: 298 - 307.
7. Abel M, Carrasco L. Ehlers -Danlos syndrome: classifications, oral manifestations, and dental considerations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2006; 102: 582 - 90.
8. Malfait F, De Paepe A. Molecular genetics in classic Ehlers - Danlos syndrome. Am J Med Gene t C., 2005; 139: 17 -23.
9. Malfait F, Coucke P, Symoens S, Loeys B, Nuytinck L, De Paepe A. The molecular basis of classic Ehlers Danlos syndrome: a comprehensive s tudy of biochemical and molecular f indings in 48 unrelated patients. Hum Mutation, 2005; 25: 28 - 37.
10. Fichard A, Chanut-Delalande H, Ruggiero F. The Ehlers - Danlos syndrome: the matrix architecture in question. Sci Med, 2003; 19: 443 -53.
11. Giunta C, Elcioglu N, Albrecht B, Eich G, Chambaz C, Janecke AR, Yeowell H, Weis M, Eyre DR, Kraenzlin M, Steinmann B. Spondylocheiro dysplastic form of the Ehlers - Danlos syndrome. An autosomal recessive entity caused by mutations in the zinc transporter gene SLC 39 A 13. Am J Hum Genet, 2008; 82: 1290 - 305.
12. Dutertre JP. Information letter to healthcare professionals concerning the combination of cysteamine (Cystagon) and Ehlers - Danlos type

syndrome. AFSSAPS, May 25, 2007.
13. Miller RL, Elsas LJ, Priest RE. Ascorbate action on normal and mutant human lysyl hydroxylases from cultured dermal fibroblasts. J Invest Dermatol, 1979; 72: 241 - 7.
14. Elsas LJ 2nd, Miller RL, Pinnell SR. Inherited human collagen lysyl hydroxylase deficiency: ascorbic acid response. J Pediatr, 1978; 92: 378 -84.