CASE REPORT

A rare case of Ehler–Danlos syndrome with literature review

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Abstract

The Ehlers–Danlos syndrome (EDS), “rubber man disease” comprises of a group of generalized connective tissue disorders, which is characterized by fragile skin, skin hyperextensibility, and joint hypermobility. More than 10 types of EDS have been identified based on genetic and biochemical studies. In the majority of patients with molecularly characterized as classic EDS (Type I and Type II), the disease is caused by a mutation leading to a non-functional COL5A1 allele and resulting in haplo-insufficiency of Type V collagen. Most mutations identified so far result in a reduced amount of the Type V collagen in the connective tissues available for collagen fibrillogenesis. Inter and intra-familial phenotypic variability are observed, but no specific genotype-phenotype correlations have been observed. No specific treatment protocol for the underlying defect is presently available for EDS. However, there are a series of preventive guidelines applicable. Periodontal disorders, increased bleeding tendency, delayed eruption of teeth and joint subluxation are few concerns during dental management of such patients. This case report discusses the features of classic EDS presented in a 7-year-old female patient and reviews the recent literature.

Keywords

Classic type, Ehler-Danlose syndrome, Rubber man disease

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Introduction

The classic Ehlers–Danlos syndrome (EDS) is a heritable connective tissue disorder characterized by skin hyperextensibility, fragile and soft skin, delayed wound healing with formation of atrophic scars, easy bruising, and generalized hypermobility of joint. It comprises EDS Type I and EDS Type II, but it is now apparent that these form a continuum of similar clinical findings and differ only in phenotypic severity.\(^\text{[1,2]}\) Presented here is a rare case of a 7-year-old girl with features of classic EDS.

Case Report

A 7-year-old female patient reported with her parents to the Department of Oral Medicine and Radiology concerned about a decayed tooth in the lower right back jaw region.

A thorough review of the family history indicated that she was the first and the only child of her parents who had married consanguineously. On further investigation, the parents reported that the child had an unremarkable prenatal course of development and birth. She had no significant illnesses or hospitalizations as reported. She had a normal course of development.

Her medical history did reveal prolonged epistaxis occasionally. The ophtalmic assessment was done at the age of 2 years, and she was diagnosed with astigmatism for both the eyes. On a re-evaluation a week ago she was also diagnosed with hypermetropia.

The patients’ dental history was, according to her parents, uneventful, although she had never had routine professional care. Tooth eruption and exfoliation had occurred without difficulty. She reported brushing her teeth twice daily.

Physical examination revealed a thin white female kid with the translucent skin with the blue sclera and dark circles around her eyes [Figures 1 and 2 a, b]. There was hyperextensibility of her fingers in both hands and legs, elbows, and knees with a bilateral shoulder subluxation [Figure 3]. Her height was 125 cm and weighed 19.20 kg, afebrile at the time of presentation. Laboratory examination for the patient revealed normal complete blood count, platelets, prothrombin time, and partial thromboplastin time; however, her bleeding time was found to be > 16 mm.

Oral examination revealed early mixed dentition [Figure 4] with a Class I relationship of her first permanent molars and primary canines. Severe crowding of incisors and posterior cross bite on her right side was present. Dentinal caries was present with respect to lower right deciduous molar. There was generalized gingivitis with fair oral hygiene.
A provisional diagnosis of EDS was made based on the clinical finding, and the patient was sent to the genetic center at the Indira Gandhi Institute of Child Health. On genetic analysis, it was found that she had a pathogenic variant of COL5A1 gene. On the basis of the genetic analysis and clinical features a confirmed diagnosis of EDS was made.

The parents were referred to a genetic counselor to explain regarding the condition and the possibility of the condition repeating in the next offspring.

The patients’ dental treatment was performed at the pediatric department, which was uneventful.

The patient is placed under regular recall at the dental hospital and was referred to the clinical pediatrician for subsequent care and review.

Discussion

The classic EDS is a heritable connective tissue disorder, which is characterized mainly by the hyper extensibility of skin, abnormal wound healing, and joint hypermobility.

Prevalence

EDS truly is a rare disease, affecting just one in a million people worldwide. There are many subtle forms of the condition, leading to missed diagnosis or misclassification. Therefore, the incidence rates stated are skewed. The statistics for EDS in India per se has hardly been noted, most of the authors referencing to worldwide statistics. The prevalence of EDS varies between 1:10,000 and 1:150,000 depending on the author.

Pathophysiology

There are three different mechanisms by which the EDS traits are produced. The first of these features is a deficiency of the collagen-producing enzymes, such as lysyl-hydroxylase and pro-collagen peptidase. The second is the dominant-negative effect of the mutant collagen α-chains. The third is haplo-insufficiency of COL5A1 gene that encodes the proalpha1(V) chain of the Type V collagen. The term haplo-insufficiency refers to the presence of a single functional copy of any particular gene within
diplaid organisms, with the other homologous allele (which is supposed to be a functioning duplicate gene) inactivated.\textsuperscript{[6]}

The diagnosis of EDS, classic type is generally established by clinical examination and family history. The diagnostic criteria were developed by a medical advisory group in a conference held at Ville Franche in 1997.\textsuperscript{[2,9]} The combination of three major diagnostic criteria is highly specific for the presence of the condition:\textsuperscript{[2]}

1. Skin hyper extensibility: Skin hyper extensibility should be tested at a neutral site (the one not subjected to mechanical forces or scarring), such as the volar surface of the forearm. It is measured by pulling up the skin until any resistance is felt. In young children, the hyper extensibility of skin is difficult to assess because of abundant subcutaneous fat.

2. Widened atrophic scar formation (manifestation of tissue fragility).

3. Joint hypermobility: Joint hypermobility depends upon age, gender, family and ethnic backgrounds. Joint hypermobility in classic EDS is generalized, affecting both the large and the small joints and can range in severity from mild to severe.\textsuperscript{[2]} It is usually noted when a child starts walking.\textsuperscript{[2]}

4. A positive family history.\textsuperscript{[2]}

The minor diagnostic criteria were also established, and the presence of one or more of these minor criteria contributes to the diagnosis of classic EDS though not sufficient to establish the diagnosis:\textsuperscript{[2]}

1. The smoothness of skin, velvety texture.

2. Molluscoid pseudotumors (fleshy, heaped-up lesions associated with scars formation over pressure points such as the elbows and knees).

3. Subcutaneous spheroids (small, hard cyst-like nodules, freely moveable in the sub-cutis over the bony prominences of the legs and arms, which have an outer calcified layer with a translucent core on the radiograph).

4. Complications of hypermobility of joint (e.g.: sprains, dislocations or subluxations, and pes-planus).

5. Muscle hypotonia with delayed gross motor development.


7. Manifestations of tissue hyper extensibility and fragility (e.g.: Hiatal hernia, anal prolapse in childhood, and cervical insufficiency).

8. Surgical complications including postoperative hernias.\textsuperscript{[2]}

Oral manifestations of EDS need special consideration during dental treatments (Table 1).\textsuperscript{[10]}

Dental visits of short duration are preferable in order to avoid causing any iatrogenic problem in the temporomandibular joint. Inferior alveolar nerve blocks should be given with utmost care to avoid causing any hematoma.\textsuperscript{[10]}

Forces applied in the orthodontic treatment should be lighter than usually given considering the fragility of the periodontal ligament. As the teeth move rapidly on the application of well-controlled forces, the root resorption does not seem to be a major problem. Also as relapse is frequent in such treatment, a longer period of retention is advisable.\textsuperscript{[11]} The buccal mucosa is vulnerable to aberration injury from such appliances.\textsuperscript{[10]}

It is imperative to test blood coagulation values before proceeding with any surgery. Sutures, which do not hold well, should be covered with acrylic dressings for better stability and healing. The dentist should perform various treatments observing precautions appropriate to this condition.\textsuperscript{[10]}

Differential diagnosis of the other EDS-subtypes:

1. EDS hyper-mobility type (EDS Type III)

2. Familial joint hyper-mobility syndrome

3. EDS vascular type (EDS Type IV)

Differential diagnosis including other heritable connective tissue disorders:\textsuperscript{[2]}

1. Marfan syndrome

2. Cutis–Laxa syndromes

3. Loeys–Dietz syndrome

The discussed case presented with smooth velvety skin, skin hyper-extensibility, joint hyper-mobility, with a history of easy

| Table 1: Oral manifestations of Ehlers-Danlos syndrome and the dental considerations |
|------------------------------------------|---------------------------------|-----------------|
| Oral examination                        | Various clinical signs          | Common complications |
| Extra oral examination                  | 1. Scarring of forehead and chin | 1. Frequent luxations, subluxations of the TMJ |
|                                        | 2. Hypertelorism, epicanthus     | 2. Hyperelasticity of skin |
|                                        | 3. Narrow curved nose            |                            |
|                                        | 4. Thinning of hair              |                            |
|                                        | 5. Deformed ears                 |                            |
| Intraoral soft tissue                   | 1. Tongue supple in consistency  | 1. Buccal mucosa- Fragile with reduced healing capacity, easy bruising tendency |
|                                        | 2. Gingival hyperplasia and multiple fibrous nodules | 2. Periodontal tissue-Bleeding after brushing common also vulnerable to gingivitis and periodontal disorder |
|                                        | 3. Increased post extraction bleeding | 3. Increased post extraction bleeding |
| Intraoral hard tissue                   | 1. High palatal vault            | 1. Teeth: Fragile, tendency to fracture |
|                                        | 2. Deep fissures, long cusps     |                            |
|                                        | 3. Supernumerous, Microdontia,   |                            |
|                                        | 4. Pulp calcifications           |                            |
|                                        | 5. Abnormal root structure       |                            |

TMJ: Temporomandibular joint
Diwakar and Das

bruising and epistaxis, muscle hypotonia, features suggestive of a clinical diagnosis of the classical EDS.

**Clinical management**

There are not many treatment options available, yet the optimal management of EDS patients through a series of lifestyle modifications is recommended, such as by minimizing skin trauma brought about during trauma or excessive exposure to the sun, as well as a regular exercise regimen in order to strengthen muscles tone, which in turn decreases the risk of joint injury (such as the previously discussed spontaneous dislocation). Patients with the vascular and the ocular forms of EDS should avoid dangerous contact sports, such as martial arts and football, etc. There is even anecdotal mention that increase in the intracranial pressure resulting from valsalva effect can be problematic, especially with the vascular and the ocular forms; patients may be advised to refrain from such activities as playing musical instruments (trumpet, trombone) as well as activities that require constant squatting or bearing down. [6]

The limited treatment choices available for EDS patients are unsatisfactory, with most care being supportive in nature. Patients requiring surgical interventions should be treated with the utmost of caution due to enhanced problems of bleeding from the spontaneous vascular rupture, scar formation, and potential compromises in airway maintenance. Surgical re-excision of the scars and keloids might provide for some cosmetic benefit although this plastic surgery can also lead to problems as previously noted. [6]

**Conclusion**

EDS, the classic type is inherited disorder of autosomal-dominant type. It is estimated that approximately 50% of the affected individuals have inherited the mutant gene from an affected parent, and about 50% of the affected individuals may have a de novo disease-causing mutation. [2]

Although about 50% of the individuals diagnosed with classic EDS have an affected parent, the family history may seem to be negative because of failure to recognize the disorder in family members. Requests for prenatal testing for conditions such as classic EDS that do not affect intellect of the individual or life span are not common. Differences in perspective may exist among various medical professionals and within families regarding the use of prenatal testing. [3]

From oral physician’s perspective, it is important to be aware of the risks of bruising, bleeding and joint hyper extensibility during various dental procedures being carried out in the patient. Also, it is important to make the patient and related aware of the importance of the need for optimum maintenance of oral hygiene to avoid the oral disorders patient is more susceptible to.

**References**

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