

COLLAGEN DISORDERS

Abstract

Contemplating the vast knowledge about life has always been a topic of major interest. Not only does it help us to understand the normal biological mechanisms, it also helps us to grasp the idea of any deviation from that said normality. Proteins are the most available molecules in living systems. Collagen is one such protein. Since mouth is the mirror of body it is an oral physician's job to perform early diagnosis and management of these conditions.

Keywords: Alport syndrome, Amelogenesis imperfecta, Collagen, Collagen Disorders, Dentinogenesis Imperfecta, Ehlers-Danlos Syndrome, Epidermolysis Bullosa, Fibrodysplasia, Oral Submucous Fibrosis, Ossificans Progressiva, Marfan Syndrome, Osteogenesis Imperfecta, Stickler syndrome, Systemic Lupus Erythematosus.

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I. COLLAGEN DISORDERS

Contemplating the vast knowledge about life has always been a topic of major interest. Not only does it help us to understand the normal biological mechanisms, it also helps us to grasp the idea of any deviation from that said normality. And among all living beings, proteins are the most available molecules.¹

Collagen is a protein that is present throughout all the animal kingdom.^{1, 2}

The term "collagen", introduced in the nineteenth century, was made up of the Greek words "kolla" (glue) and "genos" (formation).²

The total amount of collagen is estimated as 25% - 30% of total body proteins. There are total 28 types of collagens.³

Collagen Disorders

1. Ehlers-Danlos Syndromel: Ehlers-Danlos syndrome (EDS) is a heritable heterogeneous tissue disorder. EDS shows skin hyperextensibility, joint hypermobility that usually leads to dislocations, and tissue fragility. As frequent abnormalities in the structural aspect of scleroprotein fibrils in EDS patients was observed, it was theorised that EDS is a disorder of metabolism of fibrillar collagen.

Mutation in COL1A1 and COL1A2 genes is believed to be the cause of this disease.

The characteristic features of this syndrome are

- Joint hypermobility.
- Skin hyperelasticity and fragility.
- Delayed healing of wounds.
- Ecchymosis.

The patients may also show:

- Cardiovascular problems
- GIT complications, and
- Ocular complications.⁴

2. Oral manifestations of EDS include:

- The mucous membrane becomes fragile, which may lead to bleeding during dental procedures. Suturing becomes difficult.
- Pulp stones, short and deformed roots are seen.
- Higher chances of deciduous teeth caries.
- Spontaneous fractures of teeth.
- Early onset of generalized periodontitis.
- Approximately 50% patients can touch the tip of their noses with their tongue (Gorlin's sign).

- TMJ hypermobility.^{5,6}
- 3. Marfan syndrome:** Marfan syndrome (MFS) is a heritable, heterogenous, connective tissue disorder. It affects 3 systems in human body - skeletal, ocular and cardiovascular systems. In 1896, French paediatrician Antoine Bernard-Jean Marfan first described this syndrome.

Mutation is seen in the gene *FBNI*. This gene encodes fibrillin. This glycoprotein is the main component of the microfibrils of the extracellular matrix. Reduced or abnormal fibrillin-1 causes weakness of tissues, transforming growth factor β signalling is increased and loss of cell–matrix interactions. Several genes that are suspected to be defective in Marfan syndrome, are located on the long arm of chromosome 2. Two of these genes are COL3A1 and COL5A2, and a third member of the collagen gene family: COL6A3.⁷

- 4. Osteogenesis imperfecta:** Osteogenesis imperfecta (OI) is a dominant autosomal, heterogeneous disorder of connective tissue. It is known as “brittle bone disease”. It is characterized by abnormalities of connective tissue and fragility of bones.

According to **Sillence et al. (1979)** there are 4 four types of OI.⁸ Majority of patients show mutations in either the COL1A1 or COL1A2 genes. Both of these genes encode the chains of type I procollagen.⁹

- 5. Epidermolysis bullosa:** Epidermolysis bullosa (EB) is a group of heterogenous heritable disorders. It is characterized by formation of blisters at sites of minor friction or trauma.¹⁰

Oral manifestations include

- Milia.
 - Increased risk of squamous cell carcinoma.
 - Decreased normal tongue mobility.
 - Obliteration of the oral vestibule.¹¹
- 6. Systemic Lupus Erythematosus:** Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune heterogenous disease. Pathologically it shows abnormal B- and T-cell function. Major organ involvement causes severe morbidity and mortality. Various investigations on the pathogenesis are focused on immunity to collagen. The exact role of collagen autoimmunity is yet to be discovered, but there have been studies that indicate the presence of autoantibodies against endothelial cells in vascular diseases.^{12, 13}

Oral Manifestations: mucosal ulcers, xerostomia, periodontal disease, burning sensation of mouth, salivary gland disorders, TMJ disorders, oedema, bleeding and petechiae.¹⁴

7. **Alport syndrome:** Alport syndrome (AS) is a heritable disorder that affects the basement membranes. Mutations occur in genes on the X chromosome. Classical X-linked Alport syndrome affects gene COL4A5. While recessive forms show COL4A3 and COL4A4 gene mutation. Clinical features include renal implants, hearing loss, abnormality in lens, hypertension, proteinuria and haematuria.¹⁵
8. **Stickler syndrome:** Stickler syndrome (SS) is an autosomal dominant syndrome. Clinical features include retinal degeneration, premature osteoarthritis, loss of hearing and orofacial abnormalities. Mutation occurs in COL2A1, COL11A1 and COL11A2 procollagen genes of Type 2 and 11 collagens.¹⁶
9. **Amelogenesis imperfecta (AI):** Amelogenesis imperfecta (AI) shows enamel abnormalities in both deciduous and permanent dentition. Most observed features include discolouration of teeth and changes in enamel appearance.

AI can be of 3 types which are-

- The Hypoplastic type,
- The Hypocalcified type, and
- The Hypomatured types.

Hypoplastic AI is caused due to the failure at secretory stage during enamel formation. Hypocalcified AI is due to inadequate calcium ion transportation. Defect in enamel matrix protein removal results hypomaturated type of AI.^{17, 18}

A study by **Kim et al. 2006** found disease-causing mutations in AI. They are AMELX, ENAM, KLK4, MMP20, AMBN, DLX3 and TUFT1.¹⁸

After further studies mutation in several other genes have been identified such as FAM83H, WDR72, KLK4, COL17A.

10. **Dentinogenesis Imperfecta (DI):** Dentinogenesis Imperfecta (DI) was first classified Shields in 1973. Although primary teeth are more severely affected, both the primary and permanent teeth can be affected in some cases, appearing bluish-gray or amber brown or opalescent. In radiographs the crowns of teeth appear bulbous, with narrow roots, and small or obliterated pulp chambers. As the defective dentin causes enamel to break off easily and exposes the underlying dentin, the teeth undergo severe attrition. According to Shields, DI is classified into three main groups.¹⁹ DI shows mutation in COL1A1 or COL1A2, the two genes that encode the chains of type I procollagen.
11. **Oral Submucous Fibrosis:** Oral Submucous Fibrosis (OSMF) was first described by Schwartz in 1952. It is a precancerous condition characterised by chronic, progressive scarring of the oral mucosa. Based upon human leucocyte antigen (HLA) associations and circulating immune complexes and auto-antibodies, a possible underlying autoimmune mechanism with a genetic predisposition has been proposed in some cases. The pathogenesis of OSMF involves the disruption of collagen metabolism by the components of areca nut. Alkaloids stimulates fibroblasts to produce collagen, whereas flavonoids inhibit collagenase (an enzyme that catalyses collagen breakdown). In

addition, considerable amounts of copper are found in areca nut products. Copper upregulates lysyl oxidase, which is an enzyme involved in collagen cross linking which renders collagen fibrils resistant to degradation by collagenase.

II. CLINICAL FEATURES

This condition affects oral mucosa and at times pharyngeal mucosa and occurs insidiously, usually diffusely initially appearing with

1. Burning sensation and stomatitis
2. Vertical fibrous bands occur on oral mucosa during later stages, and
3. Restricted mouth opening due to excessive fibrosis. An interincisal distance of less than 20mm is considered severe. Severe fibrosis can even affect the soft palate, pharynx, oesophagus and uvula. The uvula can be shrunken and deviated.

When fibrosis extends to the pharynx and oesophagus, the patient may experience difficulty in swallowing the food. Referred pain in the ears, deafness, and nasal voice have also been observed. The earliest and most common clinical sign is blanching which imparts a marblelike appearance to the oral mucosa. Blanching may be localised, diffused or in the form of a lace like network.²⁰

III. CONCLUSION

Life in itself remains the biggest mystery of the human kind. Even after countless scientists and their research, only a small part of it has come to light. Asking boundless questions regarding the human biology and endless seeking of their answers has led us to a point where medical field is using that knowledge to alleviate the quality of life.

Collagens are in a way the base of almost every biological entity. So, any disorders of them lead to a variety of multiple different diseases with their own unique clinical features and manifestations.

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