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Review Article on Ehler Danlos Syndrome Type IV

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Abstract: *Ehlers- Danlos syndrome (EDS) type IV is also called as vascular type of Ehlers- Danlos syndrome. It is an inherited connective disorder characterized by facial features .Prevalence rate is 1/25000 and equal in both women and men. Complications of the EDS are observed like vascular, digestive and uterine. Pregnancy increases the risk of vascular and uterine complications. EDS type IV is caused by mutations in the COL3A1 gene coding for type III pro-collagen. In children complications are rare. Diagnosis based on clinical signs and identification of mutations in the COL3A1 gene. There is no specific treatment for Ehlers- Danlos syndrome (EDS) type IV.Treatment based on the symptoms.A brief discussion on effect of celiprolol on prevention of cardiovascular events that occurs in Ehlers- Danlos syndrome (EDS) type IV*

I. Introduction:

Ehlers- Danlos syndrome is an inherited disorder it is divided into 6 types EDS I, EDS II, EDS III, EDS IV EDS V, EDS VI based on collagen involved. The amount of collagen is reduced in the body. Alteration of gene takes place and makes collagen weaker. Mutated genes passes from parents to children so the disease called as inherited disorder. EDS

II. There are six major types of Ehlers-Danlos syndrome

- arthrochalasia
- classic
- dermatosparaxis
- hypermobility
- kyphoscoliosis
- vascular

Epidemiology

The prevalence in America is approximately 1 in 400,000 people

International

EDS prevalence in international wide found to be 1 case in approximately 400,000 people, but mild cases and incomplete cases are underdiagnosed

Mortality/Morbidity

EDS –type IV and type-VI is most severe form. Patient with type-IV EDS have a short life span because of the rupture of the large artery or perforation of internal organs. Other types are usually not so dangerous, affected individual can live a healthy with some restricted life.

Race

Whites are probably more affected than other races

Sex

The prevalence's are almost equal in both men and women

Age

The disease can be recognized easily in early childhood

Etiology:

EDS in most cases are inherited condition, minority of cases are not inherited. The genes provide instructions for making the proteins that work with collagen except for ADAMTS2,

- ADAMTS2
- COL1A1

- COL1A2
- COL3A1
- COL6A2
- PLOD1
- TNXB
- COL5A1

Defects in these genes weaken the process and formation of collagen. Collagen is made up of molecules that give structure to connective tissues in the body.

III. Clinical presentation

- fragile blood vessels
- thin skin
- transparent skin
- thin nose
- protruding eyes
- thin lips
- sunken cheeks
- small chin
- collapsed lung
- heart valve problems

IV. Pathophysiology

- collagens are the protein's that helps in organization of extracellular matrix, at least 19 proteins coded by at least 35 non-allelic genes dispersed in the genome.EDS type IV is caused by a deficit of type-III collagen, which belongs to the fibrillar collagens. All fibrillar collagens are homo or heterotrimetrics formed by the linking of three monomers or **α** chains. Type III collagen is a homotrimeric formed by the linking of three **α**1 (III) chains, with the central part of the molecule adopting a triple-helix structure. The amino acid sequence of the triple helix is characterized by repeated glycine-X-Y sequences, where X and Y are often the amino acids proline and hydroxyproline respectively. In order to ensure correct linking of **α** monomers, there should be no interruption in the repetition of the glycine-X-Y triplets and the length of the triple helix should remain similar for each **α** chain.
- Type III collagen is a constituent of arterial walls. Its quantitative or qualitative deficit in EDS type IV accounts for the propensity of arterial tears or dissections which characterize this illness. The walls of the digestive tract are also rich in type III collagen, which explains why digestive perforations are another frequent complication of EDS type IV.

Diagnosis:

- Genetic test
- Skin biopsy
- Echo cardiogram

Vascular Ehlers-Danlos syndrome: Villefranche diagnostic criteria (adapted from [3]

Major diagnosis criteria	Arterial, digestive or uterine fragility or rupture
	Thin, translucent skin
	Extensive bruising
	Characteristic facial appearance
Minor diagnosis criteria	Positive family history, sudden death in a close relative
	Acrogeria
	Hypermobility of small joints
	Tendon and muscle rupture
	Talipes equinovarus (clubfoot)
	Early onset varicose veins
	Spontaneous pneumothorax or haemothorax

V. Treatment:

There is no specific treatment for Ehlers Danlos syndrome. Surgical intervention is required to prevent the fatal complications which may cause death.

A prospective randomized, open, blinded –end points trial was conducted studies on prevention of cardiovascular events in vascular Ehlers- Danlos syndrome by using the drug celiprolol.Because celiprolol is a B_2 receptor antagonist to prevent arterial dissection and ruptures in vascular Ehlers- Danlos syndrome.

There is no major adverse drug reactions reported by the celiprolol except fatigue during the study. The study was conducted in multicenter, randomized, open trail with the blind assessment of clinical events center in France and in Belgium. This study is registered with clinical trails.gov, number NCT00190411.

So this study suggest that celiprolol is the choice of drug for physicians aiming to prevent major complications in patients with vascular Ehlers- Danlos syndrome.

This can also treat the patient with similar clinical symptoms and prevents the mutations that takes place.

VI. Counselling the patient

Once the diagnosis has been confirmed that patient is having vascular Ehlers- Danlos syndrome. Entire family should screened because EDS type IV is a monogenic disorder, the patient who has affected have 50% risk of transmitting the disease to each of their children.

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