

CLINICAL QUIZ (p196) ANSWER

What is the Diagnosis?

With indication in hyper-extensibility, lax skin, easy bruising and poor wound healing, genetic testing on Ehlers-Danlos syndrome is immediately performed. Genetic panel test on Ehlers-Danlos syndrome reveals a c.1502delC change in exon 12 of the *COL5A1* gene, which led to frameshift of the DNA and resulted in abnormal mRNA production. The genetic test also reveals that the patient is heterozygous for *COL5A1* gene. Inheritance of Ehlers-Danlos Syndrome is autosomal dominant, the recurrence risk for offspring is 50% with a *COL5A1* mutation.¹

What is Ehlers-Danlos Syndrome?

Ehlers-Danlos syndrome (EDS), classic type (also known as EDS type I or II) is an autosomal dominant disease that affects connective tissues that support skin, bones, blood vessels and many other organs. The classic type of EDS is characterised by skin hyper-extensibility, abnormal wound healing and joint hyper-extensibility.

The skin of EDS patient is hyper-elastic and fragile. Its hyper-elastic features are demonstrated in both easy extension of skin and immediate snapping back after release. For area that is prone to minor trauma (e.g. forehead or chin) and joints (e.g. knees and elbows), splitting of dermis will be resulted. Continuous stretching of scars after primary wound healing and the lack of Type V collagen, therefore, lead to abnormal wound healing. Joint hyper-extensibility can be assessed using the below Beighton score (Table 1).² Dislocations of shoulder, patellar digits hips, radius, and clavicle are usually observed. Apart from the above phenotype, patients suffer from hypotonia, muscle cramps and fatigue, and easy bruising.

Table 1 Beighton score for joint hyper-mobility

Joint	Negative	Unilateral	Bilateral	Patient's score
Passive dorsiflexion of the 5th finger >90°	0	1	2	2
Passive flexion of thumbs to the forearm	0	1	2	2
Hyperextension of the elbows beyond 10°	0	1	2	2
Hyperextension of the knees beyond 10°	0	1	2	2
Forward flexion of the trunk with knees fully extended and palms resting on the floor	0	1	1	1
# Total Score ≥5 defines joint hyper-mobility				9

The following diagnostic criteria could be used when there is suspicion on individual suffering from classical EDS. The combination of the first three major diagnostic criteria should have a high specificity for classic type EDS. The presence of one or more minor criteria contributes to the diagnosis of classic type EDS but is not sufficient to establish the diagnosis. The patient satisfied 3 of the major and 1 of the minor diagnostic criteria: skin hyper-extensibility, widened atrophic scars, joint hyper-mobility and easy bruising.

Major Diagnostic Criteria

- Skin Hyper-extensibility
- Widened Atrophic Scars
- Joint Hyper-mobility
- Positive Family History

Minor Diagnostic Criteria

- Smooth, Velvety Skin
- Molluscoid pseudotumours
- Subcutaneous spheroids
- Complications of Joint Hyper-mobility
- Muscle Hypotonia
- Easy Bruising
- Manifestations of tissue extensibility and fragility
- Surgical complications

Traditionally, Ehlers-Danlos syndrome is tested by taking skin biopsy for electron microscopy and biochemical testing, but the diagnostics is sometimes not definite. Molecular genetic diagnosis by sequencing and deletion/duplication analysis is now a less invasive option that could account of $\geq 50\%$ affected individuals.

What is the Molecular Genetics behind Ehlers-Danlos Syndrome?

Mutations in a numerous of genes are found to be corresponded to EDS. Currently, it is estimated that around 50% of EDS classic type patients have mutations in *COL5A1* and/or *COL5A2* gene. A large proportion of them are characterised by a mutation leading to a non-functional *COL5A1* gene, while the others have a mutation that lead to production of functionally defective *COL5A1* allele.² The severity of phenotype among patients could vary greatly.

COL5A1 and *COL5A2* code for Type V collagen alpha 1 or alpha 2 respectively. The production of collagen involves a complicated 6-step synthesis. Defects in formation of one of the intermediates: tropocollagen will lead to Ehlers-Danlos syndrome.

What is the Management of Ehlers-Danlos Syndrome?

Clinical examination should be given immediately after diagnosis of Ehlers-Danlos syndrome to assess skin hyper-extensibility, presence of atrophic scars and bruises, and other manifestations of classic type EDS.

Physiotherapeutic program and non-weight-bearing muscular exercise should be given to classic EDS children who are suffering from delayed motor developed and hypotonia. For individuals with muscle hypotonia and joint instability with chronic pain, advice should be given to adjust their lifestyles, which behaviour and psychological therapy will also be practical.³ Anti-inflammatory drugs may also help in relieving joint pain. Since EDS patients demonstrate abnormal wound healing, dermal wounds should be closed without tension, in two layers and with application of deep stitches.

As aforementioned, the patient in the clinical quiz aimed to carry a child. Therefore, management measures for pregnancy were also given. Ehler-Danlos syndrome has an autosomal dominant inheritance. There is a 50% chance for the patient to pass the pathogenic mutation down to her offspring in each pregnancy. The availability of prenatal diagnosis or preimplantation genetic diagnosis should be discussed with the care physician and obstetrician before pregnancy.

Moreover, Ehlers-Danlos mothers are more vulnerable to premature rupture of membranes, which results in prematurity.⁴ Since EDS patients are affected by hypotonia, probability of breech presentation will be more frequent. Dislocation of hips or shoulder of the newborn will result if the newborn is also affected by EDS. While and after delivery, tearing of perineal skin by forceps, extension of episiotomy incisions and prolapse of uterus and/or bladder may also occur. Therefore, pregnant women should be closely monitored throughout pregnancy and in the postpartum period. Vitamin C (Ascorbic acid) should also be given to relieve easy bruising.

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References

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