



## Twin pregnancy with untyped Ehlers-Danlos syndrome requiring prompt genetic testing: A case report

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### ABSTRACT

Ehlers-Danlos syndrome is a rare genetic disorder that presents with a variety of pathologies depending on the disease type. Among them, vascular Ehlers-Danlos syndrome requires extremely careful management as there have been many reports of fatal perinatal complications such as uterine rupture. Although hypermobile Ehlers-Danlos syndrome is less likely to cause fatal complications, symptoms such as arthralgia, hip dislocation, and depression may be seen throughout pregnancy. We report here a case of twin pregnancy in which Ehlers-Danlos syndrome was first suspected at 19 weeks of gestation. Vascular Ehlers-Danlos syndrome could not be ruled out based on family medical history, making it difficult to determine the perinatal management strategy. Prompt genetic testing did however rule out the vascular type and the patient was diagnosed with hypermobile Ehlers-Danlos syndrome from the clinical symptoms, enabling us to manage the pregnancy safely until 34 weeks of gestation.

### 1. Introduction

Ehlers-Danlos syndrome (EDS) is a rare inherited connective tissue disease that presents with systemic connective tissue fragility in the skin, joints, vasculature, and internal organs [1]. EDS is classified into 13 subtypes based on its genetic cause and symptoms [2]. Among them, vascular EDS (vEDS) is caused by mutations in *COL3A1* and is the most life-threatening subtype [3].

We report here a twin pregnancy in which vEDS could not be ruled out based on family medical history. The patient needed prompt genetic testing for determination of the perinatal management strategy.

### 2. Case Presentation

The 20-year-old patient was carrying dichorionic diamniotic twins in her first pregnancy. She was introduced to the department at 19 weeks of gestation with suspected Ehlers-Danlos syndrome (EDS) based on family medical history and her past and present symptoms. Her mother had

died of sudden cardiovascular rupture at 47 years of age during cardiac catheterization, and autopsy at another hospital revealed suspected EDS of unknown type. The patient had a history of multiple episodes of joint dislocation from childhood and presented with marked skin hyperextensibility. She was considered likely to have vEDS, given her mother's cardiovascular rupture.

Since the risk of uterine rupture after the midpoint of pregnancy is extremely high in cases of twin pregnancy with vEDS, she was provided genetic counselling and testing. From her family history, it was found that her maternal aunt had been diagnosed with hypermobile EDS (hEDS) based on recurrent joint dislocation and joint hypermobility (Fig. 1). However, it was difficult to explain her mother's history of cardiovascular rupture with hEDS.

Targeted exome sequencing was performed of genes associated with connective tissue disease, namely, *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *TGFB3*, *ACTA2*, *COL3A1*, *EFEMP2*, *FBN1*, *FBN2*, *FLNA*, *MYH1*, *MYLK*, and *SLC2A10*. The test detected only a low-frequency variant in *FBN2* (c.6833C > T), which is a missense variant found in 0.6% of the

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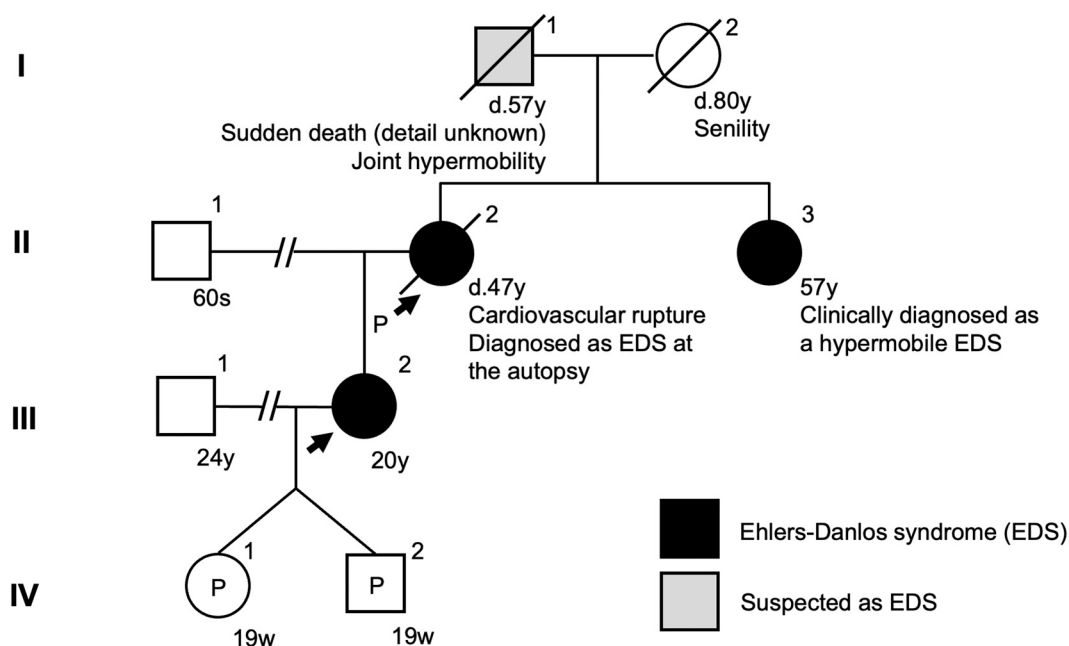
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**Fig. 1.** Family tree of the present case with twin pregnancy and untyped EDS. EDS, Ehlers-Danlos syndrome.

Japanese population without pathological significance. The patient was finally diagnosed with hEDS based on clinical criteria, because no pathogenic variants were detected in *COL3A1*, the gene responsible for vEDS.

The patient was placed on inpatient bed rest from 29 weeks of gestation due to a worsening of hip pain that had been present since early pregnancy. The hip pain improved with bed rest, but back and pelvic pain gradually worsened. As the foetuses grew, it became difficult for her to lie in bed due to pain, and it seemed to be difficult to maintain the pregnancy any longer. An elective caesarean section was performed at 34 weeks 0 days of gestation. Both infants were healthy at birth but were followed up by a paediatrician because of suspicion of joint hypermobility. After delivery, the patient's arthralgia improved, but she developed postpartum depression and was referred to the psychiatry department.

### 3. Discussion

Pregnancy with vEDS is associated with serious complications such as vessel rupture, uterine rupture, and wound dehiscence. Total maternal mortality in pregnancy with vEDS is estimated to be 5%–6% [1,4]. In the present case, the patient's mother had died from cardiovascular rupture. On the first visit, the patient had a twin pregnancy at 19 weeks of gestation and her uterus was already markedly distended, so it was necessary to rule out vEDS reliably and rapidly. Her aunt had been diagnosed with hEDS based on clinical symptoms, but it took some time to obtain information about her aunt's specific diagnosis. While waiting for the aunt's specific diagnosis, targeted exome sequencing was performed of the genes associated with connective tissue diseases, including *COL3A1*. However, although the accuracy of *COL3A1* testing for vEDS by targeted exome sequencing is high, it is not 100% because there are a few reports of vEDS caused by copy number variation [5,6]. Therefore, the patient was maintained on perinatal management in readiness for emergency changes up until the postpartum period.

She was ultimately diagnosed with hEDS based on her clinical symptoms. No causative genes for hEDS have been identified, even though it is the most prevalent type of EDS [2]. In contrast to vEDS, hEDS is less likely to be a direct cause of maternal death, but it often leads to postural orthostatic tachycardia syndrome, and a tendency to

anxiety and depression during pregnancy and throughout the postpartum period [7]. Twin pregnancy placed considerable stress on the mother, and the diagnosis of hEDS in this case did not mean that the pregnancy was low risk. Even with a singleton pregnancy, caesarean section, as was required in the present case, has been reported to be associated with recurrent joint dislocation and pain [8].

### 4. Conclusion

Since precautions in perinatal management vary depending on the type of EDS, it is important to provide genetic counselling and confirm a diagnosis, especially when vEDS is suspected.

#### Contributors

Shiori Ogawa drafted the manuscript.

Tasuku Mariya contributed to patient management and manuscript editing.

Yuya Fujibe contributed to patient management and manuscript editing.

Marie Ogawa contributed to genetic counselling and testing, and manuscript editing.

Keiko Ikeda contributed to genetic counselling and testing, and manuscript editing.

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#### *Patient consent*

Written informed consent was obtained from the patient for the publication of this case report according to the guidelines of the Declaration of Helsinki.

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#### *Conflict of interest statement*

The authors declare that they have no conflict of interest regarding the publication of this case report.

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