

Ehlers-Danlos Syndrome and Congenital Heart Anomalies

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Two sisters with Ehlers-Danlos syndrome, inherited as an autosomal recessive trait, and congenital heart disease are herein reported. One was a 20-year-old woman with Ehlers-Danlos syndrome and multiple aphthous stomatitis, bronchial asthma, an emphysematous lung, a ventricular septal defect and a bilateral inguinal hernia due to hyperextensibility and joint hypermobility. The other was a 17-year-old girl with the same syndrome and an atrial septal defect, a ventricular septal defect and patent ductus arteriosus. The combination of Ehlers-Danlos syndrome and congenital heart anomalies in these siblings suggest a common genetic defect to be the cause of these diseases.

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Introduction

Ehlers-Danlos syndrome is known as a rare hereditary disease characterized by hyperextensibility of the skin and joints and fragile connective tissue (1). Considerable clinical and genetic heterogeneity exists, and more than nine separate forms have been recognized. The fundamental biomolecular defect has been elucidated in some subtypes of the disorder. We herein describe a case of Ehlers-Danlos syndrome revealing various physical symptoms while also being complicated with other diseases. Congenital cardiac defects have previously been reported to accompany Ehlers-Danlos syndrome (2–4). Based on our observations of these two sisters we support the hypothesis that Ehlers-Danlos syndrome and congenital heart anomalies have a common cause stemming from a genetic defect.

Case Report

A 20-year-old Japanese woman presented with a history of recurrent multiple aphthous stomatitis and occasional asthma attacks since the age of 5. She had a ventricular septal defect and bilateral inguinal hernias, which were mild and were expected to heal spontaneously, however, as she became older these symptoms persisted. Increasingly severe asthma attacks recurred from the age of 15; at age 17 she noticed a gradual enlargement of the antero-posterior diameter of the thorax. Neither genital ulcers, eye lesions nor pathergy were noted in

her history. Both her elder brother and parents were healthy. Her parents had a stillborn child of unknown sex before her birth. The proband's younger sister, a 17-year-old, had a congenital dislocation of the hip joint and congenital heart anomalies consisting of an atrial septal defect, a ventricular septal defect and patent ductus arteriosus. The younger sister had also previously undergone a curative operation for congenital heart anomalies in her childhood.

On examination the proband's habitus was normal. Her skin was hyperextensible but not easily bruisable. Bilateral inguinal hernias were observed. Joint hypermobility was prominent in the hands, feet and hip joints (Fig. 1a–d). A systolic murmur was audible in Erb's area. A Rumpel-Leede test was negative. The following laboratory values demonstrated no abnormality; the hemoglobin level, leukocyte count, differential cell count, platelet count, bleeding time, and a urinalysis. The serum fibronectin levels of the proband and the younger sister were 240 µg/ml and 295 µg/ml, respectively (normal level; 250–460 µg/ml). The proband's chest roentgenogram revealed an emphysematous lung (Fig. 2). Spirometry showed the %VC to be 155.6% while the FEV_{1.0%} was 67.0% in a non-asthmatic state. The serum α₁-antitrypsin level was 182 mg/dl and within the normal range (170–274 mg/dl). The IgE level was high (520 U/ml) and a high IgE level specific for house mites was also detected (78.5 UA/ml). An electrocardiogram revealed an incomplete right bundle branch block. Cardiac sonography confirmed the presence of a ventricular septal defect.

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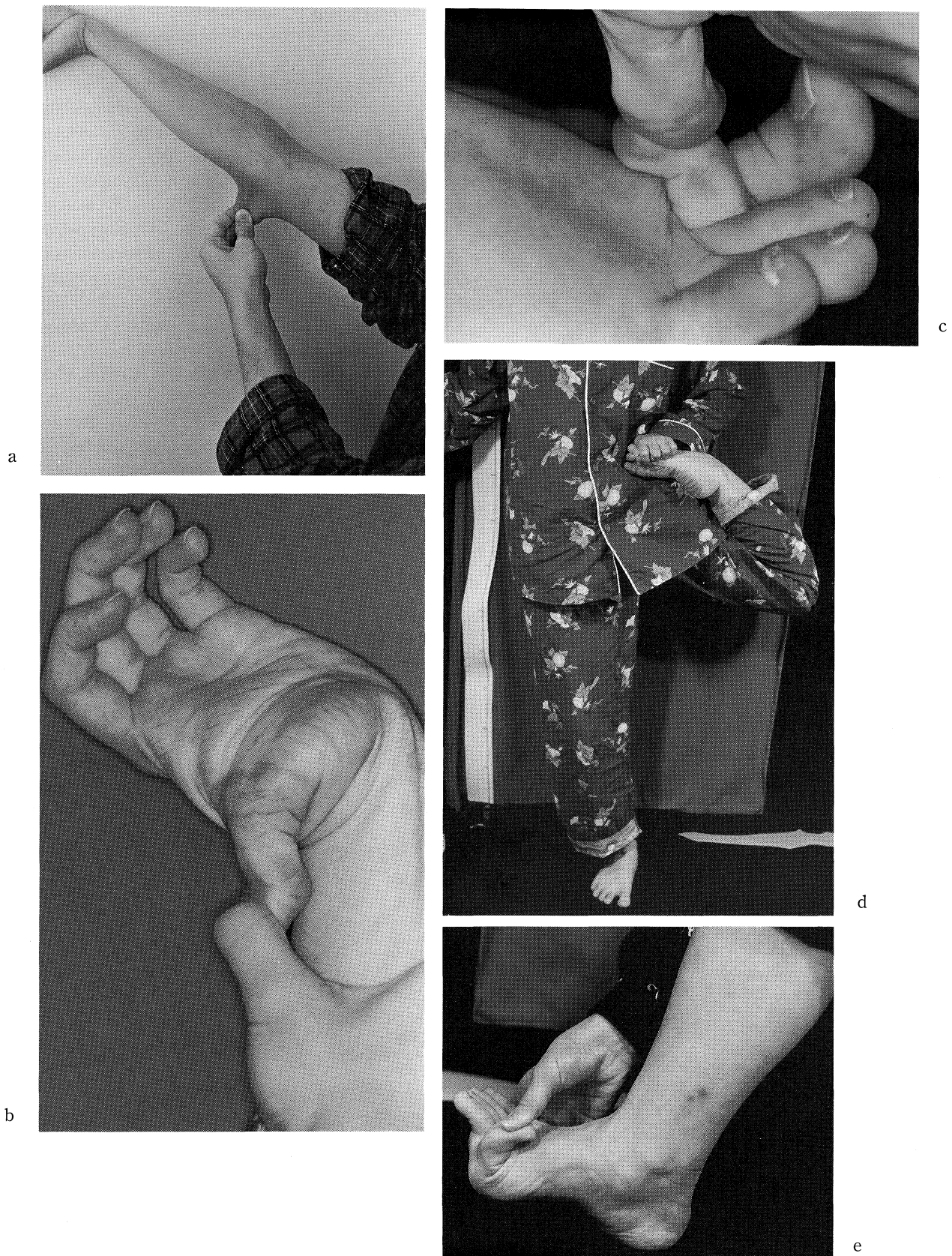


Figure 1. a) Skin hyperextensibility in the proband. b) Passive hyperextension of the thumb toward the forearm. c) Passive hyperdorsiflexion of the toe. d) A hypermobile hip joint. e) A hyperdorsiflexible toe of the younger sister.

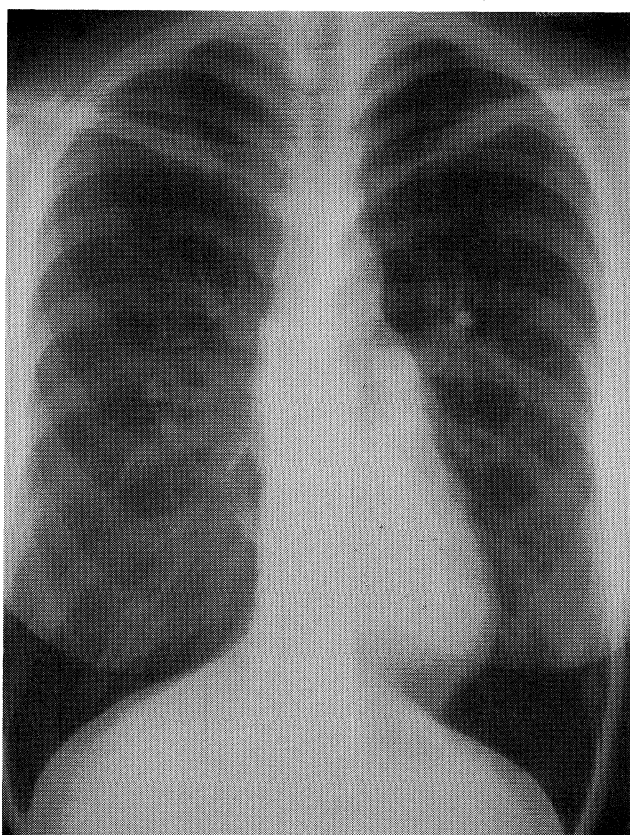


Figure 2. The proband's enlarged lung in a chest roentgenogram.

Recurrent stomatitis showed good improvement after the oral administration of colchicine. The asthma was thought to be an allergic type which was sensitized by dust mites. She had previously received an oral administration of β -adrenergic stimulants and theophylline for the treatment of bronchial asthma.

Her younger sister also had hypermobile joints (Fig. 2). The eventual diagnosis of Ehlers-Danlos syndrome was based on the familial recurrence of hyperextensibility of the skin and hypermobility of the joints.

Discussion

The diagnostic triad of the Ehlers-Danlos syndrome comprises hyperextensibility of the skin, hypermobility of the joints and connective tissue fragility. Various complications can also occur in other systems. The proband's fragile connective tissue might have led to a continuation of the ventricular septal defect, the bilateral inguinal hernia, and may also have caused the recurrent stomatitis because of her fragile oral mucosa. In addition, this syndrome may also have caused her younger sister's congenital dislocation of the hip joints. Structural cardiac abnormalities only rarely occur in patients with the Ehlers-Danlos syndrome. However, when they occur they include an atrial septal defect, ventricular septal defect, tetral-

ogy of Fallot, a persistent atrioventricular canal, a bicuspid aortic valve and a bicuspid right atrioventricular valve (2-5). Here, the two sisters had congenital cardiac defects while no such disorders were present either in other family members or their relatives as far as they reported. The Ehlers-Danlos syndrome in this case was thought to be inherited as an autosomal recessive trait. The combination of these two disorders in the biological siblings suggested that the disorders appeared to stem from a common biomolecular defect. Pulmonary complications are uncommon in patients with Ehlers-Danlos syndrome (5), nevertheless the gradual enlargement of the thorax with recurrent severe asthma attacks in the present proband indicated that pulmonary emphysema was likely caused by a combination of tissue fragility from Ehlers-Danlos syndrome and chronic bronchial asthma. In this case various clinical signs and symptoms far from the cardinal manifestations of the syndrome also appeared and each symptom seemed to be independent until the diagnosis was made and they also proved to be obstacles for the previously consulted physicians and surgeons to determine the basis for these embarrassing clinical features. The clinical features of Ehlers-Danlos syndrome are so heterogeneous that a subcategorization of Ehlers-Danlos syndrome may be difficult or even impossible (5). According to the subcategorization of Ehlers-Danlos syndrome of Beighton et al (6), autosomal recessive inheritance appears in the acrogeric type of the vascular type (EDS IV-B), in the ocular-scoliotic type (EDS VI) (7), in some cases of arthrochalasia multiplex congenita (EDS VII-C) and in fibronectin abnormality (EDS X) (8). The Ehlers-Danlos syndrome in our case could not be classified into any of these categories because of discrepancies in the clinical features. The elucidation of the fundamental genetic abnormalities underlying the heterogeneous clinical features will hopefully, in the future, allow subcategorization of the unclassified cases.

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