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Case Report

Clinical and molecular features of first two-sibling-Cambodian girls with musculocontractural Ehlers-Danlos syndrome

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ABSTRACT

Musculocontractural Ehlers-Danlos syndrome (mcEDS) is a rare autosomal recessive connective tissue disorder. To our knowledge, mcEDS has not previously been reported in Cambodia. Here, we report clinical presentations and a novel variant of CHST14 causing mcEDS in the two siblings in Cambodia. These patients from a non-consanguineous parents presented with clubfeet at birth, contractures of thumbs and feet, a typical facial appearance, and normal cognitive development. The elder sister had severe phenotypic features than the younger sister. They have been prone to ecchymosis and hematomas with minor accidents since young age, without accurate diagnosis, or confused with von-willebrand disease. Genetic consultation and confirmed by a genetic analysis revealed a novel variant, c.994-997dup, (Pro333Glnfs×23) of CHST14. Treated with oral desmopressin and daily vitamin C supplementation over 1-year-period of follow-up, the bleeding has been improved. The purpose of this article is to describe the clinical and molecular features and to show the missed or inaccurate diagnosis of this rare syndrome, which, consequently, results in suboptimal symptomatic management.

Keywords: McEDS, Ehlers-Danlos syndrome musculocontractural type, CHST14, Subcutaneous hematoma

INTRODUCTION

Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous group of heritable connective tissue disorders characterized by skin hyperextensibility, joint hypermobility, tissue fragility, and normal cognitive development.[1,2] Musculocontractural Ehlers-Danlos syndrome (mcEDS) is a rare type caused by biallelic loss-of-function variants in CHST14 (mcEDS-CHST14) or DSE (mcEDS-DSE). Major diagnostic criteria for mcEDS-CHST14 are multiple congenital contractures, characterized by adduction-flexion contractures and talipes equinovarus, Characteristic craniofacial features, evident at birth or in early infancy and characteristic cutaneous features including hyperextensibility, bruisability and fragility with atrophic scars, and increased fine palmar creases.[1,2] To our knowledge, mcEDS has not previously been reported in Cambodia. Here, we report the clinical and molecular features of the first two siblings and the literature reviewed.

This article aims to describe the clinical and molecular features and show the missed or inaccurate diagnosis of this rare syndrome, which consequently results in suboptimal symptomatic management. Genetic consultation and evaluation are useful for patients presented with bleeding tendencies and multisystem involvement.

CASE REPORTS

These two patients were diagnosed based on clinical presentations, physical examination, and genetic analysis.

Case 1

A 17-year-old female of Cambodian origin was referred to our department for suspecting with bleeding disorder. She presented with a huge, deep, and painful hematoma at the left shoulder, arm, forearm, and right lower back after minimal trauma. In her past medical history, clubfeet and abnormal physical features were noticed at birth. The patient archived head control and sat without support at 4 and 8 months, respectively, due to delayed gross motor development in acquiring the ability to control the large muscles. At 2 years of age, she underwent surgery for her clubfeet. Later, she could not walk independently due to hypotonia and multiple joint dislocations, then frequently easy bruising, multiple joint dislocations, and hematoma through the age of 5 years, insulting multiple admissions.

She was prone to ecchymosis and hematomas with minor accidents. At 16 years of age, she had a huge spontaneous hematoma of the left shoulder that required percutaneous surgical drainage along with several blood and plasma transfusions. Her menstruation was likely normal bleeding (PBAC score<150). She was the second child out of three female siblings in a family. The first child was 20-year-old female with normal phenotypic condition. A younger sibling who had a milder phenotypic condition. Her parents were not consanguineous.

Physical examination revealed pale and a large subcutaneous hematoma on her left arm and forearm (Figure 1A) and right lower flank (Figure 1B), very thin skin with visible vessels on the thorax, and bruising in multiple sites. Abnormal craniofacial features with strabismus (exotropia), broad forehead with an unusual red skin tag on the left side, thin upper lip vermillion, hypertelorism, and low-set ears (Figure 1C) were noted.

The variable extension and flexion contractures of distal and proximal interphalangeal joints with slender-shaped fingers (Figure 1D, 1E), atrophic skins of hands (Figure 1D), and atrophic fine palmar creases (Figure 1F) were observed. Bilateral talipes equinovarus and wide first web space with small features of feet (Figure 1G) are associated with hyperextensibility, easy bruising, and fragility with atrophic scars (Figure 1H). The left foot is shorter than the right side and has small features. The result of the neurological examination was normal.

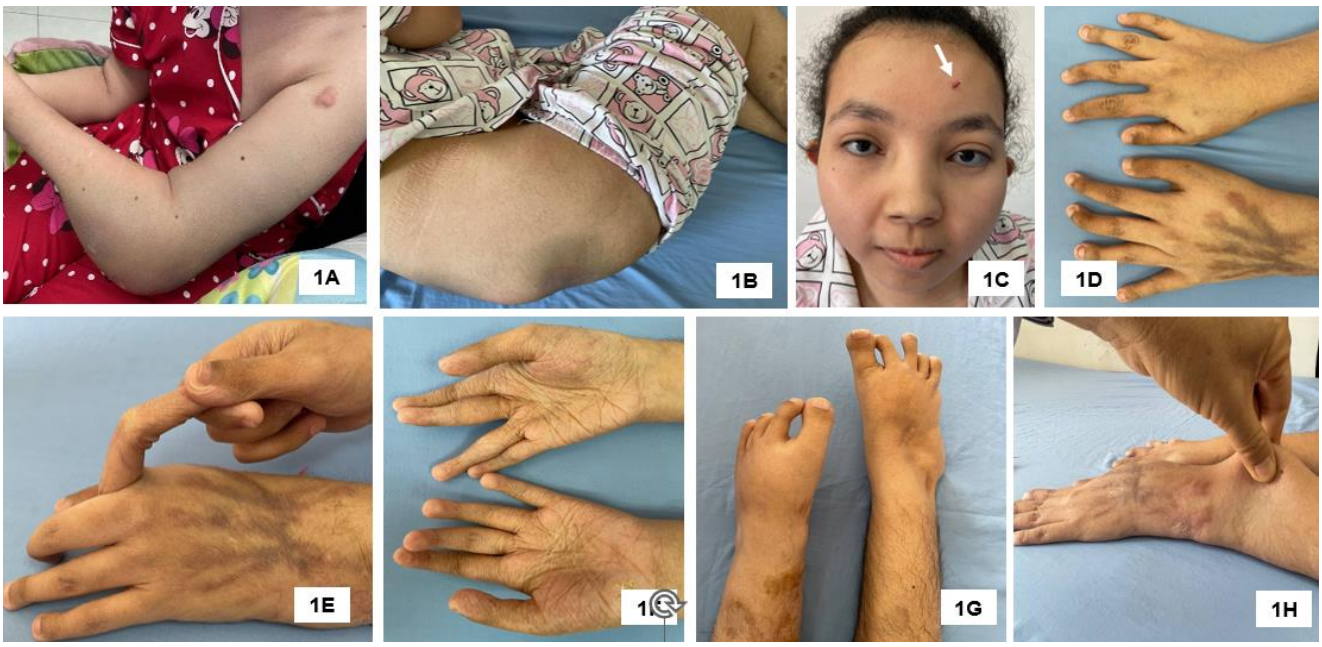

Figure 1 (A-H): Characteristic features of case 1.

Huge hematoma on the left arm and forearm (1A), large subcutaneous hematoma on lower flank (1B), abnormal craniofacial features with strabismus (exotropia), unusual red skin tag on the left forehead, thin upper lip vermillion, hypertelorism, and low-set ears (1C), Atrophic skins of hands (1D), variable extension and flexion contractures of distal and proximal interphalangeal joints with slender-shaped fingers (1D, 1E), atrophic fine palmar creases (1F), bilateral talipes equinovarus and shorter left foot with small features of feet (1G), hyperextensibility, bruisability and fragility with atrophic scars (1H).

Laboratory and imaging findings: Complete Blood Count (CBC) revealed severe anemia with a hemoglobin level of 6.8 g/dl, normal platelet count of $299x10^9$/l, whereas hemostatic testing was in the normal range such as Prothrombin Time (PT:12.3 seconds), Activated Partial Thromboplastin Time (APTT:32.3 seconds), Bleeding

Time (BT:3 minutes), Fibrinogen:2.5 g/l, Factor VIII: 95%, Factor IX:75%, von Willebrand Factor:Ristocetin CoFactor (vWF:RCoF:88.9%), von Willebrand Factor:Antigen (vWF:Ag:122.7%). The ultrasound showed a huge hematoma of the left arm descending to the forearm. The echocardiogram showed a normal result. A provisional diagnosis of EDS type I was made and conservative medical treatment was given by packed red cell transfusion, oral Desmopressin with daily vitamin C supplementation, and bandage support. Five days later, the size of the hematoma was reduced. The patient did well at the one-year follow-up, with less frequent hematoma and faster resolution under desmopressin and physiotherapy.

Case 2

A 14-year-old female of Cambodian origin was referred to our center with dysmorphic features and extremity deformities. In her past medical history, clubfeet and abnormal physical features were seen at birth. The patient archived head control and sat without support at 4 and 8 months, respectively, with a delay in acquiring the ability to control the large muscles for crawling, sitting, and walking. Surgical correction for her clubfeet was undergone at 2 years old. She had several admissions due to joint dislocations with hematomas, which were not large in size, and easy bruising. She walked independently but frequently fell due to weakness and contractures in her knees and ankles. Normal menstruation was reported (PBAC score<150). She is the third child in her family. Physical examination showed very thin skin with visible vessels on the thorax, bruised easily with minimal trauma. Broad forehead with an unusual red skin tag on the left side, hypertelorism, strabismus (exotropia), and low-set ears (Figure 2A). The variable extension and flexion contractures of distal and proximal interphalangeal joints (Figure 2C) with slender-shaped fingers (Figure 2B) and atrophic fine palmar creases (Figure 2D), bilateral talipes equinovarus (Figure 2E) associated with small features of feet, hyperextensibility, bruisability and fragility with atrophic scars (Figure 2E, 2F) were observed. The results of a neurological examination were also normal. By consultation with an ophthalmologist for progressive blurry vision for years, myopia and intra-ocular hypertension were noted. Medication for anti-glaucoma and glass-wearing. Laboratory and imaging findings showed normal CBC and hemostatic testing. The Echocardiogram was unremarkable. Initial clinical diagnosis is considered as EDS type I as her older sister, and conservative treatment was given. Oral desmopressin and daily vitamin C supplementation are prescribed.

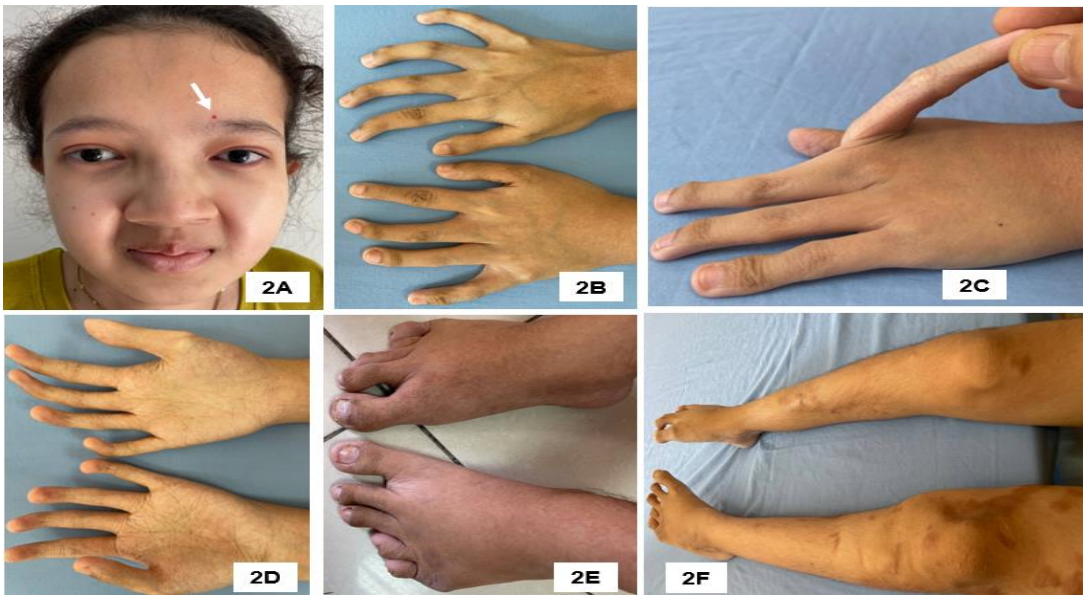

Figure 2 (A-F): Characteristic features of case 2.

Abnormal craniofacial features with strabismus (exotropia), unusual red skin tag on the left forehead, hypertelorism, and low-set ears (2A), Slender fingers (2B), multiple interphalangeal joint contractures (2C), and atrophic fine palmar creases (2D), bilateral talipes equinovarus with wide first web space with small features of feet (2E), hyperextensibility, bruisability and fragility, and atrophic scars (2E, 2F).

Genomic DNA analysis

After informed consent, genetic analysis of the patients was performed at the Department of Medical Genetics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. DNA was extracted from patients' peripheral blood specimens following standard protocols (QIAGEN GmbH). PCR amplification and Sanger sequencing of exon 1 of CHST14 (NM_130468.4) revealed a homozygous likely pathogenic novel variant, c.994_997dup, (p Pro333GlnfsTer23), in both patients (Figure 3, 4). The variant resulting in a frameshift change

starting at codon 333 from Proline to Glutamine and leading to a premature stop codon at nucleotide 356 (p Pro333GlnfsTer23), the peptide contains 356 aa instead of normal 376 aa residues. Parental blood was not available to confirm the carrier status.

Table 1: Clinical findings of the patients.

Variables	Case 1	Case 2
Sex	Female	Female
Age at examination (year)	17	14
Age of onset	Birth	Birth
Broad forehead	Yes	Yes
Skin tag on the left forehead	Yes	Yes
strabismus (exotropia)	Yes	Yes
Myopia	No	Yes
Vascular involvement	Yes	Yes
Easy bruising	Yes	Yes
Typical hand features	Yes	Yes
Interphalangeal joint contractures	Yes	Yes
Joint dislocations	Yes	Yes
Congenital talipes equinovarus	Yes	Yes
Small features of feet	Yes	Yes
Large hematoma	Yes	No
Independent walking	No	Yes

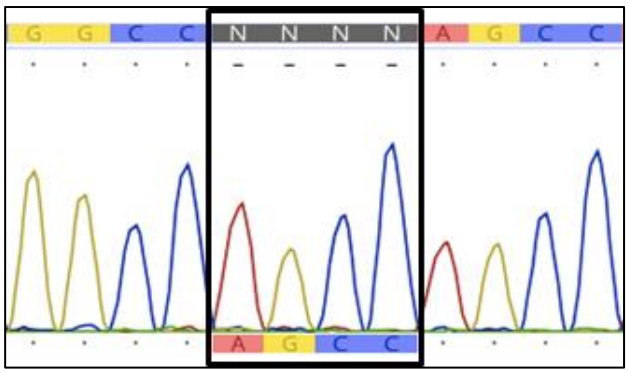

Figure 3: Genomic DNA analysis, patient 1.

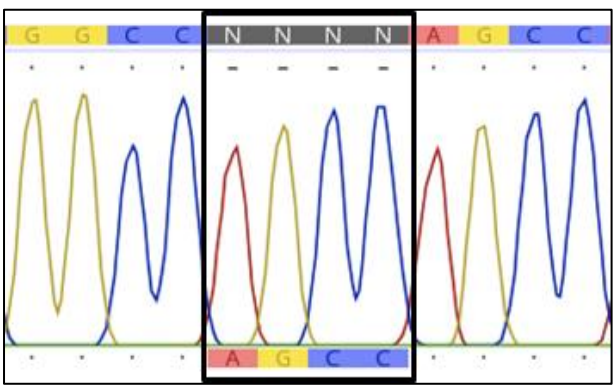

Figure 4: Genomic DNA analysis, patient 2.

The clinical findings for the two patients are shown in Table 1. In reference to the 2017 International. Classification of the Ehlers-Danlos syndromes, both patients were definitively diagnosed with homozygous (mcEDS).

DISCUSSION

The prevalence of Ehlers-Danlos syndrome is estimated to be between 1 in 5,000 and 1 in 100,000, based on the EDS subtype. Musculocontractural EDS is a rare type and is thought to affect less than 1 in a million people worldwide, as is myopathic EDS.[2-4] In 2017, a new international classification of EDS was proposed with 13 different variants.[5,6] Musculocontractural Ehlers-Danlos syndrome caused by pathogenic variants in CHST14 (mcEDS-CHST14) is a recently delineated connective tissue disorder characterized by congenital multiple contractures, and characteristic craniofacial and skin features including hypertelorism, short and down-slanting palpebral fissures, thin upper lip vermilion, low-set and rotated ears, and high palate, all of which were present in our patients. Progressive connective tissue fragility-related manifestations are reported.[1,2,4] To date, the diagnostic guidelines of EDS indicate major and minor criteria for each EDS subtype, phenotype due to the heterogeneity and overlap of phenotypes among subtypes, a genetic diagnosis is preferred for all subtypes except hEDS.

Here, we describe two siblings with a diagnosis of mcESD-CHST14. The mcESD is a genetic connective tissue disorder that causes multiple congenital contractures and characteristic craniofacial and skin features.[1,2] Although they are siblings with the same genetic cause, the clinical condition in patient 2 was apparently milder than that of patient 1, in which patient 2 has less frequent bleeding symptoms, no episode of large hematoma, proper standing, and independent walking. This finding supports the expression of intrafamilial variables in this disease. Moreover, we found a novel variant in CHST14 causing the classic phenotype of mcESD.

Characteristic cutaneous findings such as skin hyperextensibility, easy bruisability, skin fragility with atrophic scars, and increased palmar wrinkling, along with various skeletal findings including adduction-flexion contractures, talipes equinovarus, scoliosis, and joint dislocation which were also seen in our both cases. The mcEDS can cause different vascular complications, such as hematomas, arterial dissections and aneurysms, intracranial hemorrhage, gastrointestinal bleeding, and prolonged menstrual bleeding.[7] In contrast, our patients are likely presenting with recurrently subcutaneous hematoma. Generally, major coagulation's abnormality is not observed in mcEDS patients as were our cases.8 Additionally, the formation of large subcutaneous hematomas with only minor trauma represents a common and painful experience in mcEDS, increases the risk of

hypovolemia, and frequently requires surgical treatment. Because there is neither curative nor specific treatment for this syndrome, the treatment of this disease is focused on managing symptoms to prevent any potential life-threatening complications, such as fitness support with strengthening, gentle stretching, and proprioception exercises. However, some medications are proposed to prevent severe hemorrhage. Administration of 1-desamino-8-D-arginine vasopressin (DDAVP) after injuries has been reported to prevent further hematoma formation.[9] Desmopressin may help to normalize bleeding time for patients with Ehlers-Danlos syndrome, but further studies are needed to establish the safety and efficacy of this medication in the treatment and/or prevention of bleeding.[10] Daily intake of ascorbic acid (vitamin C) supplementation has been used, although it is not considered standard of care.

Lack of fundamental knowledge, diagnostic tools, and more effective therapeutics for mcEDS and other EDS disease subtypes will remain mysterious. EDS patients may endure years without proper diagnosis and treatments.[11] Indeed, the diagnosis of mcEDS in our cases was lately made at 17 and 14 years of age, respectively, by characteristic craniofacial and skin features and confirmed by molecular basis of mcEDS-CHST14, which was established with targeted mutation analysis. The identification of these two siblings could increase awareness of the condition and corroborate our knowledge regarding the clinical presentations. However, a delay in making an accurate diagnosis worsened the symptoms and the prognosis of these two patients.

CONCLUSION

In conclusion, the practitioners' awareness of this condition is generally poor, and most patients await years or, perhaps, decades before reaching the correct diagnosis, which consequently provokes inadequate management and serious complications, even life-threatening as our first two cases. In addition to promoting fitness support with strengthening, gentle stretching, and proprioception exercises, oral Desmopressin and daily vitamin C supplementation may help improving the quality of life of patients with mcEDS living in limited-resource countries like Cambodia.

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