Neurology Asia 2025; 30(3) : 943 – 946

A novel case with *CHST14*-related musculocontractural Ehlers-Danlos syndrome

[1]Didem Ardicli, [1]Aydan Degerliyurt, [1]Busra F. Genc, [2]Ofcan Oflaz, [3]Serdar Ceylaner

[1]Department of Pediatric Neurology, Ankara Bilkent City Hospital, Ankara, Turkey; [2]Department of Medical Genetics, Faculty of Medicine, Lokman Hekim University, Ankara, Turkey; [3]Intergen Genetics and Rare Diseases Diagnosis Center, Ankara, Turkey

Abstract

Musculocontractural Ehlers-Danlos syndrome (mcEDS) is a relatively newly identified and rare subtype of Ehlers-Danlos syndrome. Multiple congenital contractures, characteristic craniofacial features at birth or in early infancy, and typical cutaneous features are the major criteria for mcEDS. The cause is defects in the synthesis of dermatan sulfate and related proteoglycans, due to biallelic mutations in the *CHST14* and *DSE* genes. In addition to symptoms related to connective tissue, patients may have problems involving various organ systems such as the eye, heart, kidney, brain, and spinal cord. Herein, we present a patient of a 4-year-old girl with mcEDS in whom a novel mutation in the *CHST14* gene was identified by whole exome sequencing. The patient presented with hypotonia, motor delay, multipl joint deformities, kyphoscoliosis, and dysmorphic facial features. Initially, she was followed-up with a pre-diagnosis of congenital muscular dystrophy or congenital myopathy. Laboratory investigations revealed mildly elevated serum creatine kinase levels, hydrocephalus, tethered cord, and hydroureteronephrosis. mcEDS manifests itself with hypotonia, arthrogryposis, and motor retardation in newborns and young children, and it may be difficult to differentiate it from congenital neuromuscular disorders. The presence of accompanying typical dysmorphic features and multisystemic involvement should be a warning for the diagnosis of mcEDS.

Keywords: Ehlers-Danlos syndrome, *CHST14*, musculocontractural EDS, arthrogryposis, kyphoscoliosis, motor developmental delay

INTRODUCTION

Ehlers-Danlos syndrome is a group of hereditary connective tissue disorder characterized by skin hyperextensibility, joint hypermobility, and tissue fragility. It shows a wide clinical spectrum, from severe neonatal-onset life-threatening symptoms such as aneurysms or organ rupture to mild clinical findings in adulthood.[1] Advances in molecular genetics over the last two decades have shown that EDS is not only linked to genes encoding the collagen fibrillar structure and modifier enzymes but also to defects in various extracellular matrix (ECM) molecules. According to the 2017 EDS classification, there are 20 genes encoding 13 different subgroups.[2]

Musculocontractural EDS (mcEDS) is a rare EDS subtype, formerly known as "Adducted Thumb-Clubfoot Syndrome" caused by biallelic mutations in genes encoding the enzymes CHST14 (carbohydrate [N-acetylgalactosamine 4–0] sulfotransferase 14) and DSE (dermatan sulfate epimerase), which are involved in the biosynthesis of dermatan sulfate (DS), and the condition presents with distal arthrogryposis and muscular hypotonia in the neonatal period.[3,4] DS proteoglycans are expressed in various tissues and play roles in ECM organization, neurite outgrowth, wound healing, anticoagulation, cell adhesion and migration, and proliferation.[4] Mutations in the *CHST14* disrupt DS synthesis, leading to irregular and loose packing of collagen fibrils in connective tissue.[5] The presence of many different congenital malformations in mcEDS, in addition to symptoms related to connective tissue maintenance, supports the role of the *CHST14*/*DSE* genes and, accordingly, DS and DS-proteoglycans in multisystemic embryonic development.[3,5]

Address correspondence to: Didem Ardicli MD, Ankara Bilkent City Hospital, Children's Hospital, Department of Pediatric Neurology, Çankaya, Ankara, 06800 Turkey. Tel: +903125526000, e-mail: didem.aydogdu@gmail.com

Date of Submission: 6 April 2025; Date of Acceptance: 28 May 2025

https://doi.org/10.54029/2025yfc

Herein, we report a case with distinct phenotypic features of mcEDS, in which a novel pathogenic variant in the *CHST14* gene was identified by whole exome sequencing.

CASE REPORT

A 4 years-old girl presented with kyphoscoliosis and delayed motor development. She was delivered via cesarean section at 37th weeks with a birth weight of 2100 g, without perinatal complications. Prenatal history revealed oligohydramnios, hydrocephalus, and foot deformities, detected on fetal ultrasonography. She underwent serial casting due to pes equinovarus for 12 months, followed by two achillotomies, a shunt operation for hydrocephalus at 18 months, and a tethered cord surgery at the age of 4 years. She sat without support at 2 years of age. There was no consanguinity between the parents. Physical examination at the age of 4 years revealed a normal head circumference, weight, and height percentiles. She had prominent dysmorphic facial features including wide forehead, flat profile, blue sclerae, hypertelorism, down-slanting palpebral fissures, flat and wide nasal root, short nose, long philtrum, thin upper lip, small mouth, crooked teeth, micro-retrognathia, and low-set posteriorly-located ears with large anterior fontanelle. She also had skin hyperextensibility, kyphoscoliosis, adducted thumbs, elbow flexion contractures, wrist hyperlaxity, and bilateral pes equinovarus. (Figure 1a, 1b).

Laboratory investigations, including complete blood count, routine biochemistry, thyroid function tests, and basal metabolic work-up were within normal limits. Serum creatine kinase (CK) levels were mildly elevated, ranging from 242-514 U/L (upper limit: 211 U/L). Brain magnetic resonance imaging (MRI) showed Dandy-Walker malformation, thin corpus callosum, and triventricular hydrocephalus (Figure 1c, 1d). Spinal MRI revealed mild scoliosis, and a tethered cord. Echocardiography was normal. Hydroureteronephrosis was detected on urinary ultrasonography. Genetic tests, including chromosomal analysis and micro-array were normal. A pre-diagnosis of King-Denborough syndrome was suspected at first due to facial dysmorphism, joint contractures, kyphosis/scoliosis, and mild CK elevation. Whole exome sequencing revealed a homozygous novel likely pathogenic variant in the *CHST14* gene (NM_130468.4): c.403_410delinsGGCACCCA (p.Arg135_Leu137delinsGlyThrGln). The

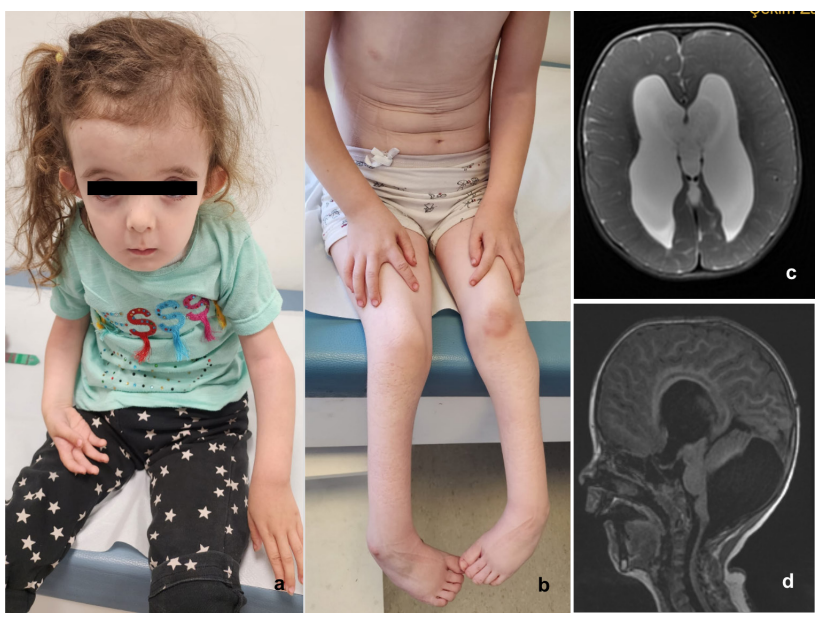

Figure 1. Physical examination of the case at the age of 4 years shows prominent dysmorphic facial features such as wide forehead, flat profile, blue sclera, hypertelorism, down-slanting palpebral fissures, flat and wide nasal root, long philtrum, thin upper lip, crooked teeth, micro-retrognathia, low-set ears (1a) with adducted thumbs, elbow flexion contractures, bilateral pes equinovarus, and skin hyperextensibility on the anterior abdominal wall (1b). Brain MRI shows Dandy-Walker malformation with thin corpus callosum, and triventricular hydrocephalus (1c, d).

mutation was found in heterozygous form in both parents. This variant was not found in the GNOMAD v4.1.0 and in ClinVar database. The homology model was investigated based on the basis of Q8NCH0 theme (Figure 2). When mutations were examined at the molecular level, it was observed that the hydrophobicity, charge, and H-bonding properties of the mutation site changed. As a result of these changes, it is expected that the mutation will destabilize the alpha helix motif, thereby potentially affecting the structure of the binding site for 3'-phosphoadenylyl sulfate, located approximately 14 Å away from the mutant region.[6,7] This structural change in the protein is believed to directly affect its function.

In the follow-up, patient's eye examination revealed high myopia, and glaucomatous cupping and glaucoma in both eyes, for which treatment was started. She also experienced prolonged bleeding following a dental extraction and developed bruising and hematomas, required hematology consultation. Her mental development was age-appropriate, and by 4.5 years of age, she could walk a few steps without support.

DISCUSSION

mcEDS is a ultra-rare and newly identified subtype of EDS. Symptoms such as skin hyperextensibility, joint laxity, and bleeding tendency, which are typical for EDS, become more evident in older children and adolescents.[8] In newborn and infancy, mcEDS is mostly characterized by facial dysmorphism, wide fontanelles, cleft lip/palate, cryptorchidism, atrial septal defect, pectus deformities, kyphosis/scoliosis, congenital contractures, hydrocephalus, tethered cord, and symptoms such as hypotonia, and motor developmental delay, which involve multiple systems. Therefore, the diagnosis of mcEDS is often delayed.[1]

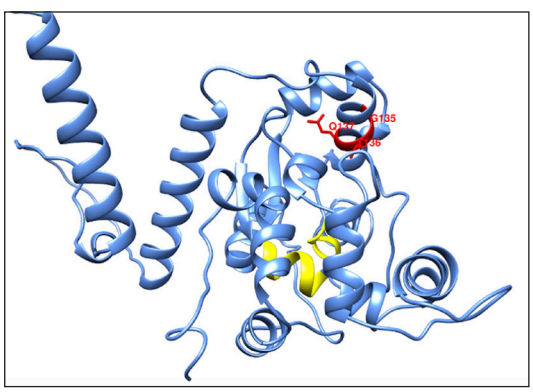

Figure 2. The mutant type (PDB: Q8NCH0) is the homology model. The mutation site is colored in red, and the binding site for 3'-phosphoadenylyl sulfate is colored in yellow.

Our case exhibited features like dysmorphic face, joint hyperlaxity, kyphoscoliosis, arthrogryposis, motor developmental delay, and mild CK elevation, initially leading to a suspected diagnosis of King-Denborough syndrome.[9] KDS is a rare myopathy characterized by the triad of dysmorphic features (hypertelorism, down-slanting palpebral fissures, malar hypoplasia, high-arched palate, dental crowding, micrognathia, low-set ears), myopathy, and malignant hyperthermia susceptibility, and *RYR1* mutations have been found in some of the cases.[9] Due to the overlapping symptoms of hypotonia, joint hyperlaxity, and contractures mcEDS can be clinically confused with congenital muscular dystrophies (CMD) or congenital myopathies. Some cases with mcEDS may show myopathic features on electroneuromyography, and may have elevated CK levels.[9,10] mcEDS should be considered in the differential diagnosis of children with congenital myopathies and CMDs, if the clinical picture includes multisystemic symptoms, facial dysmorphism, and hydrocephalus. It should be emphasized that the presence of congenital multiple contractures and characteristic craniofacial features are sufficient major criteria for the diagnosis of mcEDS in patients at birth or in early childhood.[2] Thus, a prolonged diagnostic process with unnecessary examinations can be prevented. Early diagnosis is crucial to provide genetic counseling, predict prognosis, and initiate early treatment for glaucoma and other serious complications that may arise.

DISCLOSURE

Ethics: Informed consent for publication and permission for the use of clinical photographs and radiological images was obtained from the patient and his parents.

Financial support: None

Conflict of interest: None

REFERENCES

1. Van Damme T, Colman M, Syx D, Malfait F. The Ehlers-Danlos syndromes against the backdrop of inborn errors of metabolism. *Genes (Basel)* 2022; 13:265. doi: 10.3390/genes13020265.

2. Malfait F, Francomano C, Byers P, *et al*. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet* 2017;175(1):8-26. doi: 10.1002/ajmg.c.31552.
3. Dündar M, Müller T, Zhang Q, *et al*. Loss of dermatan-4-sulfotransferase 1 function results in adducted thumb-clubfoot syndrome. *Am J Hum Genet* 2009;85(6):873-82. doi: 10.1111/ped.12878.
4. Janecke AR, Li B, Boehm M, *et al*. The phenotype of the musculocontractural type of Ehlers-Danlos syndrome due to CHST14 mutations. *Am J Med Genet A* 2016;170A(1):103-15. doi: 10.1002/ajmg.a.37383.
5. Kosho T, Mizumoto S, Watanabe T, Yoshizawa T, Miyake N, Yamada S. Recent advances in the pathophysiology of musculocontractural Ehlers-Danlos syndrome. *Genes* (Basel) 2019;11(1):43. doi: 10.3390/genes11010043.
6. Takano Y, Kondo HX, Nakamura H. Quantum chemical studies on hydrogen bonds in helical secondary structures. *Biophys Rev* 2023;14(6):1369-78. doi: 10.1007/s12551-022-01034-5.
7. Patgiri A, Jochim AL, Arora PS. A hydrogen bond surrogate approach for stabilization of short peptide sequences in alpha-helical conformation. *Acc Chem Res* 2008;41(10):1289-300. doi: 10.1021/ar700264k.
8. Voermans NC, Kempers M, Lammens M, *et al*. Myopathy in a 20-year-old female patient with D4ST-1 deficient Ehlers-Danlos syndrome due to a homozygous CHST14 mutation. [published correction appears in Am J Med Genet A 2013 Feb;161A(2):403]. *Am J Med Genet A* 2012;158A(4):850-5. doi: 10.1002/ajmg.a.35232.
9. Dowling JJ, Lillis S, Amburgey K, *et al*. King-Denborough syndrome with and without mutations in the skeletal muscle ryanodine receptor (RYR1) gene. *Neuromuscul Disord* 2011;21(6):420-7. doi: 10.1016/j.nmd.2011.03.006.
10. Minatogawa M, Unzaki A, Morisaki H, *et al*. Clinical and molecular features of 66 patients with musculocontractural Ehlers-Danlos syndrome caused by pathogenic variants in CHST14 (mcEDS-CHST14). *J Med Genet* 2022;59(9):865-77.doi: 10.1136/jmedgenet-2020-107623.