J Pediatr Res 2022;9(3):297-301
DOI: 10.4274/jpr.galenos.2022.51482

Case Report

A Life-Threatening Complication in a Patient with Ehlers-Danlos Syndrome Musculocontractural Type

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ABSTRACT

Ehlers Danlos syndrome musculocontractural type (mcEDS) is a rare hereditary connective tissue disorder caused by biallelic pathogenic variants in the *CHST14* or dermatan sulfate (DS) epimerase genes resulting in defective DS biosynthesis. It is characterized by congenital malformations and contractures, distinctive facial features and multisystemic fragility-related complications. To date, less than 100 patients with mcEDS have been reported. Vascular complications remain the major morbidity and may lead to mortality in the affected individuals. In this clinical report, we report on a currently 12-year-old boy with a novel homozygous CHST14 variant who presented with typical mcEDS symptoms and subsequently developed a life-threatening subcutaneous skull hematoma following a minor trauma, which required intensive care unit admission and surgical drainage along with several blood transfusions. This case expands the clinical and genetic spectrum of CHST14-related mcEDS which is essential for providing accurate prognosis, management and genetic counseling.

Keywords: EDS, Ehlers-Danlos syndrome musculocontractural type, CHST14, DSE, subcutaneous hematoma

Introduction

Ehlers-Danlos syndrome (EDS) is a genetically and clinically heterogenous connective tissue disorder mainly characterized by joint hypermobility, skin hyperextensibility and generalized connective tissue fragility. According to the revised "Villefranche classification", EDS is classified into 13 subtypes (1). Musculocontractural type EDS (McEDS) was first described clinically as "adducted thumb-clubfoot syndrome" in 1997 by Dündar et al. (2). Since 1997, less than 100 patients have been described (3,4).

Musculocontractural EDS is an autosomal recessive disorder which is caused by pathogenic variants in *CHST14/D4ST1* (carbohydrate sulfotransferase 14/Dermatan-4 sulfotransferase-1, MIM #601776) on chromosome 15q15 or dermatan sulfate epimerase [(DSE), MIM #605942] on chromosome 6q22 (3). Both genes encode enzymes involved in the biosynthesis of DS, a linear polysaccharide which forms DS-proteoglycans by attaching to core proteins and plays a role in cell surfaces and extracellular matrices. DS is an essential component of connective tissue and it is found mainly in skin, blood vessels, cartilage and tendons (4-6). Vascular complications which may sometimes be life threatening may be seen in these patients (7). In this clinical report, we described a mcEDS patient with a novel

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Received: 05.01.2022 **Accepted:** 17.04.2022

CHST14 variant who was admitted to hospital with massive subcutaneous hematoma after a minor fall complicated with hemorrhagic shock in the clinical course.

Clinical Report

The currently 12-year-old boy of Turkish origin with parental consanguinity was first referred to our center with dysmorphic features and extremity deformities at the age of 12 months. The patient was born to a 28-year-old healthy mother by spontaneous vaginal delivery at 35 weeks of gestation with a birth-weight of 2,400 g. The family history was significant for a younger sibling who was born at 27th gestational week with extremity deformities and passed away 30 minutes after delivery. The patient achieved head control, sat with and without support at 3, 6 and 9 months, respectively. He walked independently by 2 years. He was prone to ecchymosis and hematomas with minor accidents (Figure 1D). At his initial admission, the patient was hypotonic, and a large anterior fontanel, hypertelorism, adduction contracture of thumbs, hypoplastic interphalangeal flexural creases, bilateral talipes equinovarus, and cryptorchidism were noted on physical examination. The patient underwent surgery for talipes equinovarus and cryptorchidism at the ages of 6 months and 2 years, respectively. Ophtalmologic examination was normal. Transfontanelle and abdominal ultrasonography revealed cerebellar vermis hypoplasia and bilateral dilatation of the urinary collecting system, respectively.

Cranial magnetic resonance imaging (MRI) revealed Dandy-Walker malformation (Figure 2, A-C). Echocardiography showed mitral and tricuspid valve prolapse. His serum creatine kinase (CK) level was 643 U/L (normal range: 39-308 U/L). Muscle biopsy at the age of 4 years revealed mild dystrophic and myopathic changes. Dysmorphic features included brachycephaly, broad forehead, hypertelorism, down-slanting palpebral fissures, malar hypoplasia, blue sclera, low set ears, thin lips, and small mouth. He also had short neck and narrow shoulders. Easy bruising, skin hyperextensibility, joint laxity and adducted thumb led to a clinical diagnosis of mcEDS (Figure 1). At the age of 10 years, the patient was admitted to the emergency room with progressive bulging on the right side of his head after a minor trauma. Cranial computed tomography (CT) revealed a massive subgaleal hemorrhage on the occipitoparietal scalp with a 11.5 cm transvers in diameter without a skull fracture (Figure 2D, E). Two days later, follow-up CT image revealed prominent enlargement and upward displacement of the huge subgaleal hematoma

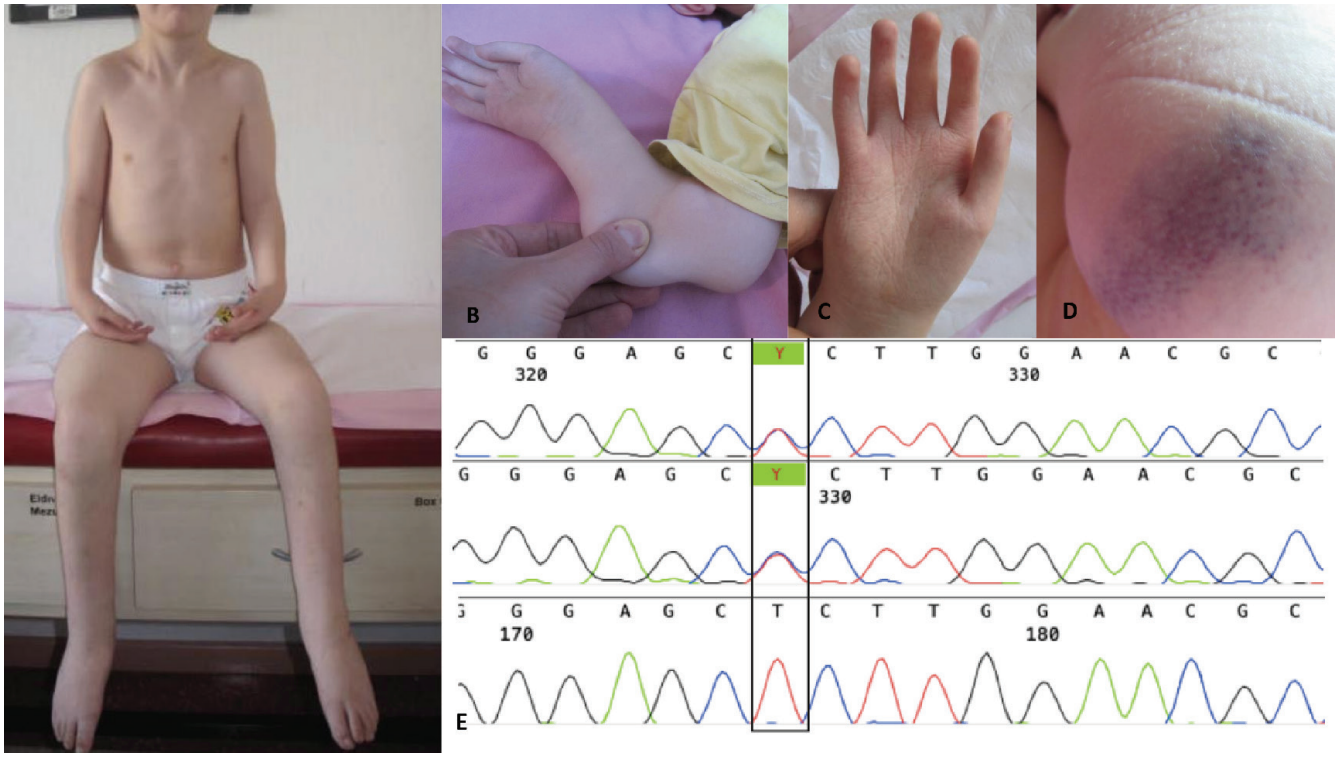

Figure 1. Please note the short neck, narrow shoulders, hypoplastic interphalangeal flexural creases, increased fine palmar creases, thenar and hypothenar atrophy, tapering of fingers and adducted thumb

(Figure 2G). The coagulation parameters were all normal. Scalp necrosis developed as a complication for which he was operated on twice. Necrotic tissue was debrided and a fasciocutaneous flap was applied. During the follow-up, he was admitted to hospital several times due to poor wound healing.

Materials and Methods

The parents' consent was taken for this report. Genomic DNA was extracted from a peripheral blood sample of the patient and his parents using QIAamp DNA Blood Mini Kit (Qiagen Valencia, CA) after informed consent was obtained. WES analysis was performed on the patient using an Ion Ampliseq Exome RDY kit and Ion Proton sequencer. Sanger sequencing on the patient and his unaffected parents was performed. Exon 1, which is the only coding exon of *CHST14*, was sequenced with exonic-intronic boundary using BigDye Terminator on an ABI 3500 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Exome Sequencing

Exome sequencing (ES) was carried out using an SeqCap EZ Exome+UTR Library and TruSeq Version 2 sequencing instruments. Exome data were analyzed using Varsifter uins, an exome-based targeted panel approach, to identify variants in known neuromuscular and *EDS* genes. Pathogenicity was assessed using the American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology guidelines for the interpretation of sequence variants, which includes population data, computational and predictive data using various lines of computational evidence (CADD, Polyphen, Sift) and segregation data.

Results

ES analysis revealed a novel homozygous missense variant in exon 1 of *CHST14* (NM_130468.8: c.644C>T, p.Pro215Leu) and this was confirmed by Sanger sequencing. Both parents were heterozygous (Figure 1). The pathogenicity of the identified variant was assessed using online prediction tools including CADD scores (https://cadd.gs.washington.edu/),PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), MutationTaster (http://www.mutationtaster.org), and SIFT (https://sift.bii.a-star.edu.sg/sift4g/SIFT4G_codes.html). The CADD score (GRCh37-v1.6) was calculated to be 32 (deleterious). The variant is classified as "likely pathogenic" according to ACMG 2015 (PM1, PM2, PP2, PP3), "probably damaging" according to Polyphen-2, "damaging" according to SIFT,

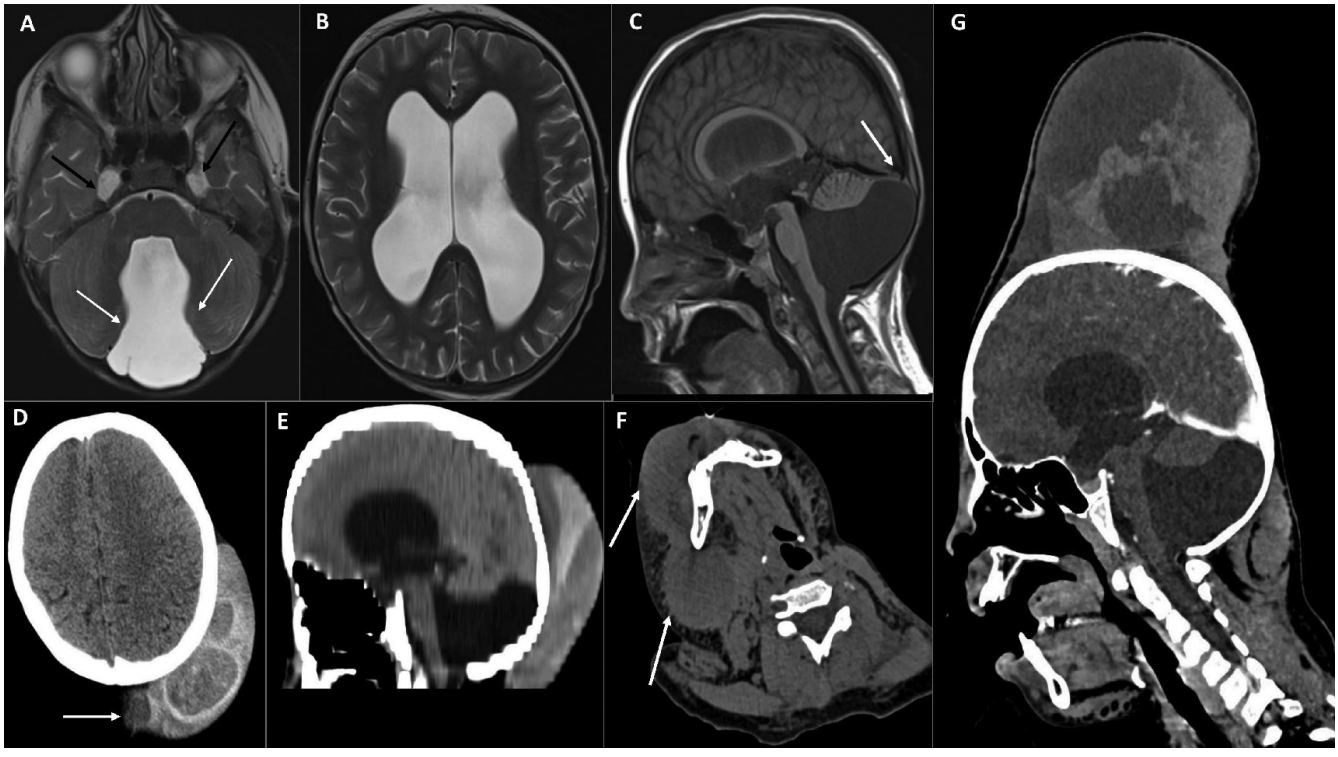

Figure 2. Cranial MR (A-C) obtained 7 years before trauma and CT imaging (D-G) obtained at the period of trauma. CT image reveals an acute subgaleal hematoma on the left parieto-occipital region with a 11.5 cm transvers in diameter without skull fracture (D)

MR: Magnetic resonance, CT: Computed tomography

and "disease causing" according to Mutation Tester. The variant is absent in the gnomAD browser.

Discussion

In this clinical report we described a patient harboring a novel homozygous *CHST14* variant, p.Pro215Leu, who experienced a life-threatening vascular complication requiring PICU admission.

Characteristic facial features of mcEDS include hypertelorism, short and down-slanting palpebral fissures, blue sclerae, thin upper lip vermilion, small mouth, low-set and rotated ears, and high palate, all of which were present in our patient. 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, pectus deformity and joint dislocation were also present in our patient. In the follow-up, he experienced joint pain as well as hyperalgesia to pressure, which is not a common finding among these patients.

Although intellectual disability is not common in mcEDS, motor developmental delay is frequently reported due to muscle weakness. Decreased fetal movements, severe hypotonia at birth, inability to suck, and swallowing difficulties are also frequently reported (3). In addition, patients are usually evaluated for myopathic diseases with muscle biopsy and EMG as was the case with the present patient. Our patient had thenar and hypothenar atrophy and a high serum CK level at the age of 4 years without clinically progressive weakness. Voermans et al. (8) reported a patient with generalized muscle hypotonia, a mildly elevated CK level and hypoplasia of the intrinsic hand muscles in whom muscle biopsy and EMG revealed myopathic involvement. Various central nervous system abnormalities including ventricular dilatation, cerebral and cerebellar atrophy, short corpus callosum, absence of septum pellucidum, spinal cord tethering, gray matter heterotopias, cortical dysplasia, hypoplasia of hippocampi, septo-optic dysplasia, and Dandy-Walker malformation are reported in mcEDS patients (3,4). Cranial MRI revealed Dandy-Walker malformation in our patient as well.

Vascular complications such as hematomas, arterial dissections and aneurysms, intracranial hemorrhage, gastrointestinal bleeding, perioperative hemorrhage, and prolonged menstrual bleeding can be seen in EDS patients. Large subcutaneous hematomas are also reported after minor traumas or even spontaneously in patients with mcEDS (7). Large subcutaneous hematomas were previously reported in 46 out of 58 (79%) mcEDS patients (3). No major coagulation abnormality is observed in mcEDS patients as was the case in our patient (5). Tendency to massive bleeding in mcEDS is generally explained by vascular abnormalities leading to vascular fragility which is thought to be caused mainly by a lack of DS (6,7).

DS, an important glycosaminoglycan necessary for fetal development, forms side chain of decorin which is an essential proteoglycan in connective tissues. It connects collagen fibrils, plays a role in the cell surface and plays role in matrix assembly and cell differentiation (9,10). It was observed that in the skin fibroblast samples of mcEDS patients, DS disaccharides on decorin was absent, while chondroitin sulfate (CS) was abundant (2,5,10). This imbalance between CS and DS is thought to be responsible for multi-systemic findings affecting various organ systems in early development (5,9,10). In *DSE*-mcEDS patients, clinical findings are milder because, although DS is absent on decorin in *CHST14*-mcEDS, small fractions are found in DSE-mcEDS. Also, it is thought to be compensated by *DSE2* enzyme (9,10). No genotype-phenotype correlation has been established in *CHST14*-mcEDS patients so far (3,9).

The missense variant reported in this study, c.644C>T; p.Pro215Leu, is located in a highly evolutionary conserved region in the sulfotransferase domain. The change of proline, a ring shaped amino acid, to leucine, a branched-chain amino acid, is thought to disrupt the protein structure. Another *CHST14* variant, p.Arg213Pro, located near the region of the variant detected in the present study was reported previously by Dündar et al. (2) and Janecke et al. (5). Janecke et al. (5) demonstrated a 50% reduction in levels of *CHST14* mRNA, decreased amounts of DS, reduced 4-sulfation and increased 6-sulfation in fibroblasts. New short D4ST1 species were demonstrated in cells expressing p.Arg213Pro, that arise as a result of proteolytic cleavage and different intracellular processing in these cells from wild type cells. Trace amount of D4ST1 which was thought to be due to premature degradation of new species before reaching golgi was found in transfected cells with this missense variant (2).

In conclusion, mcEDS is one of the hereditary connective tissue and muscle overlap disorders with a recognizable phenotype, yet with a challenging diagnosis on some occasions. The fragility of connective tissue renders patients susceptible for potentially life-threatening vascular complications requiring multidisciplinary care. Caution

must be taken and adequate supportive therapy should be provided accordingly.

Acknowledgements

We would like to thank Ying Hu for her help in the laboratory. We would like to thank NIH Intramural Sequencing Center for their help with the ES. CGB is supported by intramural funds of the National Institute of Neurological Disorders and Stroke, NIH.

Ethics

Informed Consent: Written informed consent was obtained from the patient's parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.D., P.Ö.Ş.K., R.G., G.E.U., K.B., G.H., Concept: T.D., P.Ö.Ş.K., Design: T.D., P.Ö.Ş.K., G.H., Data Collection or Processing: T.D., P.Ö.Ş.K., R.G., Analysis or Interpretation: S.D., R.G., C.B., Literature Search: T.D., P.Ö.Ş.K., G.H., Writing: T.D., P.Ö.Ş.K.

Conflict of Interest: The authors declared that there were no conflicts of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

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