CASE REPORT

Novel mutation in the *CHST14* gene causing musculocontractural type of Ehlers-Danlos syndrome

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SUMMARY

Musculocontractural type of Ehlers-Danlos syndrome (MC-EDS) is a recently recognised connective tissue disorder. MC-EDS is caused by homozygous or compound heterozygous mutation in the carbohydrate sulfotransferase 14 (*CHST14*) gene on chromosome 15q15. Herein, we report a case of a 3-year-old boy with MC-EDS in whom a novel mutation in the *CHST14* gene was discovered. Besides being the second report of this rare disorder from India, the child till 3 years has not had any bleeding tendency as described in the earlier reports of this disorder.

BACKGROUND

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of heritable connective disorders characterised by tissue fragility, joint hypermobility and skin hyperlaxity due to abnormal collagen synthesis.[1] Previously, EDS were classified into six major types based on clinical features and underlying molecular and biochemical defects.[2] Currently, 13 subtypes types have been described.[3–5] Musculocontractural type of EDS (MC-EDS) is a rare type which presents in the neonatal period with muscular hypotonia and distal arthrogryposis. It comes under the differential diagnosis of congenital connective tissue and neuromuscular disorders. It results from mutations in the carbohydrate sulfotransferase 14 (*CHST14*) gene involved in dermatan sulfate biosynthesis. Up till now, <50 cases have been reported in the literature.

We present a case of a 3-year-old boy born out of a consanguineous relationship who had characteristic clinical features and molecular analysis showed a homozygous mutation in the *CHST14* gene inherited from both the parents.

CASE PRESENTATION

A 3-year-old boy, born out of a third-degree consanguineous marriage was referred to us by the paediatric surgeons on suspicion of an underlying genetic disorder. He was being followed by them for bilateral hydronephrosis with bilateral pelviureteric junction obstruction (right >left). The child was born by normal vaginal delivery with a birth weight of 2.7 kg. The length and head circumference at birth were not recorded. At birth, he was noted to have bilateral clubfeet. The child started sitting at around 7–8 months of age however had difficulty in standing and walking. At the current age of 3 years also, he is able to stand with support only for few minutes. In the other sectors of development like cognition and language, the child showed appropriate gain and currently is able to tell short stories and enjoys playing with family members. Anthropometry at the age of 3 years showed weight to be 12.6 kg, length to be 88 cm and head circumference of 47 cm at 3 years of age. For the initial 1–1.5 years of life, the parents were mainly concerned about clubfeet in their child and were taking opinion of local practitioners for the same. During an episode of acute febrile illness, he was coincidently diagnosed to have hydronephrosis and in view of cryptorchidism noted by the examining physician was referred to our centre for evaluation and management.

On examination, the child had facial dysmorphism in the form of synophrys, hypertelorism, down slanting palpebral fissures, low set ears, thin upper lip, high arched palate and prominent nasolabial folds (figures 1A and 2A–C). He had tapering fingers with bilaterally thin and adducted thumbs (figure 1B). The deep palmer creases were absent and only a few fine creases were seen. Feet showed bilateral talipes equinovarus deformity (figure 1C). The skin was hyperelastic and hypermobility of fingers, elbow and knee joints was noted. Generalised hypotonia was present. The child also had bilateral cryptorchidism. No bruises or haematomas were seen and even on repeated asking the parents denied any bleeding tendency. As the child had congenital arthrogryposis in the form of adducted thumbs and talipes equinovarus and characteristic craniofacial features, the possibility of MC-EDS was considered and bidirectional Sanger sequencing for the *CHST14* gene was performed.

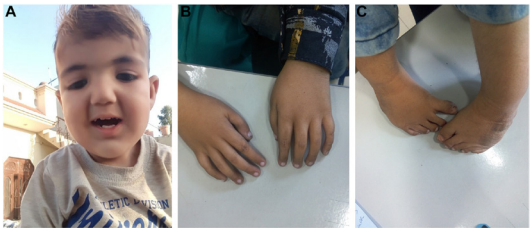

Figure 1 (A) Characteristic facial features of the index case with MC-EDS. Note synophrys, hypertelorism, down slanting palpebral fissures, low set ears, thin upper lip and prominent nasolabial folds. (B) Hands of child showing tapering fingers with bilaterally thin and adducted thumbs. (C) Feet showing bilateral talipes equinovarus deformity. MC-EDS, musculocontractural type of Ehlers-Danlos syndrome.

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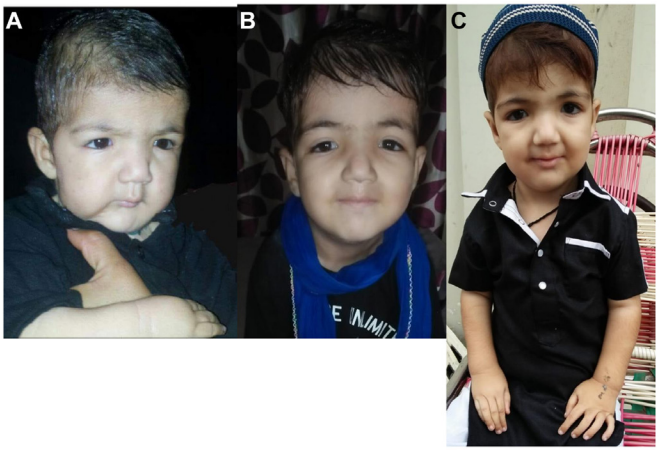

Figure 2 Photographs of the affected child taken at (A) 3 months, (B) 1 year, (C) 2 years.

INVESTIGATIONS

Molecular analysis of patient and parents

A homozygous non-sense mutation NM_130468.3:c.797dupA (p.Tyr266*) in exon1 of the *CHST14* gene was found (figure 3) in the child. This non-sense mutation results in premature truncation of the protein and is classified as pathogenic according to the ACMG (American College Of Medical Genetics) criteria.[6 7] Both the parents were tested for carrier status and found to be heterozygous for the non-sense mutation detected in the child. Hence, a final diagnosis of MC-EDS was made and genetic counselling was offered to the family.

DISCUSSION

EDS consist of a heterogeneous group of connective tissue disorders causing skin hyperelasticity, joint hypermobility and tissue fragility. The Villefranche Nosology which was published in 1998 identified six major subtypes and for most subtypes described in this classification, the causative genes were either genes involved in collagen biosynthesis or its post-translational modification. However, with the advent of next-generation sequencing, a number of other genes have been implicated in the pathogenesis of EDS and in 2017, the revised EDS classification has identified 13 subtypes of EDS. MC-EDS is a rare autosomal-recessive EDS which is characterised by predominant involvement of musculoskeletal system leading to hypotonia, joint hypermobility, hand and foot anomalies like clubfoot along with characteristic craniofacial dysmorphism.[8 9] It has also been referred to as adducted thumb-clubfoot syndrome (ATCS); adducted thumbs-arthrogryposis Dundar type, EDS type VIB (EDS6B), Dundar syndrome, arthrogryposis distal with peculiar facies and hydronephrosis (OMIM#601776). The craniofacial features include brachycephaly, hypertelorism, downslanting palpebral fissures, microcornea, prominent nasolabial folds, short philtrum, small mouth with thin upper lip, high arched palate, low-set and posteriorly rotated ears. In fact, our child resembled very much with the patients described by Janecke *et al* such that along with the other major signs such as clubfoot, skin hyperelasticity, cryptorchidism and hydronephrosis, we were very sure clinically of this diagnosis and therefore went ahead with the targeted sequencing of the *CHST14* gene.

MC-EDS is further classified into type 1 and type 2. MC-EDS type 1 and type 2 are caused by mutations in *CHST14* and dermatan sulfate epimerase (*DSE*), respectively.[10] Both these genes encode enzymes that are required for dermatan sulfate biosynthesis, a glycosaminoglycan. The *CHST14* gene encodes *N*-acetylgalactosamine 4-O-sulfotransferase 1 (D4ST1). D4ST1 catalyses the 4-O-sulfation of *N*-acetylgalactosamine (GalNAc) residues in dermatan sulfate. Dermatan sulfate is the main component of various connective tissues and it also interacts with heparin cofactor II and inhibits thrombin in vessels and

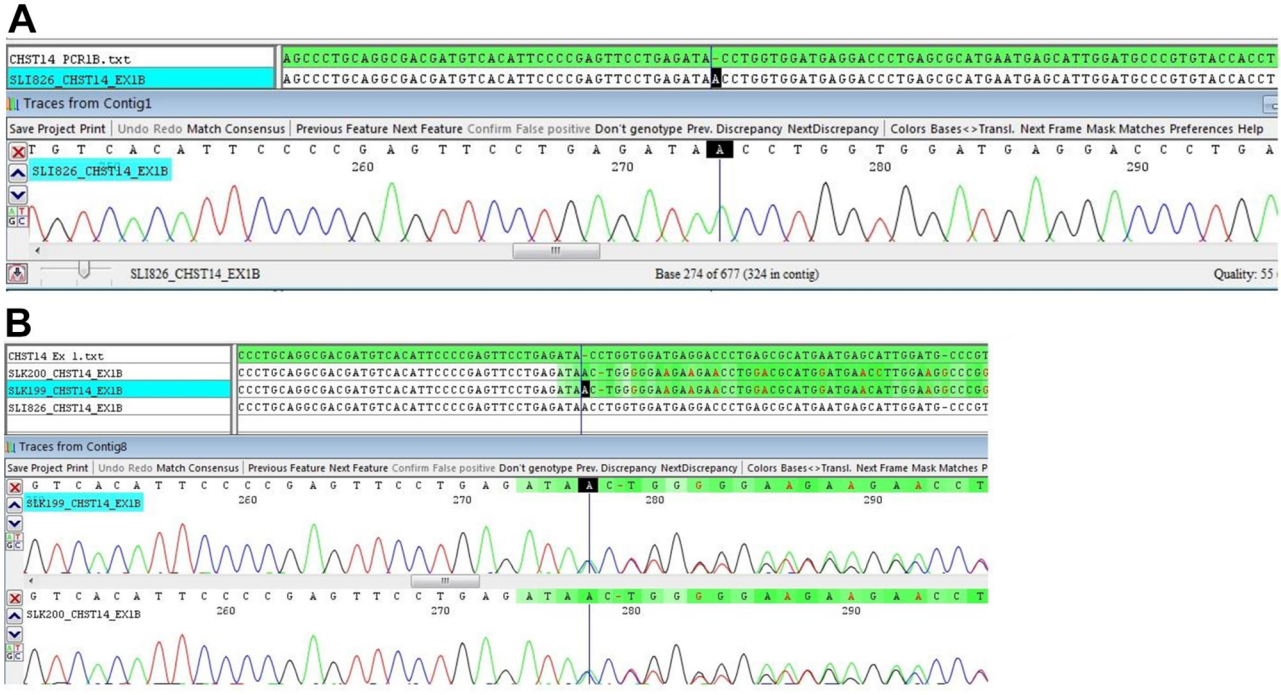

Figure 3 Bidirectional Sanger sequence of (A) proband showing homozygous non-sense mutation NM_130468.3:c.797dupA (p.Tyr266*) (B) parents showing the heterozygous carrier status.

modulates thrombus formation following trauma to endothelium.[11 12] *CHST14* mutations decrease D4ST1 activity by early protein truncation and altered intracellular protein processing. It results in the deficiency of dermatan sulfate leading to abnormal regulation of collagen fibrils assembly, producing generalised connective tissue disorder.[10 13 14]

CHST14 is a 1 exon gene coding for a 376 amino acid protein. Eight non-sense and 10 missense mutations have been described till now. Most mutations cause premature truncation of the protein leading to loss of its sulfotransferase domain and its role in dermatan sulfate synthesis. The mutation found in our case also is a non-sense mutation (NM_130468.3:c.797dupA (p.Tyr266*)) located in this functionally important domain of the protein where the amino acid residues are known to be highly conserved.

This syndrome is rare and only a few cases have been reported in the literature. Janecke *et al* had reviewed previously reported 34 patients of this syndrome with proven *CHST14* mutations in 31 and *DSE* mutations in 3 patients. In addition, they described seven more patients from four unrelated families. All these patients were identified based on characteristic craniofacial features and distal arthrogryposis.[10] Only one case of a 12-year-old girl of Indian origin with a homozygous 20 bp duplication (NM_130468.2:c.981_1000dup (p.Glu334Glyfs*107) has been described till now. This girl besides having the other well described features of this syndrome, suffered at 8 years of age from duodenal obstruction due to malrotation.[13]

While the child presented in our report demonstrates all the features described as always present in the review by Janecke *et al*, he at the age of 3 years has not had any subcutaneous bleeds or bleeding anywhere else in the body. Platelet count and partial thromboplastin and activated partial thromboplastin assays were performed, which were documented to be normal. However, careful follow-up on this and other complications such as retinal detachment and intestinal malrotation are warranted in all such cases.

In conclusion, physicians should consider MC-EDS as one of the differential diagnoses in evaluating children with distal arthrogryposis, joint hypermobility and craniofacial dysmorphism. The report shall increase the awareness about the syndrome and aid in its recognition.

Learning points

- Musculocontractural type of Ehlers-Danlos syndrome (MC-EDS) is a recently described connective tissue disorder with multisystem involvement. It is caused by homozygous or compound heterozygous mutation in the carbohydrate sulfotransferase 14 gene.
- Craniofacial dysmorphism along with distal arthrogryposis gives a clue toward a clinical diagnosis.
- DNA sequencing (Sanger/next-generation sequencing) is the diagnostic modality of choice.

OUTCOME AND FOLLOW-UP

The couple received the diagnosis of their child being affected by an autosomal-recessive disorder and are now aware of the recurrence risk and how to make prenatal diagnosis in future when they want to expand their family. As for the affected child, the parents as well as the paediatric surgeons were made aware of the risk of bleeding and the precautions to be hence forth taken when the child is taken up for surgery for hydronephrosis. We plan to follow-up the child 3–6 monthly and monitor for any complications.

Contributors All authors contributed to conception and design; drafted the manuscript; critically revised the manuscript; gave final approval; agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Patient consent Parental/guardian consent obtained.

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