CASE REPORT

Kyphoscolitic Type of Ehlers-Danlos Syndrome with Prenatal Stroke

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Background: The kyphoscoliotic type of Ehlers-Danlos syndrome (EDS type VIA) is an autosomal recessive disorder characterized by connective tissue dysplasia. **Case characteristics**: We report two children with perinatal stroke; accompanied by neonatal joint hypermobility, hypotonia; and early development of kyphoscoliosis. **Outcome:** Molecular analysis revealed a *PLOD1* gene mutation. Our definitive diagnosis was a EDS VIA. **Message:** Prenatal brain stroke is a rare clinical feature of EDSVIA.

Keywords: *Diagnosis, Neonatal hypotonia, PLOD1 gene, Scoliosis.*

The kyphoscoliotic type of Ehlers-Danlos syndrome (EDS type VIA) is a rare autosomal recessive disorder characterized by connective tissue dysplasia [1], and is due to a mutation in the *PLOD1* gene [1]. The syndrome's clinical characteristics are hypotonia associated with malignant kyphoscoliosis, hyperlaxity, hyper-elasticity, and skin fragility. Presence of vascular disorder during the neonatal period does not immediately lend itself to this diagnosis [2].

We, herein, report two cases of EDS type VIA with neonatal hypotonia, and prenatal brain stroke.

CASE REPORT

Two siblings born to third degree consanguineous parents are reported. When *Case 1* was 4½ years old, her sister (*Case 2*) was born. ***Table* I** reports the description of the two cases. An EDS diagnosis was suspected when *Case 1* was two years old. The diagnosis was based on joint hypermobility; delayed motor development (walking at 24 months, level 2 on Bimanual Fine Function; and on Gross Motor Function Classification System scales at 24 months). Suggestive facial dysmorphology, such as blepharochalasis, drooping cheeks, bluish sclera, tallness with a Marfanoid habitus, and arachnodactyly also contributed to this diagnosis. Her skin was hyperelastic with multiple bruises and a lassis venular. Furthermore she had a ligament laxity at 8/9.

After the second child's birth, our work-up used DNA blood sampling as well as a skin biopsy taken from the *Case 1* to investigate classic (II) and vascular (IV) types of EDS. The *COL3A1*, *TGFBR1*, and *TGBR2* genes exhibited no sequence abnormality. By using DNA blood samples from sisters, all coding exons and the neighboring intronic regions of the *PLOD1* gene were amplified from the DNA by PCR (polymerase chain reaction). These were then sequenced directly with flanking primers and *PLOD1* gene dosage analysis was performed by quantitative Real Time PCR including 19 amplicons in exon 1-19. We then took a blood sample from the parents. By qPCR a duplication of exons 10 and 16 was detected in the *PLOD1* gene, confirming the diagnosis of EDS type VIA in both sisters. This duplication was found present on both alleles.

DISCUSSION

Our report illustrates a rare phenotype of EDS type VIA with a prenatal brain stroke. When a combination of prenatal brain stroke and neonatal hypotonia is noted, the possibility of EDS should always be contemplated. Finding the cause of this hypotonia requires a rigorous diagnostic approach using the Dubowitz algorithm [3]. Neonatal hypotonia consistently appeared as a clinical symptom in a review of 12 cases with variations of kyphoscoliotic EDS phenotype [1].

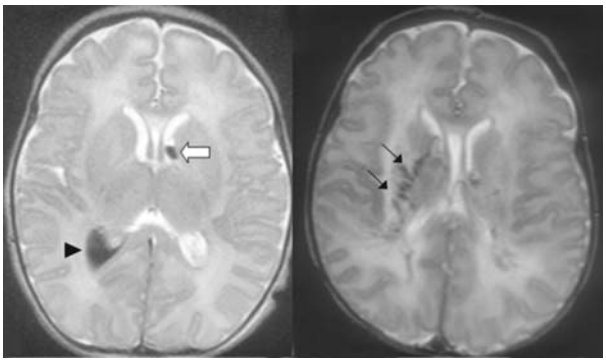
The presence of prenatal brain stroke and the absence of kyphoscoliosis noted in the neonatal period evoke an EDS type IV. This disease, often found in young adults, is linked to mutations in *COL3A1* gene and has a different phenotype [4]. An autosomal recessive mode of inheritance is most probable, especially with consanguineous parents, and we carried out *COL3A1* genetic screening by molecular analysis of skin biopsies. These proved to be negative, and we therefore discarded a diagnosis of EDS type IV [5].

TABLE I DESCRIPTION OF TWO CASES OF KYPHOSCOLITIC EHLERS-DANLOS SYNDROME

	Case 1	*Case 2*
Antenatal data	Without any complications	USG: Foot varus and suspected immobility at 24 wks ` gestation.
Mode of delivery	Spontaneous vaginal delivery	Induced vaginal delivery due to immobility and oligohydramnios
Gestational age	$37^{0/6}$ weeks of gestation	$37^{4/6}$ weeks of gestation
Apgar score, M1, M5, M10	10/10/10	10/10/10
Measures	Birth weight 2900 g (-1SD), 52 cm (+2SD) length, head circumference of 36 cm (+2SD)	Birth weight 298 g (-1SD), 54 cm (+3SD) length, head circumference of 37 cm (+2SD)
Physical examination at birth	Joint hyperlaxity, hip dislocation, arthrogryposis with talus feet and club hands, and poor gesticulation that was contrasted with good visual contact	Major generalized neonatal hypotonia, along with arthrogryposis. Her hands were locked in flexion and dislocated. The tegument appearance, joint hypomobility, and dysmorphology all resembled that of her sister's
Brain ultrasonography	Day 2 of life: IVH Grade IV	Day 3 of life: IVH grade IV
Brain MRI (***Fig*.1**)	Day 3 of life: Parenchymental extension (the right centrum semiovale) of germinative layer haemorrhage	Day 3 of life: Parenchymental extension (ischemic lesions of the anterior limb of the left internal capsule and right caudate nucleus) of germinative layer haemorrhage
Evolution	5 mo of age: kyphosis, followed by a rapidly progressive kyphoscoliosis which required a brace, and then a corset, Age 3 yr: surgical intervention	Developed kyphoscoliosis, required corset at 1 yr age. At age of 5 yr she presented with progressive multiple disabilities such as late walking at 24 months and diffused neuromotor disorders based on the Touwen's neuro-developmental examination.

No anomalies were found on ophthalmological examination, imaging studies or muscle biopsy. Karyotype was 46 XX for both. Thrombophilic workup normal.

The key diagnostic criteria were severe hypotonia, tendon laxity, scoliosis and scleral fragility. Assaying the enzymatic activity of *PLOD* from a skin biopsy showed 10-16 exon gene duplication. Neither strokes nor hip dislocation are typical of this syndrome with hip dislocation being found in only 25% of EDS type VI cases [1]. Similarly, in EDS type VI there is a possibility of vascular rupture. A prenatal case is described in a recent review of 15 patients and in an index case reported by Yis, *et al.* [6]. Tosun, *et al*. [2] suggest that although one of their patient's subdural and intraparenchymal hemorrhage could be attributed to a breech delivery or difficult birth, the patient's abnormal collagen structure may be a facilitating factor. Finally vascular ruptures are probably underestimated in this syndrome. In particular, 15% of mutant mouse *PLOD* -/- die of aortic dissections due to smooth muscle and collagen degeneration in the vessel wall [7]. Thus, a prenatal vascular event without any etiology with hypotonia and kyphosis ought to prompt a search for EDS type VI besides, *COL4A1/A2* mutations without EDS were already evaluated in the etiology of intraventricular hemorrhage detected *in utero* [4].



(*a*) (*b*)

FIG. 1 *Brain MRI of cases*: *(a) patient 1. Axial T2 sequence showing an cerebral intraventricular hemorrhage (arrow head) in T2 hypointensity, a subependymal hemorrhage (white arrow) and hemorrhagic infarction of the right centrum semiovale with diffusion restriction on axial DWI MRI images. (b) patient 2. Axial T2 sequences showing ischemic lesions of the anterior limb of the left internal capsule and right caudate nucleus, hypoT2 linear images may result of the periventricular and lenticulostriate vessels hemorraghic infarction (thin black arrow).*

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REFERENCES

1. Rohrbach M, Vandersteen A, Yiº U, Serdaroglu G, Ataman E, Chopra M, *et al*. Phenotypic variability of the kyphoscoliotic type of Ehlers-Danlos syndrome (EDS VIA): clinical, molecular and biochemical delineation. Orphanet J Rare Dis. 2011;23;6-46.
2. Tosun A, Kurtgoz S, Dursun S, Bozkurt G. A case of Ehlers-Danlos Syndrome Type VIA with a novel *PLOD1* gene mutation. Pediat Neurol. 2014;51:566-9.
3. Dubowitz L, Ricciw D, Mercuri E. The Dubowitz neurological examination of the full-term newborn. Ment Retard Dev Disabil Res Rev. 2005;11:52-60.
4. Parapia LA, Jackson C. Ehlers-Danlos syndrome : A historical review. Br J Haematol. 2008;141:32-5.
5. Kutuk MS, Balta B, Kodera H, Matsumoto N, Saitsu H, Doganay S, *et al*. Is there relation between COL4A1/A2 mutations and antenatally detected fetal intraventricular hemorrhage? Childs Nerv Syst. 2014;30:419-24.
6. Yiº U, Dirik E, Chambaz C, Steinmann B, Giunta C. Differential diagnosis of muscular hypotonia in infants: The kyphoscoliotic type of Ehlers–Danlos syndrome (EDS VI). Neuromus Disord. 2008;18:210-4.
7. Takaluoma K, Lantto J, Myllyharju J. Lysyl hydroxylase 2 is a specific telopeptide hydroxylase, while all three isoenzymes hydroxylate collagenous sequences. Matrix Biology.2007;26:396-403.