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Clinical Observations

A Case of Ehlers-Danlos Syndrome Type VIA With a Novel *PLOD1* Gene Mutation

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ABSTRACT

BACKGROUND: The kyphoscoliotic type of the Ehlers-Danlos syndrome is an autosomal recessive connective tissue disorder characterized by soft extensible skin, laxity of joints, severe muscle hypotonia at birth, and kyphoscoliosis. **PATIENT:** We describe a 3-year-old girl with the kyphoscoliotic type of the Ehlers-Danlos syndrome whose parents were cousins. She was born with breech presentation by vaginal delivery at term after a normal pregnancy. At birth she manifested hypotonia and congenital kyphosis. On the second postnatal day, subdural and intraparenchymal hemorrhages were detected by magnetic resonance imaging. During follow-up at 18 months of age, strabismus, umbilical hernia, kyphoscoliosis, joint laxity, bilateral hip dislocation, muscular hypotonia, and motor developmental delay. **RESULTS:** The cranial magnetic resonance imaging revealed periventricular leukomalacia and abnormal signal related to previous hemorrhage. Metabolic investigations and neuromuscular evaluation were normal, excluding other possible explanations of hypotonia. An analysis of urinary cross-links demonstrated an increase in the lysyl-pyridinoline to hydroxylysyl-pyridinoline ratio, suggesting the diagnosis of kyphoscoliotic type of the Ehlers-Danlos syndrome. Molecular analysis of the *PLOD1* gene revealed that she had a novel homozygous p.Pro622Argfs*3 (c. 1863_1864dupCG) mutation in exon 17 that is expected to cause complete loss of the enzyme lysyl hydroxylase 1 and to cause kyphoscoliotic type of the Ehlers-Danlos syndrome. **CONCLUSIONS:** We describe a child with the kyphoscoliotic type of the Ehlers-Danlos syndrome with a novel mutation of the *PLOD1* gene. Our observations suggest that vascular lesions in the neonatal period may be a rare additional clinical feature of kyphoscoliotic type of the Ehlers-Danlos syndrome.

Keywords: Ehlers-Danlos type VIA, novel mutation, vascular lesion, kyphoscoliosis, connective tissue disorder, hypotonia

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Introduction

The kyphoscoliotic type of Ehlers-Danlos syndrome (EDS type VIA, OMIM 225400) is an autosomal recessively inherited connective tissue disorder that has an approximate incidence rate of 1:10,000 live births. Carrier frequency is estimated to be 1:150. EDS type VIA is characterized by muscular hypotonia at birth, kyphoscoliosis at birth or of later onset, joint laxity, subluxation, skin hyperelasticity, and atrophic scars on skin.[1-5] Neonatal hypotonia and developmental delay are nonspecific features which lead to several diagnostic procedures causing a late definite diagnosis of EDS type VIA.

EDS type VIA results from deficient activity of the enzyme procollagen-lysine,2-oxoglutarate 5-dioxygenase 1 (lysyl hyroxylase 1 or PLOD1), a collagen-modifying enzyme, as the result of mutations in the gene *PLOD1* located on chromosome 1p36.2-36.3 (*PLOD1*, MIM153454). This enzyme hydroxylates lysyl residues in -Xaa-Lys-Gly- collagen sequences, which are essential for the formation of intra- and intermolecular collagen cross-links. Lysyl hydroxylase (LH) deficiency results in underhydroxylation of

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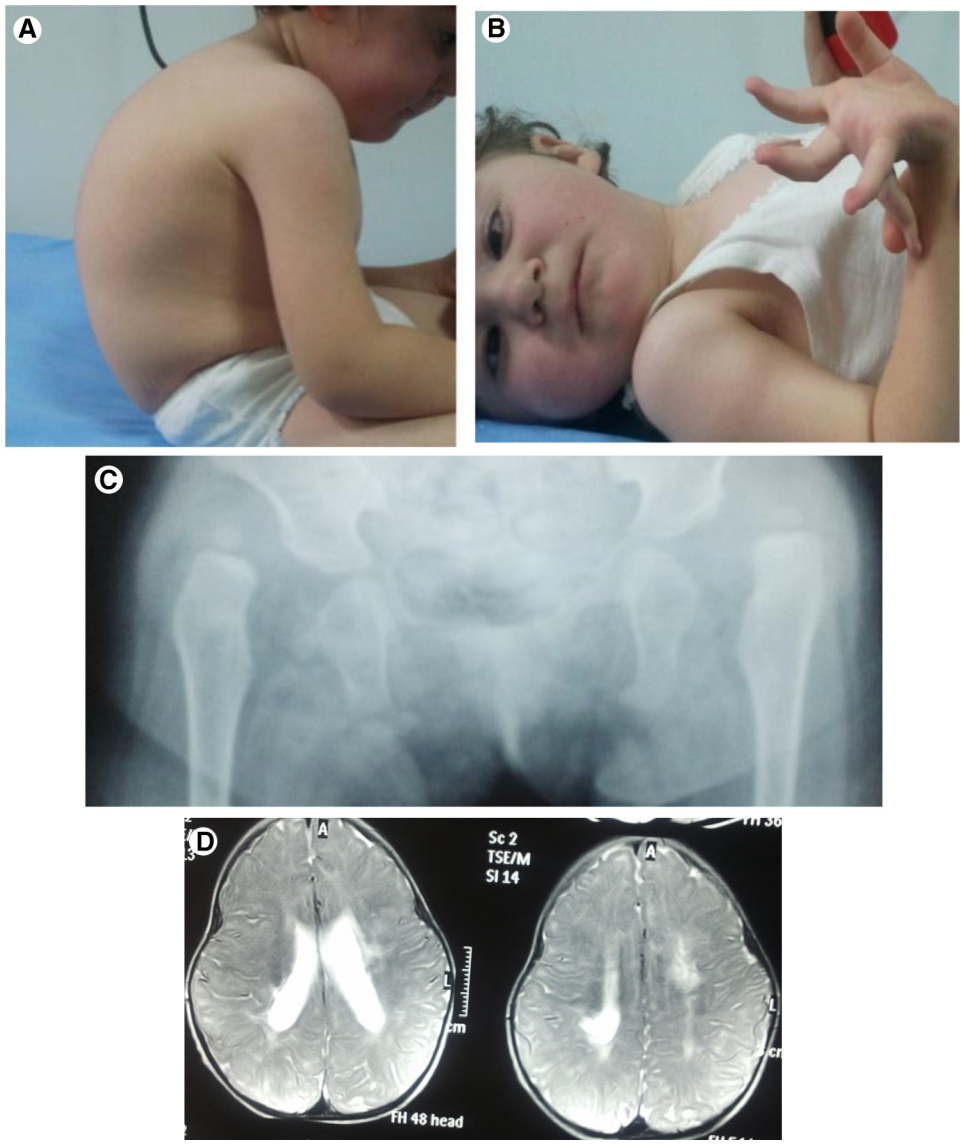

FIGURE 1.
(A, B) Kyphosis, joint hypermobility, and strabismus. (C) Radiography of the pelvis reveals bilateral hip subluxation. (D) Periventricular leukomalacia on T2-weighted axial magnetic resonance imaging. (The color version of the figure is available in the online edition.)

collagen lysyl residues and therefore, in impaired cross-link formation with consequent mechanical instability of the affected tissues, as seen in patients with EDS type VIA.[6,7] Diagnosis of EDS type VIA relies on the demonstration of an increased ratio of lysyl-pyridinoline (LP) to hydroxylysyl-pyridinoline (HP) cross-links in urine.[4,8]

Around 40 different mutations have been identified in the *PLOD1* gene, which contribute to LH deficiency and the clinical characteristics of EDS Type VIA.[5] In this report, we present a patient diagnosed with the EDS type VIA with vascular disorders in neonatal period due to a novel mutation in *PLOD1*.

Patient Description

The 18-month-old girl was referred to our clinic before strabismus surgery because of persistent leukocytosis and thrombocytosis and developmental delay. She was born 3100 g at term through vaginal delivery in breech position. Her parents were first degree cousins but otherwise healthy. On the second postnatal day, a cranial magnetic resonance imaging (MRI) identified subdural, intraparenchymal, and cerebellar hemorrhages.

Her motor developmental milestones were delayed: head control and unsupported sitting were approached at 9 months and 17 months of age, respectively. On physical examination, her weight was on third to tenth percentile, her height was on fiftieth to seventy-fifth percentile, and head circumference was on tenth to twenty-fifth percentile. Her head was trigonocephalic, and she had attached pinna. Her palate was very high and narrow. She had strabismus, thoracic kyphoscoliosis, pectus excavatum, umbilical hernia, bilateral hip dislocation, skin hyperelasticity, pronounced hyperlaxity of proximal and distal joints (Beighton score, 8/9[1]), and she had pes planus (Fig 1A-C). The deep tendon reflexes were hypo active. Muscle strength was 3 of 5 on upper extremities and 2-3 of 5 on lower extremities. Other system examinations were normal.

Her leukocyte and platelet values measured on different dates were 20300-28000/mm^3 and 690000-962000/mm^3, respectively. Routine biochemical tests, thyroid function tests, vitamin B12 levels, acute phase