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Polymicrogyria and intractable epilepsy in siblings with Knobloch syndrome and homozygous mutation of *COL18A1*

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Keywords

Knobloch syndrome; *COL18A1*; epilepsy; polymicrogyria

Introduction

Knobloch and Layer described a triad of symptoms – vitreoretinal degeneration, high myopia, and congenital encephalocele – in 5 affected siblings in a large consanguineous family.¹ The cause of what is now Knobloch syndrome (KS) was identified as mutation of *COL18A1*, the gene encoding collagen XVIII.² We present an unusual case of two brothers with severe global developmental delay, medically intractable epilepsy, diffuse polymicrogyria, and high myopia, born to non-consanguineous parents of Palestinian ethnicity. Although the brothers lack typically-associated skull defects, they were found to harbor a novel homozygous pathogenic mutation in *COL18A1*, leading to a diagnosis of KS on the severe end of the phenotypic spectrum. Epilepsy and brain malformations are uncommon in cases of KS; hence, this report expands the current clinical spectrum and reinforces the diagnostic utility of trio whole exome sequencing analysis in appropriately selected cases of polymicrogyria.

Patient Description

Patient 1 resulted from a full-term pregnancy and first presented at age 29 months with a cluster of six unprovoked seizures that were apparent generalized or secondary generalized

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Conflicts of interest: none

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tonic-clonic seizures. Magnetic resonance imaging (MRI) revealed extensive bifrontal polymicrogyria (Figure 1A); electroencephalogram showed bifrontal epileptiform sharps and slowing with bifrontal spikes. Epilepsy was initially treated with levetiracetam, which proved ineffective; seizures remained refractory to multiple medications alone and in various combinations including topiramate, divalproex sodium, clobazam, rufinamide, oxcarbazepine and lamotrigine. Ophthalmologic evaluation revealed bilateral esotropia, amblyopia, high myopia, and bilateral nystagmus. At age 3, the patient remained severely developmentally delayed, using approximately ten words; he could walk, run, and feed himself, but required a helmet for ongoing atonic seizures. At age 4, the patient was initiated on a 3:1 ratio ketogenic diet and was seizure-free after one month. By age 6, he had a 20-word vocabulary and could count to 20.

Patient 2 experienced a first seizure of life at age 16 months. MRI revealed similar extensive bifrontoparietal polymicrogyria with simplified gyral pattern, associated paucity of frontoparietal white matter, cerebral volume loss, and bilateral buphthalmos (Figure 1B). Routine electroencephalogram was normal. Developmental assessment revealed the patient could not walk or talk but could stand independently. At age 29 months, he progressed to intractable epilepsy, remaining intractable to levetiracetam, divalproex sodium, clobazam, and rufinamide. Ketogenic diet was partially effective; the patient continued to experience at least one drop seizure per day.

Whole exome sequencing revealed homozygosity for a c.4759_4760delTC (p.L1587Vfs*72) frameshift mutation in exon 40 of *COL18A1*.

Discussion

This *COL18A1* mutation is in the functional domain for collagenase NC10 (endostatin domain). Endostatin is a cleavage product of collagen XVIII that inhibits endothelial proliferation and angiogenesis.² C-terminal domain mutations of *COL18A1* may lead to polymicrogyria and resultant epilepsy by causing deficiency of all three collagen XVIII isoforms and endostatin and abnormal neuronal migration.³

Two other cases report the homozygous *COL18A1* deletion c.3514-3515delCT; these patients have polymicrogyria (bilateral frontal and temporal lobes), seizures and developmental delay.⁴ Recently, 4 sisters were identified to be compound heterozygotes with the *COL18A1* mutations c.3690G>A (p.W1230*) and c.4063_4064delCT (p.L1355Vfs*72). MRI of two of the sisters showed frontal polymicrogyria. All were reported to have seizures, varying degrees of intellectual disability, and lack of classical occipital encephalocele.⁵ A diagnosis of KS may be overlooked when presenting as polymicrogyria and epilepsy, highlighting the utility of whole exome sequencing in cases of undiagnosed brain malformation. Furthermore, the identification of KS, an autosomal recessive disorder, is critical for accurate genetic counselling regarding recurrence risk.

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Figure 1.
Axial T2 MRI of patient 1 (**A**) and patient 2 (**B**).