Autosomal recessive bilateral frontal polymicrogyria with ectopia lentis and chorioretinal dystrophy

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Abstract

Polymicrogyria is a type of cortical dysplasia due to cortical organizational defect. Bilateral polymicrogyria are distinct with genetic basis in a subset. We hereby report a case of bilateral frontal polymicrogyria (BFP) in association with chorioretinal dystrophy and ectopia lentis (EL) in a 26-year-old lady born of a consanguineous parentage. Her male sibling also had chorioretinal dystrophy and EL. This combination of autosomal recessive inheritance has not been reported earlier in the literature and suggests a role of connective tissue genes in BFP.

Key Words

Autosomal recessive, chorioretinal-dystrophy, ectopia lentis, frontal-polymicrogyria

Introduction

Polymicrogyria is a type of cortical dysplasia due to cortical organizational defect. Bilateral polymicrogyria are distinct with genetic basis in a subset. We report bilateral frontal polymicrogyria (BFP) in association with chorioretinal dystrophy and ectopia lentis (EL) of presumable autosomal recessive inheritance.

Case Reports

Patient 1
A 26-year-old female presented with epilepsy from 7 years of age. She also had a reduced vision from early childhood. Her initial generalized tonic clonic seizures later evolved as brief tonic right upper limb posturing suggestive of mesial frontal originating seizures. Magnetic resonance imaging (MRI) brain revealed BFP [Figure 1a-c]. EEG showed left parasagittal central-frontal spikes without focal slowing. Seizures were controlled on a combination of carbamazepine and clobazam.

She was born of second degree consanguineous parentage. Her antenatal, natal, and immediate postnatal periods were normal. There was a mild global delay in achieving some of her milestones. She completed her schooling with an average performance. There was no family history of similar illness in up to three generations other than her brother who had similar visual problems.

She had marfanoid body habitus. Head circumference was 54.5 cm, height 171 cm, and arm-span 177 cm. No skeletal or spinal deformities were evident. Cognitive skills were average without problems for routine daily activities. Neurologically, eye movements were normal. No focal neurological deficits were evident. Other systemic examination was normal.

Uncorrected visual acuity was counting finger close to face bilaterally. Slit lamp examination revealed infero-temporal subluxation of the lens in the right eye [Figure 1d, e and f]. Indirect ophthalmoscopy showed attached retina with optic disc pallor. There was diffuse retinal pigment epithelium (RPE) atrophy with tessellated background, arteriolar attenuation, and choroidal sclerosis in both the eyes [Figure 1g]. There were no RPE clumps or bony spicules. At 3 weeks review, the previously subluxed lens in the right eye had dislocated into the vitreous. Full field electroretinogram (ERG) showed reduced amplitude of scotopic (75-80%) and photopic responses (60-70%).

Hemogram, renal and liver functions, serum homocysteine, arterial blood gas, ammonia, lactate, aminoacidogram (urine and serum), ultrasonography of abdomen, electrocardiogram and echocardiography were normal.
Polymicrogyria syndromes are genetically heterogeneous. Autosomal recessive forms of generalized polymicrogyria have been earlier described. Two of the 13 patients described by Guerrini et al., also had consanguinity suggesting an autosomal recessive inheritance. However, there are no reports of these ocular abnormalities in association with BFP.

The molecular basis of polymicrogyria is beginning to be elucidated with the identification of a gene GPR56 and its mechanism responsible for bilateral fronto-parietal polymicrogyria. Chromosome 16q12-21 has also been linked to bilateral fronto-parietal polymicrogyria.[5,6] EL is heterogeneous and seen in a wide variety of systemic disorders associated with either structural or functional deficiencies of zonular ligaments. Marfan’s syndrome remains the commonest condition for heritable EL. The inheritance is autosomal dominant and very rarely recessive. The lens dislocation in the proband was asymmetrical and infero-temporal, unlike Marfan’s where dislocation is bilaterally symmetrical and superior temporal. Also, cardiovascular and skeletal markers of Marfan’s syndrome were absent. Association of the rod-cone dystrophy with Marfan’s is unknown. Homocystinuria was ruled out by normal serum and urine homocysteine levels. No thromboembolic symptoms were noted. Sulfite oxidase deficiency is a rare disorder associated with very early progressive neurological dysfunction with EL especially within 1 year of life. Hyperlysineemia was ruled out by normal aminoacidogram. Ehler Danlos syndrome (EDS) can occasionally be associated with EL and rarely with BFP.[9] Our patient did not have the dermatological, joint, vascular features or cataract to suggest EDS. Weill-Marchesani syndrome is a rare connective tissue disorder either as autosomal dominant or recessive with short stature, brachydactyly, and EL.[9] Very few cases of autosomal recessive EL with hereditary chorioretinal disorders have been reported.[10,11] None of these patients either had seizures or focal cortical dysplasia. Recently, mutations in a disintegrin-like and metalloproteinase domain with thrombospondin type 1 motifs-like (ADAMTSL-4) linked to chromosome 1q21 has been reported in autosomal recessive simple EL.[12] The ADAMTS super-family of proteins are important in cell migration, attachment and connective tissue organization.[13] Hypothetically, dysfunction of these proteins may lead to polymicrogyria.

**Conclusion**

This patient highlights the probable role of connective tissue genes in pathogenesis of polymicrogyria.
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