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Clinical Observations

Periventricular Nodular Heterotopia and Dystonia Due to an *ARFGEF2* Mutation

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ABSTRACT

BACKGROUND: Heterotopias are a neuronal migration disorder caused by extrinsic factors or by genetic mutations. When the location is periventricular, the most frequent genetic cause is the mutation in the *"filamin A2 gene"*, which is X-linked. New genes for periventricular nodular heterotopia with an autosomal inheritance pattern have been recently discovered. **PATIENTS:** We describe two siblings. The girl, who was prenatally diagnosed ventriculomegaly, had delayed development. At 6 months, she had no head control and variable muscle tone, alternating low axial tone with jerking movements. She became microcephalic. Magnetic resonance imaging at 12 months of age revealed enlarged lateral ventricles, periventricular nodular heterotopia, thin corpus callosum, a T_2-hyperintensity of the putamen and the thalamus, and a loss of volume of lenticular nucleus. At 18 months, she developed sporadic myoclonic seizures that were well controlled with valproic acid. Her younger brother also developed progressive microcephaly and psychomotor delay by 6 months. He exhibited axial hypotonia with a prominent dystonic-athetoid component. Magnetic resonance imaging at 15 months of age revealed asymmetric ventriculomegaly plus diffuse nodules lining the temporal horns, a thin corpus callosum, and hyperintensity signal in putamens. He had no seizures. **RESULTS:** Because of the association of microcephaly, developmental delay with dystonic movements, the imaging results, and the probable autosomal recessive inheritance pattern, genetic analysis was requested. This detected a homozygous nonsense mutation in *ARFGEF2* gene, at the DNA level c.388C>T in exon 4. **CONCLUSIONS:** The presence of dyskinetic movements in individuals with acquired microcephaly could be a manifestation of periventricular nodular heterotopia due to *ARFGEF2* mutation.

Keywords: cerebral palsy, dyskinesia, periventricular, heterotopia, *"ARFGEF2"* mutation, psychomotor delay, extrapyramidal, putamen
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Introduction

Heterotopias are a neuronal migration disorder characterized by the placement of a subset of neurons in an abnormal location. They are classified into three groups, depending on the location of the aberrant neurons: periventricular nodular heterotopia (PNH), subcortical heterotopia, and leptomeningeal heterotopia.[1] PNH can be caused either by extrinsic factors such as infections or other prenatal insults or by genetic mutations.

The most frequent genetic cause of PNH is a mutation in the "*filamin A2* gene", which has an X-linked autosomal dominant pattern of inheritance. New genes for PNH have been recently discovered which are often associated with more seriously affected individuals.

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We describe two siblings, a boy and a girl, with PNH. They have severe psychomotor retardation, microcephaly, and a major movement disorder that resembled athetoid-dystonic cerebral palsy.

Patient Descriptions

This girl was born at term, but ventriculomegaly was diagnosed with a routine ultrasonography at 32 weeks of gestation. She was born via normal delivery with a normal birth weight of 3250 g and a head circumference of 35 cm (75th percentile). Her neurological examination at birth was normal, and her ventriculomegaly was confirmed by transfontanel ultrasonography, which also demonstrated a thin corpus callosum. Congenital toxoplasmosis, cytomegallovirus, rubella, herpes virus, and syphilis infections were discarded (TORCH) infections were eliminated. About the family history, her father and her maternal grandfather are cousins.

Since the first months, her development was delayed. At 10 months, head circumference was 42 cm (<2 S.D.), and she had variable muscle tone, alternating low axial tone with jerking movements of the extremities exacerbated by the emotions. She had no sitting ability and tended to lingual protrusion. Deep tendon reflexes were normal, and she had difficulties for grasping, holding on objects just for a few seconds, due to dystonia. Development quotient score was performed, resulting 4 months in movement, posture, and language and 3½ months in cognition, coordination, and use of objects, as well as in socialization.

At 12 months, brain magnetic resonance imaging (MRI) revealed enlarged lateral ventricles, PNH along the ependyma, and a thin corpus callosum, although completely formed. She also exhibited T2-hyperintensity of the putamen and the thalamus, with a loss of volume of lenticular nucleus.

Metabolic testing was normal. She was diagnosed of dyskinetic cerebral palsy secondary to cerebral malformation. At 18 months of age, she developed sporadic seizures consisting of a widespread increase in muscle tone preceded by crying that lasted about 2 minutes. During the episodes, she was lying in the prone position and she raised her legs. The electroencephalography demonstrated a bitemporal slow background with diffuse epileptiform activity in both hemispheres. Involuntary movements were observed in electroencephalography-video that could correspond to myoclonus. Also slowing diffuse background overlapping with spike-wave complexes were found during sleep. The seizures were controlled with valproate.

Now age 3.5 years, she is not able to sit and has a dystonic extrapyramidal movement disorder.

This girl's younger brother, born 2 years later, had normal transfontanellar ultrasonography at birth, and he had no incidents during the neonatal period. However, progressive microcephaly was noted at 6 months, being 1 month later the head circumference less than the third percentile.

His examination at this age documented axial hypotonia with fluctuating limb tone, tending to wrist overpronation and prominent dystonic-athetoid component. At 9 months, his psychomotor delay was important, and his development quotient score corresponded to 4 months. MRI at 15 months revealed asymmetric ventriculomegaly (right ventricle 18 mm and left 14 mm) plus diffuse nodules lining the temporal horns, which seemed consistent with bilateral PNH. It also showed thinning of the corpus callosum mainly in the posterior half and a loss of volume of the lenticular nuclei with hyperintensity signal in each putamen (Figure).

Unlike his sister, this boy has not developed seizures. He and his sister attend early care programs and have received physiotherapy since the beginning. They have no feeding problems, although they have low weight percentiles.

With the clinical picture of acquired microcephaly, developmental delay, prominent dystonic movements, the imaging results, and the probable autosomal recessive inheritance, genetic analysis was requested, detecting a homozygous nonsense mutation in *ARFGEF2* gene, at the DNA level c.388C>T in exon 4.

Discussion

PNH is a cerebral malformation characterized by the presence of neuronal nodules along the lateral ventricles. It can be unilateral or bilateral, and the nodules can be positioned anterior, posterior, or along the surface of the ventricles. It can occur alone or in combination with other malformations of the nervous system (polymicrogyria, microcephaly, and hydrocephalus) or with cardiac or limb abnormalities.

Traditionally, PNH was included in the malformations because of abnormal neuronal migration. However, in the updated classification for malformations of cortical development, made by Barkovich et al.,[2] periventricular heterotopia was included as a subcategory of malformations resulting from abnormalities of the neuroependyma, which

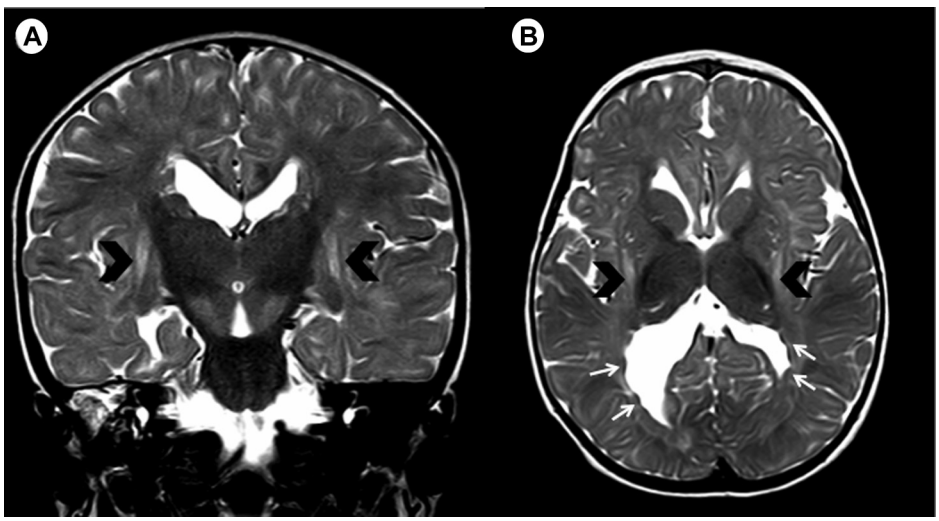

FIGURE.
Brain MRI of the younger brother at age 15 months. (A) Axial T_2-weighted TSE images and (B) coronal T_2-weighted TSE reveal asymmetrical ventriculomegaly and bilateral periventricular nodular heterotopia with the same signal intensity of gray matter (white arrows). Images also reveal bilateral loss of volume of the lenticular nucleus and hyperintensity of the putamen (black arrowheads).