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Periventricular heterotopia with complete agenesis of the corpus callosum

A case report

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Sirs: Periventricular heterotopia (PH) is an absence of or incomplete neuronal migration characterized by ectopically placed neurons along the lateral ventricle and beneath an otherwise normal appearing cortex. A single case report has previously described an association between PH and complete agenesis of the corpus callosum (ACC). The affected individual had a balanced translocation involving two zinc-finger transcripts *KIAA1803* and *ASXL2*[1]. Here we report the second reported case of a child with PH and complete ACC.

The baby girl was born by an elective caesarean section at 39 weeks gestational age (GA) to a 27-year-old gravida 2, para 2 mother. The Apgar scores were 9 and 9, the birth weight was 2608g, and the head circumference was 32.5 cm. The prenatal course was notable for cold infections and a history of alcohol use in the mother. An alpha-fetal protein level was elevated at 14 weeks GA but the amniocentesis at 18 weeks GA revealed a normal female karyotype. An ultrasound at 35 weeks GA demonstrated unexpected agenesis of the corpus callosum with ventriculomegaly.

On general examination, the newborn baby appeared entirely normal with no dysmorphic features and no neurocutaneous stigmata. On neurologic examination the baby had normal truncal and upper and lower extremity tone. She had good hand and foot grasps and a normal and symmetric Moro sign. Rooting and suckling reflexes were intact. She had good strength throughout. She was able to fix briefly on the face and tracked intermittently.

No chorioretinal lesions or retinal colobomas were identified by ophthalmological examination. A skeletal survey was normal without costovertebral abnormalities. Brain MRI revealed complete ACC, bilateral PH and ventriculomegaly along the posterior aspect of the lateral ventricles, which were indistinguishable from the previously reported case [1] (Fig. 1).

Exonic and exon/intron boundary sequencing by PCR was performed on genomic DNA using primers generated for the exons of *ASXL2 and KIAA1803* and followed previously published methods [2]. Consensus genomic sequences for *ASXL2* and *KIAA1803* were obtained through the NCBI and UC Santa Cruz databases and primers were designed using the Primer 3 software program. Over 95% of the amplified exons from the patient DNA were compared with the genomic sequence for each gene. Exonic sequencing of the two genes associated with PH and complete agenesis of the corpus callosum (ASXL2 and KIAA1803) failed to detect any mutations in the coding sequence. Thus, no balanced translocation was seen on karyotyping and no intragenic mutations were appreciated on sequencing.

The genetic causes underlying PH with ACC are not known. While ACC is associated with over 50 human congenital syndromes [3], very few of these disorders are characterized by complete ACC (Aicardi, acrocallosal, Andermann and Shapiro syndromes). Moreover, these disorders are uniformly associated with other clinical findings. In this same context, PH can be viewed as a relatively rare malformation of cortical development, caused by mutations in two genes filamin A (*FLNA*) and *ARFGEF2* (4, 5). The X-linked dominant form of PH due to *FLNA* can be associated with thinning of the corpus callosum, but has never been seen with complete ACC and posterior ventriculomegaly[4]. The autosomal recessive form of PH due to *ARFGEF2* is associated with microcephaly and shows no changes in the corpus callosum [5]. Collectively, the radiographic findings of both PH and complete ACC have only been reported in a single case

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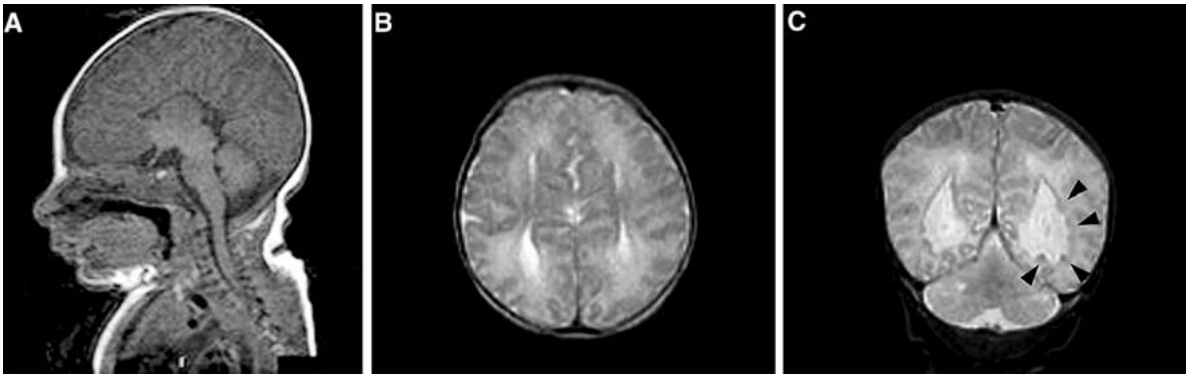

Fig. 1 Radiographic phenotype. (A) Sagittal T1-weighted MR image shows complete absence of the corpus callosum with relative preservation of the brain parenchyma, brain stem and spinal cord. (B) Axial T2-weighted MR image shows ventriculomegaly in the posterior portion of the lateral ventricles. (C) Coronal T2-weighted MR image shows bilateral nodular heterotopia (arrowheads) can be appreciated along the wall of the lateral ventricles

involving a balanced translocation of two zinc-finger encoding genes, *ASXL2* and *KIAA1803*, indicating that this is an extremely rare disorder. In the present patient case with PH and ACC reported here, the absence of a coding mutation for either gene suggests that the genetic basis of this disorder is likely heterogeneous in nature.

While clearly speculative, a common developmental mechanism may contribute to the development of both PH and ACC. In PH, some disruption in cell adhesion-extracellular matrix interactions has recently been proposed to contribute to the impairment in the early onset of neuronal migration [6]. The binding of FLNA to integrins [7], and the regulation of vesicle transport of adhesion-related proteins and lipids by ARFGEF2 [5] are probably required for the integrity of focal adhesions within neural progenitors along the neuroependyma or the extension and attachment of the leading process of migratory neurons onto radial glia. Callosal axon guidance during development of the corpus callosum similarly requires the extension of neurites and interaction of these growth cones with the extracellular matrix (ECM). Thus, much in the same manner by which neurons extend a leading process to initiate migration, callosal axons must extend processes to reach the contralateral hemispheric target; and processes from both migratory and callosal neurons must interact with the surrounding ECM.

Based on radiographic findings alone, PH and ACC represent a heterogeneous disorder. The mechanisms resulting in these two distinct malformations of cortical development, however, are likely to be related and identification of causal genes will provide better insight into this disorder.

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