COL4A1 and fetal vascular origins of schizencephaly

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Classically described by Yakovlev and Wadsworth[1] in 1946, schizencephaly is a rare congenital brain malformation characterized by clefts of the cerebral mantle extending from the pial surface to lateral ventricles lined by heterotopic gray matter. Observed associations between schizencephaly and in utero infections, trauma, fetal exposure to teratogens, and death of a monozygotic twin support the hypothesis that schizencephaly is the consequence of fetal vascular disruption during the late first or early secondary trimester of pregnancy.[2]

Recent reports have identified *COL4A1* gene mutations in as many as 50% of patients with schizencephaly.[3] Collagen α-1 (IV) is a member of the type IV collagen family that comprises the major structural component of basement membranes that line the endothelial layer of blood vessels.[4] First described by Gould et al.[5] in 2005 as a cause of perinatal cerebral hemorrhage in mice, *COL4A1* mutations in humans can present with a wide range of phenotypes with disease onset as early as in the fetal period.[4]

We report a rare case demonstrating the sequential development of schizencephaly on MRI from an in utero acute focal vascular event.

Case report

A 27-year-old primigravida mother had abnormal echogenicity detected in the right anterior parietal region of the brain on routine fetal ultrasound at 19 weeks' gestation. Fetal MRI at 21 weeks' gestation demonstrated acute diffusion restriction in the same region in a right middle cerebral artery territory distribution suggestive of ischemic infarction (figure). In addition, susceptibility foci were noted in the right frontotemporal lobes and basal ganglia representing hemorrhagic transformation of infarct. Follow-up MRI at 35 weeks' gestation identified focal volume loss in the region of previously documented ischemic injury with a parenchymal cleft extending to the ventricular margin, consistent with open lip schizencephaly. TORCH and thrombophilia screens were normal. MRI at 4 weeks postnatal age showed parenchymal volume loss, porencephaly, and schizencephaly in affected regions. The combination of ischemic and hemorrhagic brain injury prompted *COL4A1* mutation analysis, which revealed a de novo heterozygous mutation in intron 9 of the *COL4A1* (α1) gene. At 6 months of age, the infant had developed clinical microcephaly and left hemiparesis. Subsequent investigation revealed no structural ophthalmologic, cardiac, or renal abnormalities.

Discussion

The development of the human cortex is a dynamic but staged process whereby stem cells differentiate into neuroblasts or glial cells. Neuroblasts migrate from the periventricular germinal matrix towards the cortex to form the cortical plate, and the cortex becomes organized via synaptogenesis and apoptosis. Neuronal migration occurs in an overlapping fashion from approximately the 6th–24th gestational week.[6]

It is theorized that in cases of schizencephaly, a vascular insult prior to the neuronal migration period damages radial glial cells, which normally act as a guide for migrating neuroblasts leading

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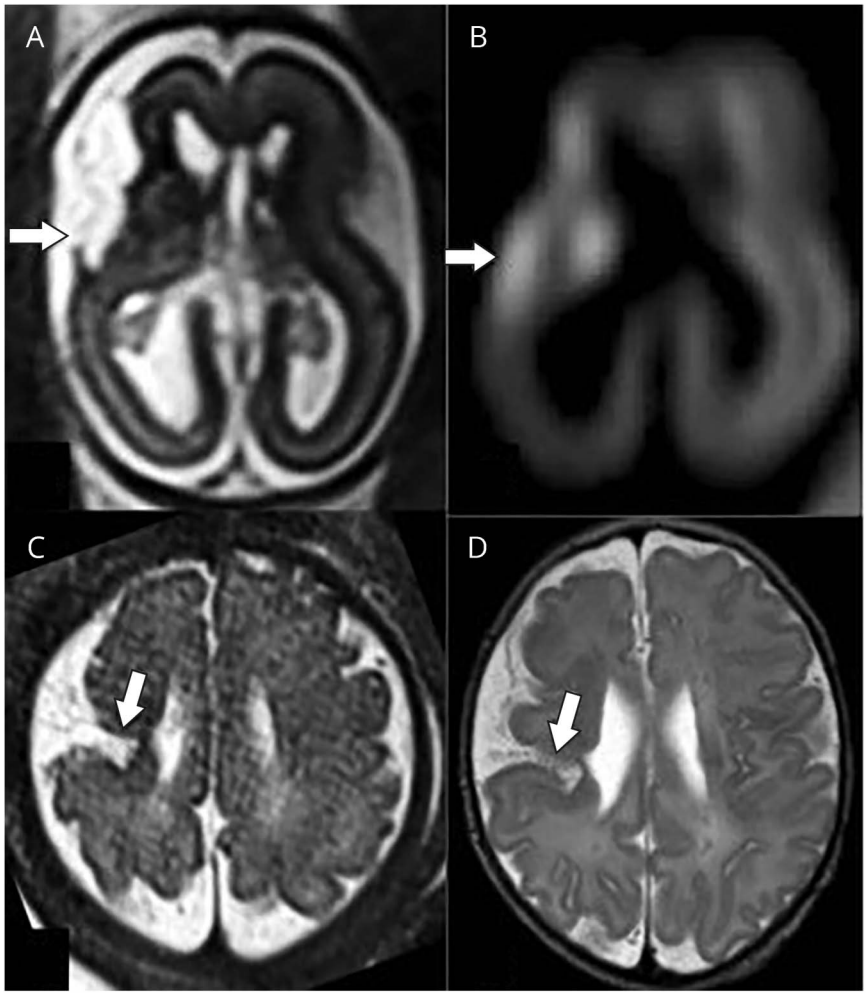
Figure Imaging series shows acute antenatal vascular disruption and the sequential development of schizencephaly



(A) Half-Fourier acquisition single-shot turbo spin echo images of the fetal brain at 21 weeks' gestation reveal increased signal intensity within the entire thickness of the cortical mantle with obscuration of the cortical layers in the affected zone. (B) Diffusion-weighted imaging of the fetal brain at 21 weeks' gestation shows areas of acute diffusion restriction within the right middle cerebral artery distribution. (C) Serial follow-up at 35 weeks' gestation reveals focal volume loss in the right cerebral hemisphere with parenchymal cleft extending to the ventricular margin. (D) Schizencephalic cleft lined by gray matter extending from the pial surface to the ventricular margin with focal tenting of the ventricular margin on postnatal imaging.

to a wedge-shaped defect of the cerebral mantle with heterotopic gray matter lining the lips of the resulting cleft.[7]

The neuroimaging in our patient demonstrates a clear timeline by which fetal brain injury at 19 weeks' gestation developed into open-lip schizencephaly in the same anatomical region by 35 weeks' gestation, lending support to the theory that schizencephaly is likely secondary to a pathologic vascular mechanism. Interestingly, our case suggests that it may not be mandatory for the inciting vascular event to occur before neuronal migration begins in order to lead to schizencephaly, but rather at any point during this critical yet dynamic period of development.

The altered neurobiological substrate and capillary fragility associated with the *COL4A1* mutation likely played a role in the causation of stroke, subsequent schizencephaly, and porencephaly. Therefore, we propose that genetic testing for *COL4A1* gene mutations be considered in patients with schizencephaly given the broad and currently undefined clinical phenotype with these mutations as well as the implications for future management and outcome.

Furthermore, it remains unclear whether schizencephaly is solely the consequence of an acute vascular insult at a critical time in an otherwise normally developing brain, a pathologic endpoint of developmentally appropriate processes on a vulnerable neurobiological substrate, or a combination of both.

Systematic MRI follow-up of fetal ischemic injury and informed genetic testing in large longitudinal cohorts is required to add to our understanding of this condition.

Author contributions

Roha Khalid: analysis and interpretation of data, critical revision of manuscript for intellectual content. Pradeep Krishnan: analysis and interpretation of data, critical revision of manuscript for

intellectual content. Kathleen Andres: analysis and interpretation of data, critical revision of manuscript for intellectual content. Susan Blaser: analysis and interpretation of data, critical revision of manuscript for intellectual content. Steven Miller: critical revision of manuscript for intellectual content. Mahendranath Moharir: critical revision of manuscript for intellectual content. Nomazulu Dlamini: study concept and design, analysis and interpretation of data, study supervision, critical revision of manuscript for intellectual content.

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