Schizencephaly associated with a severe prothrombotic syndrome caused by antithombin III deficiency

Aurore DARON,[a] Marie-François DRESSE,[b] Claire HOYOUX,[b] Malek TEBACHE,[c] Jean-Paul MISSON,[a] and François-Guillaume DEBRAY.[d]

a. Pediatric Neurology, Department of Pediatrics, CHR Citadelle, 1 Boulevard XIIème de Ligne, 4000 Liège, Belgium
b. Pediatic Hematology, Department of Pediatrics, CHR Citadelle, 1 Boulevard XIIème de Ligne, 4000 Liège, Belgium
c. Department of Medical Imaging, CHR Citadelle, 1 Boulevard XIIème de Ligne, 4000 Liège, Belgium
d. Metabolic Unit, Department of Medical Genetics, Sart-Tilman University Hospital, Domaine Sart-Tilman Bât B35, 4000 Liège, Belgium

ABSTRACT

Introduction

A 12 year old boy presented with non syndromic mental retardation. Brain MRI showed schizencephaly with a deep right parietooccipital cleft extending from cortical surface to the occipital horn of cerebral ventricle. Moreover his family was known for antithrombin III deficiency linked to the homozygous c.391C>T (p.Leu131Phe) mutation in *SERPINC1.* Coagulation studies revealed in this young boy severe antithrombin III deficiency and molecular analysis confimed the mutation.

Discussion

Schizencephaly can be considered as cerebral malformation of neuronal migration, caused by mutations in several transcription factors, but most cases occur sporadically and are believed to be associated with a vascular disruptive mechanism. In the proband, analysis of the *SHH*, *SIX3* and *EMX2* genes showed no mutation. Porencephaly and schizencephaly have also been attributed to mutations of COL4A1, linking, as in our case, genetic vascular pathology with schizencephaly. Otherwise mutations of methylterahydrofolate reductase and factor V Leiden genes seems also responsible of cases of schizencephaly. We suggest that a similar

encephaloclastic mechanism took place in our patient and hypothesize the occurrence of an early antenatal cerebral vascular injury.

Conclusion

Extensive coagulation studies should be performed in patients with schizencephaly before molecular analysis.

REFERENCE

Curry, C. J., Lammer, E. J., Nelson, V., Shaw, G. M.Schizencephaly: heterogeneous etiologies in a population of 4 million California births.Am. J. Med. Genet. 137A: 181-189, 2005.

Howe DT, Rankin J, Draper ES. Schizencephaly prevalence, prenatal diagnosis and clues to etiology: a register-based study. Ultrasound Obstet Gynecol. 2012 Jan;39(1):75-82.

Goez H, Zelnik N. Schizencephaly in infants with thrombophilia. J Child Neurol 2009 Apr; 24(4):421-4.

Yoneda Y, Haginoya K et al. Phenotypic spectrum of COL4A1 mutations:porencephaly to schizencephaly. Ann Neurol 2013 Jan; 73(1):48-57

Mellado C, Poduri A et al. candidate gene sequencing of LHX2, HESX1 and SOX2 in a large schizencephaly cohort. Am J Med Genet Nov2010;152A(11):2736-2742.

Spalice A, Parisi P, Nicita F, Pizzardi G, Del Balzo F, Ianetti P. Neuronal Migration disorders: clinical, neuroradiologic and genetics aspects. Acta Paediatr 2009 Mar;98(3):421-433.

Verrotti A, Spalice A et al. New trends in neuronal migration disorders. Eur J Paediatr Neurol 2010 Jan;14(1):1-12.

Hehr U, Pineda-Alvarez DE, et al. Heterozygous mutations in SIX3 and SHH are associated with schizencephaly and further expand the clinical spectrum of holoprosencephaly. Hum Genet 2010 Mar;127(5):555-561.