

PEDIATRIC NEUROLOGY BRIEFS

A MONTHLY JOURNAL REVIEW

J. GORDON MILLICHAP, M.D., F.R.C.P., EDITOR

Vol. 13, No. 3

March 1999

CONGENITAL MALFORMATIONS

DOUBLE CORTEX SYNDROME

The incidence of mutations in the X-linked gene *doublecortin* in patients with "double cortex" syndrome (DC; also called subcortical band heterotopia or laminar heterotopia) and familial DC with lissencephaly was investigated in a cohort of 8 pedigrees and 47 sporadic patients with DC examined at the Division of Neurogenetics, Beth Israel Deaconess Medical Center, Boston, and multiple centers in the US and abroad. Mutations were identified in all of the DC pedigrees and in 38% of sporadic cases. Single amino acid substitution mutations were identified more frequently in inherited DC, whereas protein truncation mutations were found in sporadic cases. Single amino acid substitution mutations have less reproductive disadvantage than protein truncation mutations. Two regions of the predicted amino acid sequence where mutations clustered were critical for the function of the DC protein. (Gleeson JG, Minnerath SR, Fox JW et al. Characterization of mutations in the gene *doublecortin* in patients with double cortex syndrome. Ann Neurol Feb 1999;45:146-153). (Respond: Christopher A Walsh MD PhD, Division of Neurogenetics, Beth Israel Deaconess Medical Center/Harvard Medical School, Harvard Institutes of Medicine, 77 Avenue Louis Pasteur, Boston, MA 02115).

COMMENT. Double cortex (DC) syndrome and X-linked lissencephaly are neuronal migration disorders with incomplete migration of neurons from the ventricular zone to the cortex. Neurons form a second layer of gray matter in DC, and abnormal migration leads to generalized disorganization of cortex in lissencephaly. Most DC patients are female, suggesting an X-linked dominant disease. Affected males develop lissencephaly because all the neurons express the mutant DC/XLIS allele. Females with heterozygous *DCX* gene mutations develop DC, and males with *DCX* hemizygous mutations develop lissencephaly. Lissencephaly has two genetic forms, *LIS1* and *DCX*, showing similar cortical pathology, but *LIS1* mutations are associated with more severe migrational abnormalities of the brainstem.

In an Editorial, discussing both the Gleeson article on DC syndrome and another on classical lissencephaly in the same issue (Fogli A et al. Ann Neurol

PEDIATRIC NEUROLOGY BRIEFS (ISSN 1043-3155) © 1999 covers selected articles from the world literature and is published monthly. Send subscription requests (\$58 US; \$60 Canada; \$68 airmail outside N America) to **Pediatric Neurology Briefs - J. Gordon Millichap, M.D., F.R.C.P.-Editor**, P.O. Box 11391, Chicago, Illinois, 60611, USA.

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1999;45:154-161), Clark GD and Naebels JL of Baylor College of Medicine, Houston, point out the importance of genotype-phenotype correlations in understanding the overlapping of clinical/pathological manifestations of migration disorders and the value in genetic counseling. Asymptomatic mothers of children with *DCX* mutations are at risk of further transmitting the disorder, whereas no germline transmission of *LIS1* mutations have been described.

NODULAR NEURONAL HETEROTOPIA

Brain tissue from 4 children with intractable epilepsy and subcortical or periventricular nodular heterotopia of different etiologies (megalencephaly, cortical dysplasia, polymicrogyria) was examined at the University of Oxford, Radcliffe Infirmary, UK. Histological and carbocyanine dye (DiI) tracing techniques showed fibers surrounding nodules and connectivity between adjacent nodules. Immunohistochemical tests for calretinin and neuropeptide Y (NPY), normally expressed in GABAergic cortical interneurons, found numerous calretinin-positive neurons (CPN) within nodules with incomplete differentiation, abnormal clusters of CPN in the overlying cortical plate, and many cell processes positive for NPY. Heterotopic nodules were associated with malformation in the overlying cortex and had limited connectivity with other brain regions. Abnormal connectivity could affect the balance of excitation and inhibition in neuronal circuits, leading to epileptogenic activity. (Hannan AJ, Servotte S, Katsnelson A et al. Characterization of nodular neuronal heterotopia in children. Brain Feb 1999;122:219-238). (Dr Zoltan Molnar, Institut de Biologie Cellulaire et de Morphologie, Rue du Bugnon 9, 1005 Lausanne, Switzerland).

COMMENT. The abnormal structure, composition, and connections between nodules and the overlying cortex may explain the epileptogenicity of neuronal heterotopias and its propagation to other brain regions.

POSTERIOR FOSSA MALFORMATIONS AND EPILEPSY

Risk factors for epilepsy in children with posterior fossa malformations (PFM) were studied in 22 cases of PFM with epilepsy (41%), and 32 without epilepsy (59%), seen at the University of Bologna, Italy. The most common PFMs were cerebellar hypoplasia (43%), Dandy-Walker (D-W) complex (37%), and Arnold-Chiari (A-C) malformation (13%). Epilepsy recurred most frequently in A-C malformation (71%), compared to 35% in D-W complex, and 35% in cerebellar hypoplasia. Risk factors for epilepsy in PFM cases were cerebellar lesions plus familial antecedents for epilepsy and/or febrile convulsions; 50% in PFM cases with epilepsy, and 9% in PFM without epilepsy. Epilepsy was mainly partial in 77%; benign epilepsies and febrile convulsions occurred in 27%. (Parmeggiani A, Posar A, Scaduto MC et al. Posterior fossa malformations and epilepsy. J Child Neurol Feb 1999;14:113-117). (Respond: Dr Antonia Parmeggiani, Department of Child Neurology and Psychiatry, Neurological Institute, University of Bologna, via Ugo Foscolo 7, 40123 Bologna, Italy).

COMMENT. Epilepsy may occur in 40% of children with posterior fossa malformation. A family history of epilepsy and/or febrile convulsions are significant risk factors for epilepsy in children with posterior fossa malformation.

Posterior fossa pathology other than malformation can predispose to epilepsy. Among 291 children treated for intracranial tumor at the Mayo Clinic over a 10 year period, seizures occurred in 17% - in 25% of patients with supratentorial tumors and in 12% of those with infratentorial tumors. The