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Schizencephaly and Nonlissencephalic Cortical Dysplasias

Peter G. Barth[1]

The refinements of neuroimaging have brought to the foreground a wealth of conditions that were previously the restricted domain of clinical neuropathology. This fascinating (and often bewildering) harvest, includes primary malformations and intrauterine disruptions of the brain. To the first category belong chromosomal abnormalities and genetic or cryptogenic malformations. The latter category is caused by pathologic events that interfere with the normal shaping process of the central nervous system, and includes hypoxic/ischemic accidents in utero, infectious diseases, and inherited neurometabolic disorders. Diagnosis may depend heavily on neuroimaging, which is the case in lissencephalies type I or II, or schizencephaly. In other cases, diagnosis depends as much on magnetic resonance (MR) imaging as on data derived from other procedures, demanding added professional skill to integrate the output of the various procedures. Examples are malformation syndromes such as Aicardi syndrome or Joubert syndrome. Sometimes prenatal pathology, as revealed by MR, may be distinctive enough for labeling it to a morphologic category, but not specific enough to narrow etiologic consideration to a single condition, and other diagnostic tools may not help us further. The latter situation exists in many cases of cortical dysplasia.

In this issue of the *Journal* two contributions from Barkovich and Kjos (1, 2) highlight the field. One concerns schizencephaly and the other, what is called "nonlissencephalic cortical dysplasia."

What do we know about schizencephaly? For a start, two conditions have been defined as schizencephaly by Yakovlev and Wadsworth, called, respectively, schizencephaly with closed lips and schizencephaly with open lips (3, 4). Both conditions essentially represent mantle defects of full thickness. Schizencephaly differs from the usual malformations, in that no arrest of normal brain development can be conceived that would result in such a condition. Therefore, some disruptive event that involves loss of developing tissue in the process must be implied. The covering of the "lips" of the lesion with aberrant neocortex is witness to the very early stage of development involved, probably lying between 8 and 16 weeks of gestational age. During this period, most of the neurons that will populate the future neocortex are generated at the lateral ventricular wall and, moving over a network of radial glial fibers that span the trajectory, migrate to the cortical plate, the future neocortex. The aberrant neocortical layer in schizencephaly is most likely the result of a neuronal migration failure, caused by destruction of the radial glial system.

The analysis of the authors is helped by their ability to bring together a large number of patients with this rare disorder. Correlating clinical and MR findings in patients with schizencephaly, they show that certain clinical manifestations, such as degree of motor deficit, laterality, and speech development correlate well with the outcome of the MR scaling. Although this may not seem surprising, the series contains some highly interesting observations, such as the favorable intellectual outcome for cases with small-sized unilateral schizencephaly. Equally important is their observation of contralateral cortical dysplasias in unilateral schizencephalies in three patients. The authors compare these contralateral focal cortical dysplasias to the ipsilateral schizencephaly. Based in part upon these findings, they have developed a tentative, though plausible and useful, scheme posing schizencephaly as the end of a continuum ranging from focal cortical dysplasia without mantle defects to full scale mantle defects, lined by aberrant cortex. The finding of such contralateral focal dysplasias in unilateral schizencephaly should have influence on the individual prognosis, although this has not been borne out in the study because of interference from other factors. The observation also unveils a more fundamental aspect bearing on the etiology, because bilateral lesions are more likely to result

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from systemic insults than unilateral lesions. The literature on schizencephaly until now does not link the condition to inherited or chromosomal disorders. This is contrary to typical malformations, eg lissencephaly, where Mendelian inheritance or chromosomal abnormality is the rule, or callosal dysgenesis and holoprosencephaly, where such factors may play a role. Schizencephaly compares best, it seems, with entire thickness porencephalies, a destructive event of later pregnancy. Differences can be explained by the state of development at the time that the lesion is acquired. In the case of entire thickness porencephalies, only the outer part of the pore is layered with cortex, continuous with the adjacent normal cortex, but the trajectory that links the outer pore with the ependyma often is scar tissue. Although scarring in entire-thickness porencephaly may cause the neocortex to "roll in" slightly at the edges, this should not be mistaken for a migration disorder. Moreover, in porencephaly, glial scarring is often present in the parenchyma below the superficial lesion. The propensity to glial scarring is acquired during the later phases of pregnancy (5), therefore, the presence or the absence of gliosis as evidenced by prolonged TE lesions may provide the clinician with another clue to the temporal origin of the lesion, besides the presence or absence of aberrant cortex covering the lesion. *No scarring is found in schizencephaly.* Schizencephaly is extremely rare, no reliable estimates of its incidence yet being available. This has hampered systematic studies of its link with pathologic events in early pregnancy. Allusion has been made to blood loss in early pregnancy (6), to adoption (7), and, quite recently, to prenatal exposure to cocaine and other street drugs (8). All this points to the interest of correlative studies on schizencephaly. As the number of serial studies on this rare disorder increases, we may gain important clues not only on the individuals' prognosis, but also on chances of recurrence for the parents involved, and on possible preventive measures.

In the second article (2) the authors describe their correlative investigation of 36 patients with cortical dysplasias, distinct from lissencephaly, and after exclusion of patients with known genetic syndromes. Comparison is made between the degree of involvement on MR to the degree and kind of neurologic handicap. The authors give a general definition of neocortical malformation not due to lissencephaly or schizencephaly as "cortical dysplasia." Developmental microgyria (a lesion distinct from sclerotic microgyria) may be obvious on MR imaging under ideal conditions. However, more often, focal cortical abnormalities may be picked up by MR without sufficient clue as to the histopathology of the lesion involved. Therefore, the descriptive term "cortical dysplasia" for MR purposes as applied by the authors is well chosen. Interestingly, in some cases subcortical gliosis is indicated by prolonged TE lesions. Since gliosis rarely accompanies lesions occurring earlier than a gestational age of 26 weeks, this may provide us with a clue to the temporal origin of the lesion, the more so since late acquisition of cortical dysplasia may extend to this time. While useful conclusions can be drawn from the study of this group of patients, we are left nonetheless with a relatively large, probably heterogenous group that defies our attempts at etiologic classification (9). Some cases of cortical dysplasia may be difficult to find on MR. This should be kept in mind in the case of milder developmental deficits that would not as a rule be brought in for neurologic investigation, such as dyslexia (10). What is left to consider when routine investigations beside MR fail to provide us with an answer in the case of cortical dysplasia? Of course, events in early pregnancy, infections, and chromosomal disorders should be considered. Inherited conditions are not easily ruled out in the absence of further clues. Recent experience has shown that metabolic disorders may cause prenatal disruptions of a severe kind, in addition to ongoing postnatal degeneration. Examples are generalized peroxisomal disorders, isolated disorders of peroxisomal beta-oxidation (not being x-linked adrenoleukodystrophy), glutaric aciduria type II, mitochondrial respiratory chain disorders. They all may cause cortical dysplasias, and each of these causes may be missed on "routine" metabolic screening. Therefore, the MR finding of cortical dysplasia, especially generalized cortical dysplasia, should encourage us to check for gaps in our diagnostic system. In this respect, the delineation of a large group of patients with "nonlissencephalic cortical dysplasias" represents a useful addition to an MR system for the classification of prenatal disorders, as well as a big challenge to future research.

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