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Of Muscles, Merosin, and Migration

Saturday, May 16, 1998, was a landmark day in pediatric neuroradiology. The First International Pediatric Neuroradiology Symposium was held in Philadelphia in conjunction with the Symposium Neuro-radiologicum XVI and the 36th annual meeting of the American Society of Neuroradiology. Organized by Jim Barkovich, a fascinating day unfolded for those interested in the imaging of the developing brain as international luminaries from both sides of the Atlantic presented stimulating discussions of many topics related to pediatric neuroradiology. The first session of the day, entitled *Neuroimaging Reflections of the Developing Brain*, presented excellent updates on recent advances in histology, pathology, imaging, and spectroscopy of brain development in the fetus and young child. Most intriguing for me was the lecture given by Jeff Golden, *Molecular Basis of CNS Development* (1). Dr. Golden opened our eyes to the "explosion of knowledge" in the field of molecular biology and the light that has been recently shed on the molecular basis of normal and abnormal brain development. For instance, we learned that a protein molecule secreted from the notochord, affectionately known as "sonic hedgehog" (Shh), induces the development of neuroectoderm, which gives rise to the floor plate and eventually the ventral neural tube. Deficiency of Shh leads to a loss of the basal forebrain in laboratory animals. Deficiency or misexpression of another gene product, Pax-2, leads to holoprosencephaly in the forebrain of chicks. The protein cyclin D1 regulates phases of neuronal cell cycle replication. Mice deficient in cyclin D1 have fewer than normal cells in the retina and in the CNS and fail to thrive. Proteins with intriguing names like *notch* and *astro-tactin* are integral to the orderly migration of neurons along radial glial processes and their subsequent organization into a six-layered cortex. Dr. Golden concluded with the bold, but believable prediction that the molecular, cellular, and functional basis of the brain and its development will be elucidated within the next decade. Incredible!

In this issue of the *American Journal of Neuroradiology* (page 1389), Barkovich makes an important contribution to our better understanding of the clinical classification of the congenital muscular dystrophies (CMD), a challenging group of relatively rare clinical diseases that affect brain, muscles, and eyes, and brings together some of the recent research on a unifying theory of the molecular basis of CMD. He reviewed the brain MR studies of 12 patients seen at the University of California, San Francisco, between 1986 and 1997, and classified the patients into one of four clinical groups: (1) "pure" CMD, (2) Fukuyama CMD, (3) muscle-eye-brain disease and (4) Walker-Warburg syndrome. This classification scheme is clinically useful since the muscle biopsy results in these

patients were not sufficiently diagnostic to clinically stratify the patients. Various observations of brain morphology, i.e., cerebral and/or cerebellar cortical dysplasia, cobblestone cortex, polymicrogyria, vermian hypogenesis, delayed myelination, callosal hypogenesis, pontine hypoplasia, and collicular fusion coupled with ocular abnormalities, were sufficient to divide the patients into clinically useful diagnostic groups. It appears that characterization of brain involvement is more predictive of clinical outcome in patients with CMD than the features of a muscle biopsy.

An interesting aspect of the paper by Barkovich is the discussion of merosin (a.k.a. laminin a-2). Merosin is an extracellular protein coded for by the gene at 6q22-23. Not only is merosin important in the linkage of contractile elements of muscle to their cell membrane but it is also a permissive substrate for the migration of oligodendrocyte precursors. A deficiency of merosin seen in muscle biopsy specimens of many of the patients with CMD may also occur in their brain cells, possibly leading to the abnormal myelination seen on MR. In a related paper, Lamer et al recently showed that diffuse white matter changes similar to those seen in patients with leukodystrophy were seen in CMD patients who were deficient in merosin, but not in those whose muscle biopsy specimens were positive for merosin staining (2).

Other molecules, such as *laminin 1* and *laminin 2*, which are important for muscle contraction, also play a role in brain development by stimulating and guiding migrating neurons. Perhaps the various forms of cortical dysplasia seen in these CMD patients relate to deficiency or defective function of one or more of these proteins. Other proteins found in muscle cells are also present in membranes of blood vessels, in the pia and arachnoid and in glial and retinal limiting membranes. They may also play important roles in neuronal migration and organization.

Each of these muscle/brain proteins is coded for by a specific gene, some of which have already been identified. As the Human Genome Project unfolds, we can expect that more and more specific genetic defects will be identified and localized. The genetic defect in Fukuyama CMD has already been identified and localizes to the long arm of chromosome 9 at 9q31-33, as does the gene for Walker-Warburg syndrome (3), suggesting that these two diseases may be different phenotypic expressions of the same genetic defect. If Jeff Golden's prediction comes true (and I believe it will), during the next decade most, if not all, of the congenital neurologic diseases we now diagnose by their phenotypic expression as seen on our brain imaging studies, will be classified and, possibly, diagnosed by their genotypic characteristics.

A decade ago, as neuroradiologists, we were struggling to assimilate concepts related to *T1*, *T2*, *Fourier transformation*, and *k space* into our vocabulary and

daily work lives—concepts and terms that are now second nature to our specialty. It is very possible that in another decade words such as *sonic hedgehog*, *notch*, *astrotactin*, *merosin*, *laminin 1*, and *laminin 2* will be household words for the practicing neuroradiologist, and we will be as comfortable using them in our vocabulary and discussion of diagnostic imaging studies as we have become with *T1* and *T2*.

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. . . But Will It Play in Peoria?

Call me jaded, call me cynical, or simply call me battered by the heavy and still growing load of a community managed care MR practice. More and more when I read the “literature,” I find myself spending less and less time reading those articles written for the academic audience, ones for which I will likely never find an application in pragmatic practice. Am I losing my religion? Or is it simply harder these days to produce innovative, clinically relevant research since little new is heading down the highway of the technological imperative? On the other hand, initially “impractical” developments may stimulate new avenues of implementation that ultimately produce considerable impact on clinical practice.

LeClerc et al in this issue of the *American Journal of Neuroradiology* (page 1405) present a worthwhile attempt to extend the clinical relevance of MR angiography in the evaluation of patients with cerebrovascular disease. The authors' stated purpose is to evaluate this technique's ability to image the carotid and vertebral arteries in their cervical portions, and to compare this technique with conventional angiography in this setting. The innovative wrinkle here is the combined use of an intravenous contrast bolus—a coronal 3D slab acquisition allowing rapid sampling of a vertically large field of view and a head-and-neck surface coil—another technowrinkle. The proposed use of a single contrast bolus and this coil architecture to evaluate the cervical-cranial vasculature in one fast shot certainly is seductive, particularly given the subminute study time, and, if successful, it would likely reach Peoria quickly. But two questions must be addressed. Is there a need? and Does the technique deliver?

The authors acknowledge in their introduction that three-dimensional time of flight MR angiography (3D MRA) is an effective technique, but point to its limited anatomic coverage while incorrectly stating that it does not allow the evaluation of both the anterior and posterior circulations. In our experience, working with the same MR instrument that LeClerc et al used for this study, we find the combination of multislab 3D MRA of the neck and 3D MRA of the brain quite effective in depicting both the anterior and posterior circulations in the neck and brain, albeit with the need for one half-hour time slots for each patient's

study (this includes the anatomic brain MR imaging as well). Indeed, we routinely study three to four patients a day with these techniques, such patient volume testifying to the reliability and clinical value provided to the referring clinicians. Nevertheless, the limitations of these now “conventional” MRA techniques, particularly for evaluating the arch and ostia of the major vessels, are well-known and have been elucidated in the literature. Fortunately these limitations have not deterred our referral base to any significant degree.

Yes, it would be nice to have a technique that allowed visualization of the arch origins, the cervical course, and the intracranial distribution of the cerebral blood supply. And herein lies the contribution of LeClerc et al. Their experience clearly suggests the potential role of the contrast-enhanced fast 3D technique for the evaluation of the arch origins and cervical course of the intracranial vessels. The results of the contrast-enhanced coronal FISP technique in the full coverage of the cervical-cranial distribution are, however, disappointing. The failure to demonstrate the ostium in 35% of the cases was particularly disappointing—almost as disappointing as the inability to evaluate the carotid siphon in 35% of the cases. “Conventional” MRA's difficulties with flow-related artifacts apparently haunt the contrast-enhanced technique in this early stage as well. In short, at the present time this technique cannot be used in Peoria or elsewhere to completely evaluate suspected cerebrovascular disease. It even falls short of the current MRA technique used for that purpose, assuming one is willing to trade off visualization of the aortic ostia for the carotid siphon and basilar artery evaluation. The limitations of this technique are magnified when one considers the additional costs of intravenous contrast material and the fact that it offers only a “one-shot” deal. Although the authors do describe a second contrast-enhanced MRA study performed in six patients because of the failed first go-around, the quality of those studies is not specifically addressed. The venous contrast, and that in the extracellular space, would not likely produce pleasing images.

What then will the practicing radiologist take away from this article? First, the concept of a combined