

Imaging of the Cobblestone Lissencephalies

A. James Barkovich, *Chief, Pediatric Neuroradiology, University of California, San Francisco*

The article by Aida et al in this issue of the *AJNR* (1) is a wonderful example of the impact that magnetic resonance (MR) imaging can have on the clinical practice of child neurology when the images are of high quality, meticulously analyzed, and compared with known pathological findings. In this paper, the authors have carefully evaluated the appearance of the cerebral cortex on the MR studies of a large group of patients with Fukuyama congenital muscular dystrophy (FCMD) proved via muscle biopsy. The authors were able to demonstrate characteristic cortical abnormalities on the MR studies. In addition, by analyzing sequential MR studies in three patients and by analyzing the changes in white matter signal on MR studies of progressively older patients, they were able to detect an abnormal sequence of myelination in their patient group. These observations raise three important issues: (a) the utility of high-quality MR in making definitive diagnoses that obviate the need for invasive biopsies, (b) the classification of the so-called cobblestone lissencephalies, and (c) the nature of the regulation of myelination.

The full spectrum and nature of developmental brain anomalies was poorly understood until the recent development of high-quality neuroimaging techniques. Several factors probably contributed to that lack of understanding. Early diagnostic techniques, angiography and pneumoencephalography, were invasive and insensitive, especially by today's standards. X-ray computed tomography (CT) and transfontanel sonography were significant but limited steps forward in the imaging of brain malformations. In its early iterations, CT was limited by poor contrast and spatial resolution, prolonged scan times, beam hardening in the posterior and middle fossae, and sections limited to the axial plane; these factors resulted in the identification of only the most severe malformations (2-6).

Sonography had limited ability to show much of the cerebral cortex, was insensitive to the presence of ectopic gray matter, and was no longer effective after the anterior fontanel closed at the end of the first year and beginning of the second year of life. Thus, ultrasound was most useful in gross centrally located anomalies that presented in the first year of life. Because only the most severely affected children died, autopsy findings did not reflect the full spectrum of disease. Moreover, pathologists were not able to look at a single brain in multiple planes.

MR was the first imaging modality that allowed neuroradiologists to obtain thin-section images in multiple planes with excellent contrast resolution. Subtle malformations of the cerebral cortex (7-13), cerebellum (14, 15), white matter (16-20), and deep cerebral structures (21-23) could be identified in children of nearly any age. The availability of such exquisite anatomic information allowed new insights into the pathogenesis of brain malformations. More important, it allowed a more rational classification of the disorders, one based on anatomy rather than neurologic signs and symptoms. Several such classifications are now being formulated or have been formulated (13, 24). Finally, careful analysis of MR studies allows diagnoses to be established in many cases without the need for invasive procedures such as muscle or brain biopsy. Aida et al make this important point in their paper: *characteristic imaging findings in the proper clinical setting allow the diagnosis of FCMD to be established without muscle biopsy.*

FCMD is an interesting disorder that, although known for more than 30 years (25), has only recently been classified as one of the cobblestone lissencephaly syndromes (26-28). The other well-defined disorders in this group are the Walker-Warburg syndrome (29, 30) and muscle-eye-brain disease (31, 32). This group of malformations is characterized by specific

Address reprint requests to A. James Barkovich, MD, Department of Radiology, University of California San Francisco, Box 0628, L-371, 505 Parnassus Ave, San Francisco, CA 94143-0628.

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brain anomalies (previously referred to as *type II lissencephaly*), ocular anomalies, and congenital muscular dystrophy. The brain anomalies consist of a cobblestone cortex, white matter dysmyelination or cystic changes, ventriculomegaly, brain stem hypoplasia, and cerebellar hypoplasia or dysplasia (28). The cobblestone cortex varies from widespread lissencephaly (demonstrating a characteristic nodularity of the brain surface that results from overmigration of neuroblasts and glia beyond the external glial limitans) mixed with regions of pachygyria and polymicrogyria to mixed pachygyria and polymicrogyria, as described by Aida et al (33–38). Ocular abnormalities vary in severity in all three diseases; in general, microphthalmia, retinal dysplasia/hypoplasia, and anterior chamber malformations are typical of Walker-Warburg syndrome, relatively minor strabismus and abnormal eye movements are seen in FCMD, and anomalies of intermediate severity are present in muscle-eye-brain disease. Muscle changes in these disorders range from nonspecific myopathy to frank congenital muscular dystrophy.

The substantial similarity of both the clinical presentation of the patients and the pathologic findings has created some confusion as to the classification of patients with cobblestone lissencephalies. Classically, Walker-Warburg syndrome has been differentiated from the other two disorders by its more severe malformations and consequently more severe clinical presentations. However, a number of reports have emphasized milder forms of Walker-Warburg syndrome that overlap with FCMD and muscle-eye-brain disease. As a result, many have pointed out the similarities among the diseases and expressed the opinion that the cobblestone lissencephalies are different manifestations of the same disorder, with Walker-Warburg syndrome being the most severe, FCMD the least, and muscle-eye-brain disease intermediate (35, 39–42). Others postulated that the cobblestone lissencephalies were caused by different alleles of the same developmental gene (43). The recent discoveries that the gene responsible for FCMD is located on chromosome 9q31–33 and that the gene responsible for muscle-eye-brain disease does not map to this region (44) have demonstrated that we still have a lot to learn about the genetic basis of brain malformations, despite recent advances. Thus, for the present, imaging characteristics seem to

be the single most important feature for the classification of developmental brain malformations; the diagnosis can frequently be determined on the basis of imaging characteristics alone. Supplemental genetic information is invaluable when the genetics of the disorder are completely worked out; at present, however, few disorders qualify for this category.

Aida et al note a very interesting pattern of myelination in FCMD. A debate about the cause of myelination and the relationship of myelination to onset of function has been ongoing in neuroscience ever since the turn of the century, when Flechsig made the first detailed study of myelination in the human nervous system (45). This debate has been extensively covered by Marjo van der Knaap in her doctoral thesis (*Myelination and Myelin Disorders: A Magnetic Resonance Study in Infants, Children, and Young Adults*, University of Utrecht and Free University of Amsterdam, the Netherlands 1991). Those interested in the history and MR evaluation of myelination should read Dr van der Knaap's thesis. To summarize briefly the debate about function and myelination, Flechsig showed that the white matter tracts of the brain become myelinated in a well-defined sequence. He also noted that axons of related functional systems myelinate at the same time. From this information, he suggested that tracts become myelinated at the time they become functional (46). Vogt disagreed, arguing that the sequence of myelination is determined primarily by the number and size of the axons in the pathway and is not related to the function of the pathways (47).

In the 1920s and 1930s, several groups looked at the relationship between myelination and function. Keene and Huwer reasoned that myelination is not necessarily a precursor of function in axonal pathways because reflexes are present in certain pathways before myelin develops (48). The work of Langworthy and of Tilney and Casamajor showed, however, that reflexes are slow and of low amplitude before myelination (49, 50); both groups concluded that myelination is closely correlated with the acquisition of function. Their conclusions were supported 40 years later by Yakovlev and Lecours (51), who expressed the opinion that myelination is a morphologic marker of the functional maturity of a pathway, and by Huttenlocher (52), who noted that myelination improves the efficiency of conduction of action

potentials. All of the previous arguments, however, did not convince Davison and Dobbing (53, 54), who pointed out that the period of maximum myelination occurs at the same time as many other changes in the central nervous system. Two decades later, and nearly 9 decades after Flechsigs initiated the debate over the relationship of myelination with the onset of function, Kinney et al admitted that the relationship was still poorly understood, and was probably indirect and complex (55).

The altered pattern of myelination in FCMD as described by Aida et al leaves many questions unanswered. It would be interesting to know whether the signal changes that accompany myelination follow the same order as in the normal brain, with early evolution in the dorsal brain stem and cerebellar peduncles, followed by the corticospinal tracts and visual system (56). If so, it might support the concept that specific white matter tracts are myelinated in a specific order that is related to the onset of function within the tracts. If not, the implication might be that myelination is controlled by a genetic mechanism that is altered by the genetic defect in FCMD. Moreover, the known location of the genetic locus for FCMD might give researchers a clue as to the location of one of the (possibly many) genes controlling myelination. I hope Aida et al will pursue this question by looking at the patterns of myelination in a large number of patients with FCMD.

In summary, modern neuroradiologic tools, such as MR and MR spectroscopy, have enormous potential to unlock many of the mysteries of normal and abnormal brain development. Aida et al have pointed out still another disorder that can be definitively diagnosed on the basis of MR findings in the proper clinical setting. When high-quality MR is properly performed and interpreted, it is noninvasive and allows rapid and specific diagnosis with less morbidity and overall expense than traditional methods. In these days in which it has become fashionable to bash high technology, it is important to remember that sagacious use of technology rewards everybody, especially the patient.

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