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Line-Scan Diffusion Imaging of Term Neonates with Perinatal Brain Ischemia

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traoperative scanning to a single session with the technique reported by these authors.

Other methods have been described that increase the number of times that MR images can be readily obtained during surgery in order to monitor and guide the procedure more closely. Setup time can be almost eliminated by performing surgery within the scanner, as reported by the group at Brigham and Women's Hospital (1). At our institution, we use the same 0.2-T imaging system as described by Knauth et al, but reduce patient positioning and scan setup to under 2 minutes by performing surgery adjacent to the scanner on a rotating operating table (5, 6). By modification of scan parameters, we also decrease imaging times to approximately 2½ minutes for T1-weighted images and 3½ minutes for T2-weighted images, without a significant decrease in observable image quality (6). This allows us to obtain images at much more frequent intervals during the surgical procedure.

The time required for image acquisition can also be reduced by performing MR imaging at higher field strength, as recently reported with intraoperative imaging at 1.5-T by the group at University of Minnesota (4). Other techniques with more rapid patient positioning and shortened scan times have also been described at several other institutions, and can allow a marked reduction in the added procedure time necessary for intraoperative MR imaging. It is likely that the proportion of patients in whom complete resection was attained would have been further increased had Knauth and colleagues been able to repeat intraoperative MR imaging without unreasonable lengthening of the surgical procedure.

In summary, intraoperative MR imaging is still a young technology and has only recently taken its first scientific steps toward maturity. Its bright future, however, will undoubtedly be illuminated further as others build on this excellent work of Knauth et al.

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In this issue of the *AJNR*, Robertson and colleagues (page 1658) describe and interpret their findings from line-scan diffusion imaging studies of 12 neonates with diffuse perinatal ischemic injury and seven neonates with perinatal cerebral infarction. The authors found that diffusion-weighted imaging is more sensitive than T1- and T2-weighted spin-echo images, nearly always showing an abnormality in the early post-injury period. They found, however, that even diffusion imaging is sometimes falsely negative. In addition, they reported that the extent of injury is nearly always underestimated by the initial diffusion imaging study. This article raises a number of interesting points, all of which cannot possibly be addressed fully in a short editorial. We will, therefore, focus on only a few issues: the choice of imaging techniques in the asphyxiated neonate; timing of the imaging; regional variations in maturation of the brain; differences in occlusive versus nonocclusive ischemia; and the physiologic interpretation of diffusion measurements.

In a recent issue of the *AJNR*, the topic of choices of imaging studies in asphyxiated term neonates was addressed (1). The author suggested that sonography was the best initial choice because it is portable and inexpensive, but that this technique has well-recognized limitations and is often unrevealing. MR imaging was judged to be the best technique in spite of its insensitivity to early damage. Two relatively new MR imaging techniques, diffusion-weighted imaging and proton spectroscopy, seem to have overcome the problem of lack of early sensitivity. Diffusion imaging shows a reduction in apparent diffusion coefficient within 15 minutes of injury. Proton spectroscopy shows elevation of lactate within a few hours. Both of these time frames are well within the window of opportunity for medical intervention to reduce potentially severe brain damage. Many potential treatments have been shown to reduce neonatal hypoxic-ischemic brain damage in animal models, including hypothermia, neurotropins, growth factors, calcium channel blockers, antioxidants, anti-inflammatory agents, and glutamate antagonists (2). Can we use these new techniques to detect injury in all neonates with a difficult delivery and any evidence of

potential hypoxic-ischemic damage? Are diffusion imaging and proton MR spectroscopy (MRS) the ''magic'' tools that can improve the selection of the proper neonates for treatment from all newborns with clinical or laboratory evidence of ischemia? Unfortunately, the decision is not so easy. One problem is that it is often difficult to recognize hypoxic-ischemic injury in the newborn period clinically. Not all encephalopathic neonates have suffered hypoxic-ischemic injury (3, 4). In addition, some infants may have suffered hypoxic-ischemic injury days or weeks before birth, so their clinical presentation differs from that of the acutely asphyxiated neonate (5). Another problem is transporting acutely ill neonates, which is a risky business. Most of the infants are on respirators, have multiple indwelling catheters, and are hooked up to electronic infusion pumps that steadily release minute quantities of vasopressors into the neonate's venous system. The manufacturers of the infusion pumps do not guarantee their reliability in a magnetic field. Neonates, especially sick neonates, lose heat rapidly when exposed to the elements, and the cold MR imaging suite is a hostile environment for them. Thus, neonatologists are reluctant to subject neonates to MR imaging until their status has been stabilized. For this reason, one notes that most studies of neonatal hypoxic-ischemic injury by MR techniques involve term infants with mean ages ranging from 5 to 8 days at the time of their initial scan (6–15). One potential solution to this dilemma is to develop MR scanners dedicated to neonatal imaging. The scanners may have to be close to the neonatal intensive care unit. They would have to have MR-compatible infusion pumps, respirators, and vital-signs monitors that are suitable for neonates with weights of less than 4 kilograms. Definitive advances in neonatal care await this step.

The timing of the imaging study is another important issue. As Robertson et al point out, neonatal brain injury consists of at least two phases. There is an initial reduction of blood flow. When cerebral blood flow is reduced beyond a certain level, the neonatal brain is deprived of sufficient oxygen and glucose, the substrates necessary to produce energy in the form of adenosine triphosphate (ATP). Normal cellular processes are markedly reduced or cease altogether. For reasons that are not entirely clear (more on this later), diffusion of protons is reduced. If some glucose is present, it is metabolized by anaerobic glycolysis to produce lactate, which can be detected by proton spectroscopy. Blood flow reduction, however, is always transient if the infant survives. If the period of reduced flow is short enough, animal models show that diffusion values return to normal within a few hours (16, 17). This normalization may be transient or permanent. In addition, lactate values will normalize within about 24 hours (18). In more severe injuries, diffusion values will undergo a reduction and lactate value elevation after 24 hours (18). One histologic study in young rats at our institution showed that apoptosis ensued in animals that had transient early reduction of diffusion. The time course and the extent to which apoptosis ensues in asphyxiated human neonates is not known, nor is it known what the effect of such apoptosis might have on long-term outcome. The importance of this ''period of false negativity'' is critical for determining the optimal time to perform an MR study in an asphyxiated neonate. It will be necessary to perform multiple sequential diffusion and MRS studies in the first 24 to 48 hours of life in a series of asphyxiated human neonates in order to determine an early postnatal age at which maximal information could be gained from a combined proton MRS/diffusion MR study. Such sequential measurements may help us to determine when secondary energy failure begins; capturing this phenomenon by diffusion or spectroscopic measurements would be a key step in administering effective therapy. Again, this sort of study would not be feasible on a typical inpatient MR scanner and requires the development of a dedicated neonatal MR scanner.

Another important subject that comes out of the study by Robertson et al is that of regional variation in brain maturity. It is well known that different regions of the brain mature at different times and rates. This regional variability is manifested histologically by differences in neuronal maturity and myelination, and imaging shows this variability in regional blood flow (19), glucose uptake (20), diffusion (21, 22), and and concentration of *N*-acetylaspartate, choline, and creatine (23). It is essential to take these regional differences into consideration when evaluating the imaging studies of neonates. For example, the normal neonatal ventrolateral thalamus and perirolandic cortex have slightly reduced diffusion compared with the rest of the cerebrum (21). Normal neonatal frontal white matter has reduced *N*-acetylaspartate compared with that of the thalamus and may have some detectable lactate (9, 24). Such findings might be misdiagnosed as brain injury. Indeed, even Robertson et al mistakenly identified a patient as normal even though the basal ganglia and thalami were abnormally hyperintense (Figure 3A, page 1665). Ideally, a series of normal neonates and infants should be studied in order to map mean values and standard deviations of metabolite ratios and apparent diffusion coefficients throughout the brain. Only then will we be able to confidently diagnose injury.

It is not necessary to spend too much time on the differences between occlusive ischemic injury and nonocclusive ischemic injury. Robertson et al have done an excellent job of discussing this subject. Suffice it to say that these types of injuries differ, both in physiologic and imaging manifestations, and we should not assume that the imaging characteristics will be the same.

The final topic that warrants comment in this article is the question of why diffusion is reduced in acute brain injury. The generally accepted response is that cells swell when the sodium-potassium

pump is paralyzed by lack of ATP. Cellular swelling reduces the size of the extracellular space, shortening the distance that extracellular water protons can move before being stopped by a cell membrane. This explanation has never seemed to answer the question fully. It assumes that fewer extracellular water protons are bound to macromolecules and, therefore, extracellular water protons are more important than intracellular water protons in the production of magnetic resonance signal. This model is certainly adequate for a basic understanding of the physical quantity (water motion) that we are measuring. We should remain aware, however, that the models we use to explain biological phenomena are only that—models. They give the right answer much of the time and are, therefore, useful. These models, however, are tremendous simplifications of the real situations. Let us also remember that simple answers are rarely correct in nature. As Albert Einstein often said, he had no desire to apply his intellectual talents to biology, because biology is too complicated!

Overall, the article of Robertson et al is a cautious step forward. It gives us confidence that we can use MR techniques to assess the neonatal brain soon after hypoxic-ischemic injury. It tells us that MR techniques will give us the right answer most of the time. The next challenge is to determine which technique and timing give us results that direct therapy to achieve optimal outcomes. Is line-scan diffusion imaging the final answer? Do spectroscopy and perfusion-weighted imaging have a role? What is the window in which false-negative results are most likely to occur? Answers to these questions will allow us to take the next few steps along the road to saving these neonatal brains.

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