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Diffusion-weighted Imaging of the Spinal Cord: Is There a Future?

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Tick Tock, Doc: The Rapid Evaluation of Acute Stroke to Direct Therapy and Improve Patient Outcome

Introduction of diffusion-weighted imaging (DWI), perfusion imaging (PI), and magnetic resonance angiography (MRA) into a comprehensive acute stroke evaluation paradigm is a formidable challenge in most centers' busy imaging schedules. If time is brain, the minutes required to identify the acute stroke patient, perform a CT scan, transport the patient from the emergency department to the MR scanner, wait for the scanner to become available, transport the patient to the scanning table, and then scan, process, and interpret the results, are precious minutes indeed. The time to accomplish these tasks can be shortened, as shown in the quality improvement document by Schellinger et al (page 1184) in this issue of the *AJNR*. The authors confirm that a concentrated effort to decrease the time until imaging can lead to considerably shortened MR examination time. These results challenge us all to reconsider our opinions and prejudices about our ability to perform MR imaging for early stroke.

That DWI/PI/MRA can contribute significant knowledge in acute stroke evaluation is unquestioned. The triad of a small wedge of diffusion abnormality, followed by a larger zone of perfusion delay (DWI/PI ''mismatch''), accompanied by middle cerebral artery (MCA) occlusion on MRA, speaks volumes regarding the lengths we have come in stroke imaging and its promise in patient selection. It still does not, however, clarify the dilemmas *why, where, when,* and *who* to scan.

Why? Presumably, to direct performance of some intervention, or to recommend against performance of the intervention, in order to improve outcomes in the acute stroke patient. IV Activase in the 0–3-hour window, or even beyond the currently approved 3-hour window, might be administered only if appropriate DWI/PI criteria are present (such as a ''mismatch''), but no MR data as yet suggest delaying its administration improves safety by identifying those patients who cannot improve, or reveals circumstances that may render the patient more susceptible to hemorrhage. Such circumstances might include:

(a) DWI has been suggested to show multiple infarcts in 10% of patients, perhaps from a central cardiac source, which need not be of identical age. It may be more than coincidence that 10% of hemorrhages in the National Institute of Neurological Disorders and Stroke (NINDS) trial occurred distant from the principal infarct. Thus, DWI might eliminate the risk of tissue plasminogen activator (TPA) administration when an older, silent infarct exists.

(b) If a DWI/PI ''matched'' defect was apparent prior to, or even during, IV TPA administration, the infusion could be stopped, presumably to reduce the likelihood of a hemorrhage when little benefit is expected.

(c) Failure to reveal a diffusion abnormality may obviate treatment. Or should it? False-negative DWI findings has been reported in up to 15% of posterior circulation infarcts shown by 48 hours. Are these patients who might still benefit from early thrombolytic therapy? Perfusion problems may be resolved with therapy in the absence of diffusion abnormality.

Again, the data to support these philosophies in the 0–3-hour treatment window are lacking.

Intraarterial (IA) recanalization efforts might be employed in any time window if a large perfusion abnormality and a small or absent diffusion abnormality (DWI/PI ''mismatch'') were present. Yet, MR studies to date suggest ''matched'' defects, which might eliminate recanalization therapy, occur in approximately 20% of patients selected for scanning. If treatment is delayed to identify these matches in the 20% of patients who might not benefit or who might be susceptible to hemorrhage, are the other 80% of treatment candidates subjected to important delays in therapy? Research is needed to define the greater risk.

Where and when? Presuming ultrarapid MR imaging becomes a standard of imaging, must every emergency facility be DWI/PI/MRA-capable? One might argue that in the acute treatment setting this capability might be necessary only if acute therapy can be administered at the site. If a site is not therapy-capable, is it really prepared to perform and interpret the requisite images? And if a site is neither treatment- nor performance/interpretation–capable, can the delay inherent in its participation in stroke imaging be warranted? Should stroke suspects be identified by emergency management teams and triaged to acute stroke treatment centers that have the capabilities to work rapidly, as Shellinger has accomplished? The presumption must be that faster is better, and Shellinger et al point out that major centers can become faster.

Again, is the time required to identify, transport, scan, interpret, and plan therapy time well spent, or is it lost time that only diminishes good outcomes? The evidence that delays have a negative impact is compelling. Marler demonstrated in the NINDS trial that even with IV TPA, delaying therapy 20–30 minutes may diminish the likelihood of favorable outcomes by 10–20% (1). Kanter et al reviewed the post-NINDS experience in Cincinnati and reported similar findings (2).

In addition, a number of recent IA thrombolytic therapy reports also suggest that earlier treatment

leads to better outcomes. Certainly one would not take a patient with an arteriographic thromboembolic occlusion of the M1 segment (the ultimate, ultra-early treatment candidate) off of the angiographic table to perform a DWI/PI scan. At the other end of the time spectrum, the Prolyse in Acute Cerebral Thromboembolism Trial (PROACT) II achieved good outcomes in 40% of patients when IA therapy was begun at 5.3 hours. Suarez reported good outcomes in 56% of patients at 4.75 hours in a more heterogeneous population (3). Bendszus reported good outcomes in 66% of patients with MCA occlusion treated in less than 4 hours (4). The Emergency Management of Stroke (EMS) Pilot Trial achieved good outcomes in 66% of patients with M1 and M2 occlusions when IA treatment was begun at 4.2 hours (5). Our soon-to-be-reported 1999 experience with 20 patients who had carotid-distribution occlusive disease (mean National Institutes of Health Stroke Scale Score [NIHSSS] = 20), treated with IV TPA within 3 hours, followed by arteriography, then treated with IA TPA at a mean of 3.3 hours in 16 of the 20 patients, achieved good outcomes in 65% of patients (R. Ernst, personal communication). These multi-study data points also suggest a 10–20% decrease in good outcomes with 20 minutes of delay until IA therapy. Elimination of how many genuine treatment candidates by DWI/PI/MRA scanning warrants even a 20-minute delay to rapid recanalization efforts at the latter early time windows? If good outcomes can be achieved in two thirds of the patients within 4 hours with recanalization efforts anyway, should we delay treatment to scan? Will DWI/PI/MRA somehow eliminate the other third from treatment in the first place? How will clot removal devices, and immediate recanalization, affect this management paradigm?

Who? Some argue that the heterogeneity of vascular occlusive disease diminishes the significance of any clinical finding in the acute stroke patient, and rapid vascular imaging (eg, MRA) may be mandatory to begin the treatment triage. Many disease processes may mimic thromboembolic cerebrovascular disease, including migraine, seizures, and inflammatory disease. Should everyone with CNS symptoms/signs be urgently imposed into the daily scanning schedule of extremities and spines, even to the point of removing a patient from the scanner? Or are there clinical findings sufficiently predictive of the presence of acute major thromboembolic occlusion that warrant rapid intervention? Even in the most sophisticated centers, patients have been treated with IV TPA only to establish subsequently that the clinical problem was seizure activity. This, however, is the exception.

Some have argued that ''angiograms in suspected stroke patients don't always show blocked vessels, so how do we know these patients had strokes? IA recanalization efforts shouldn't begin without that demonstration.'' In the EMS trial (in which patients were treated with IV TPA or placebo, then underwent arteriography and treatment with IA TPA if an occlusive lesion was revealed), patients without vascular occlusion on arteriography subsequently demonstrated infarcts on imaging in 10 of 10 cases (5) with presumptive evidence of arterial occlusions. No occlusions at angiography were shown in approximately 20% of 480 PROACT II patients subjected to angiography (6), and we await the follow-up imaging and clinical outcomes in those patients.

The clinical description of stroke patients in the United States is defined by the NIHSSS. In the NINDS pilot trial, we recognized that patients with an NIHSSS $<$ 10 seldom had a major clot at arteriography following therapy. Patients typically did well by 3 months, and we hypothesized that IV therapy alone might be sufficient in the majority of such patients (7). The latter observation subsequently was confirmed in the NINDS trial; 52% of such patients had excellent outcomes. Perhaps patients with an NIHSSS $<$ 10 should be treated immediately with IV TPA, and then have a DWI/PI/MRA to determine larger vessel occlusion.

The NIHSSS in the acute stroke patient also predicts the presence of a major arterial occlusion and a potentially lysable thrombus. Patients with an NIHSSS $>$ 10 have up to a 50% likelihood of MCA occlusion, as documented by the hyperdense MCA sign (HMCAS) (7). The EMS study revealed major occlusions in all patients with an NIHSSS $>$ 14, and 78% of patients with an NIHSSS $>$ 10. In PROACT II, only 15% of 180 patients with M1 or M2 occlusions had an NIHSSS $<$ 10. Furthermore, the control group did as well as the treated patients with an NIHSSS $<$ 10 on an overall-improvement basis. So, the clinical examination does tell a lot about the arterial occlusive process and outcome, despite the heterogeneity of the arterial occlusive lesion. Is MRA/DWI/PI needed in a 65-year-old patient with atrial fibrillation and an NIHSSS of 15, whose CT at 90–120 minutes postictus reveals an HMCAS before being taken to the angiographic suite to recanalize the vessel? If not, at what point does the benefit of imaging to exclude patients (perhaps 10%. . . .or 20%. . . or 30%) outweigh the risks of inherent delay before attempted recanalization? To me, these are the real questions: what percent are eliminated, at what time, and at what risk of delay for imaging?

Once again, I have asked myself more questions than I have answered, with full realization that nihilism, prejudice, and bias lead to no new scientific knowledge. The image of the stopwatch ticking has been the poster child for acute ischemic stroke; however, perhaps it is time to change that poster image to one of a compass, to reorient us in the right direction, much like the refocusing 180-degree pulse of the spin-echo sequence. Which direction is right is the question. Certainly research efforts devoted to ''how far out'' we can treat patients is important, even if the number of treatment can-

didates is small, while the number of patients eliminated from treatment is large. A research effort to perform DWI/PI/MRA on all patients to determine *why, who, when,* and *where* is to be applauded and encouraged as we assimilate all the data being accumulated regarding stroke treatment. The effort exerted in diminishing times to MR imaging as reported by Schellinger et al, certainly demonstrates *how* we can improve, and efforts in that regard ultimately will pay dividends in better patient selection for therapies. Unquestionably, if the DWI/PI/MRA evaluation were instantaneous as the patient passed through the portals of the emergency department, its use would be a no-brainer. And some day it probably will.

Is the emphasis to be placed in the direction of MR scanner improvement, or should it be in the direction of universal patient education, faster EMS identification of stroke patients in the field, and more rapid patient triage, evaluation, and treatment, all with minimum delay? Efforts expended in the latter direction will reap the greatest immediate rewards for more patients in the early time window. In addition to our efforts in speeding up the imaging process itself, in order to help those individuals not seen until a later time window, it should be the responsibility of neuroimagers and neurointerventionalists to cooperate maximally with the stroke therapy infrastructure to achieve that end as well.

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Bleed or Stroke? Diffusion Measurements in Intracranial Hematomas

In the brief time that it has been readily available in the clinical arena, diffusion-weighted imaging (DWI) has become an integral part of many protocols, notably those directed at imaging the patient suspected of harboring an acute ischemic infarct (1). As experience has been gained, however, it has become clear that not all lesions that reduce diffusion are infarcts. Indeed, reduced diffusion has been reported in acute encephalitis, in acute demyelinating diseases such as multiple sclerosis, in abscesses, and in lymphomas. Calling everything that reduces diffusion an acute infarct is a pitfall to be avoided.

At the same time that technical advances in MR imaging have made diffusion imaging fast and widely available, advances in acute stroke therapy have mandated that imaging studies be performed and interpreted rapidly. To this end there has been a move in some institutions toward immediate MR imaging in the setting of suspected acute ischemic infarction, rather than the traditional performance of the noncontrast CT to assess for intracranial hemorrhage or other processes that may mimic acute ischemic infarction clinically. Therefore, if the patient suspected of having an acute infarction undergoes only MR imaging, with an abbreviated protocol that may include only diffusion and perfusion imaging, possibly with fluid-attenuated inversion recovery (FLAIR) and MR angiography, a thorough understanding of the appearance of blood products is necessary to interpret appropriately the diffusion images. In this issue of the *AJNR,* Atlas et al (page 1190) report the appearance of 17 intracranial hematomas on both conventional and diffusion-sensitive MR images, and discuss how this information furthers our understanding of the evolution of signal characteristics of hematomas over time.

Sixteen consecutive patients with 17 intracranial hematomas (proven by CT, surgery, or both, and not related to tumor, infarction, or trauma) were studied with T1- and fast spin-echo T2-weighted imaging, as well as DWI from which apparent diffusion coefficient (ADC) maps were calculated. All phases of hematoma evolution were represented based on conventional MR imaging criteria. The authors found that the hematomas could be segregated clearly into two groups based on their average ADC values. Those hematomas containing intact red blood cells (eg, hyperacute, acute, and early subacute hematomas) had significantly reduced diffusion compared to those containing lysed cells (subacute to chronic hematomas). Also of note, the ADC values of all early hematomas were reduced significantly compared to normal white matter. Potential causes offered to explain this phe-

nomenon included: a decrease in volume of the extracellular space with clot retraction, a change in the osmotic environment of extravascular blood such that the shape of the red blood cell is altered, formation of the fibrin network associated with clot, conformational changes of the hemoglobin molecule, or a contraction of intact red blood cells with a decrease in intracellular space. There is evidence that the relative size of intracellular and extracellular compartments may influence the appearance of ischemic infarcts on DWI significantly (2), and this is probably relevant to the diffusion properties of hematomas as well. Relative contributions of this and other mechanisms remain to be investigated in the future.

Intracranial hematomas change over time in many ways, two of which are particularly important: first, the oxygenation state of hemoglobin changes, and second, red blood cells lyse. During the hyperacute, acute, and early subacute phases of hematoma evolution, hemoglobin is oxygenated initially, then undergoes deoxygenation, and finally becomes oxidized and forms methemoglobin; all of this occurs within an intact red blood cell. In the late subacute to chronic phases of hematoma evolution, the red blood cell membrane lyses and methemoglobin becomes extracellular. Hemoglobin in its various states has variable magnetic susceptibility effects, which contribute significantly to the appearance of a hematoma of a given stage on conventional MR images. Diffusion-weighted MR sequences are primarily sensitive to changes in water motion, a parameter that is influenced by a number of factors including: the relative size of the intracellular and extracellular spaces, the presence or absence of intact cell membranes, and the degree of anisotropy of a given tissue. One might therefore expect that the presence or absence of intact red blood cell membranes would influence significantly the appearance of an intracranial hematoma on diffusion-weighted images. Of course, one must work within the caveat that the diffusion-weighted image is many things, ie, it is not only sensitive to microscopic motion of water, but it is also sensitive to T2 and magnetic susceptibility effects due to its long echo time and echo-planar acquisition. Furthermore, the postprocessing of diffusion-weighted images to obtain ADC maps presupposes the presence of some signal on the images. We have observed cases where acute hematomas, presumably composed of deoxyhemoglobin, have appeared purely as signal voids on T2- and diffusion-weighted images, and so the interpretation of postprocessed diffusion attenuation images and ADC maps does not yield meaningful information with regard to diffusion properties. This problem is shown in part by Figure 2 (page 1193) in the article by Atlas et al; the black rim around the hematoma on the diffusion-weighted image presumably is due to susceptibility effects and does not yield useful information on the ADC map, whereas the bright center corresponds to a region of reduced diffusion and is portrayed accurately on the ADC map.

The data presented in this paper suggest that early hematomas (containing intracellular oxyhemoglobin, deoxyhemoglobin, or methemoglobin within intact red blood cells) could appear identical to the signal intensity of acute infarction on diffusion-weighted images and ADC maps despite their clear differentiation on conventional MR images. Therefore, diffusion-weighted images and ADC maps obtained in the context of acute neurologic deficit always should be interpreted in the context of conventional MR images (at the very least the echo-planar T2-weighted image that is obtained as part of the diffusion-weighted sequence with b = 0). We would agree with this concern and would add the further caveat that one must review the diffusion-weighted image carefully and not simply draw conclusions from the ADC map alone. In the same way that diffusion-weighted images can be ambiguous on the basis of ''T2 shine-through'' (3), ADC maps can be ambiguous if they are derived from diffusion-weighted images that lack signal completely due to, for example, magnetic susceptibility effects. Our acute stroke protocol at present includes sagittal T1-weighted images, axial FLAIR images, diffusion and perfusion imaging, intracranial MR angiography, and postcontrast T1-weighted imaging, with the latter two eliminated in the uncooperative patient. In addition to viewing the source of diffusion-weighted images, we perform postprocessing to obtain diffusion attenuation images and ADC maps. We agree with Atlas et al's note of caution with regard to the potential for misinterpretation of diffusion imaging in the context of acute neurologic deficit, and echo the notion that data from each sequence must be incorporated into a coherent clinical and imaging picture.

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Diffusion-weighted Imaging of the Spinal Cord: Is There a Future?

MR imaging of the brain has benefited over the past few years by the routine use of a number of innovative pulse sequences, prominent among which has been diffusion-weighted imaging (DWI). The efficacy of this technique, well known to virtually all radiologists, has found its greatest use in the evaluation of cerebral ischemia, although application to other brain abnormalities has been shown in numerous publications. The incremental information that DWI brings to brain imaging is formidable, so naturally the desire would be to add DWI to the MR study of a patient with spinal cord dysfunction. One could envision many situations in which DWI would be extremely helpful, both in terms of diagnosis and evaluation of the efficacy of medical and surgical treatment. Clearly, spinal cord infarcts resulting from either arterial or venous abnormalities come to mind first, not just because their cerebral counterparts can be identified so well, but because cord infarct/ischemia is frequently a difficult diagnosis to make on the basis of MR findings. Other entities, such as acute transverse myelopathy, Wallerian degeneration, or acute disseminated encephalomyelitis might be diagnosed earlier and characterized better if proper technical parameters for obtaining spinal cord DWI and calculations of apparent diffusion coefficients could be achieved. Unfortunately, there are many technical and physiologic problems to overcome before DWI of the spinal cord becomes an accepted and routinely used protocol.

In this issue of the *AJNR*, Robertson et al (page 1344) describe their work on line-scan diffusion imaging of the spinal cord in 12 children, and in three cases they compare line-diffusion scanning with echo-planar diffusion imaging (EPDI). As one might expect, line scanning resulted in a better signal-to-noise ratio, and there were diminished magnetic susceptibility effects. The wide range of relative anisotropy in the normal cords is explained by both the curved nature of the spinal cord relative to the orthogonal diffusion-gradient axes, as well as the averaging of gray and white matter in their measurements. With this article in mind, and with an increased interest in cord DWI, it is clear that a number of problems must be successfully dealt with before DWI of the cord becomes part of routine spine imaging. The inherent difficulties in obtaining high-quality DWI of the cord, and techniques for dealing with these problems, deserve comment.

A major difficulty in obtaining DWI of the cord is physiologic motion, particularly CSF flow, which causes imaging artifacts. A number of strategies can be employed to overcome the artifacts that pulsating CSF generates, including novel means of data acquisition such as the navigator-echo or line-scanning technique, fast imaging methods such as single-shot EPDI or single-shot fast spin-echo (FSE) imaging, and cardiac gating. Problems exist, however, with each of these strategies. Specifically, when cardiac gating is used, the examination time is extended because only a limited number of images are acquired when cord motion is minimal (ie, during diastole). When the navigator-echo method with fast imaging or line scanning is used, lower signal is obtained. Finally, when EPDI is used, magnetic susceptibility artifacts and low spatial resolution of this relatively small structure result in suboptimal image quality.

The navigator-echo method, which uses an extra spin-echo sequence with no spatial phase encoding, provides phase shift information due to bulk motion, and these data are used to correct for phase shifts before the images are reconstructed. In addition, when the navigator-echo technique is used in conjunction with cardiac gating, diffusion-weighted images can be acquired throughout the entire cardiac cycle, not just during minimal motion, and this reduces scan time. Despite the advantages of the navigator-echo method and cardiac gating, the fast scanning techniques that are used in conjunction with them come with certain drawbacks. Specifically, EPDI, which uses multiple gradient echoes to acquire data, suffers from local susceptibility artifacts. This problem can be overcome by the use of a single-shot FSE sequence, which uses 180° refocusing pulses, rendering it less sensitive to artifacts caused by local magnetic field variations. With both single-shot FSE and EPDI, however, broad receiver bandwidths are used, which diminish the signal-to-noise ratio.

Line scanning differs in a number of ways from the conventional 2D Fourier transform imaging methods. This spin-echo–based technique acquires data from individually excited columns (or lines), and because no phase-encoding gradient is needed, artifacts due to physiologic motions are minimized. In addition, because line scanning uses a spin-echo rather than a gradient-based sequence (EPDI), susceptibility artifacts are minimized. Despite these advantages, an adequate signal-to-noise ratio is a problem in line scanning because data are received from just one column (line) of tissue rather than from an entire slice of tissue.

When one considers the issue of spatial resolution and the desire to image a patient's spinal cord with a resolution that approaches in vitro cord imaging, the problem of insufficient signal is clear. It may be that, with 1.5-T scanners and the current generation of receiver coils, none of the above-mentioned techniques offers the high signal and resulting image quality that would allow DWI of the cord to be widely and routinely implemented.

The answer to this dilemma of adequate signal combined with reasonable spatial resolution in

DWI may require a rethinking of our approach to ''physiologically based'' images of the spinal cord. Specifically, in addition to innovative acquisition techniques or faster scanning, high field strength systems (3T or higher), different types of receiver cord design, or both eventually may be a successful approach. More signal from such system redesign may be the approach needed to give DWI of the spinal cord a future.

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Redefining ''Normal''

Normalcy, like pathology, consists of a summation of various parts that, when viewed as a whole, indicate that all is as it should be with no exceptions. Normal, therefore, is often defined as the complete absence of abnormal. In dealing with pathologic processes on cross-sectional imaging, we often encounter cases in which the anatomic imaging appears normal, but the underlying function or metabolism is indeed abnormal. Thus ''normal'' becomes far more difficult not only to define, but to recognize as well. Is it not more appropriate to assume that for a tissue or organ to be truly normal, all of its parts must be normal in form, metabolism, and function?

To complicate matters even more, we are often asked in pediatric imaging research to compare a pathologic population to one that is proven to be ''normal.'' This normal population is often referred to as the ''normal control population'' and is used to assess just how far the pathologic group has strayed from the fold. The problem in pediatric imaging research, as in all imaging research, is that we are caught on a double-edged sword. Our research is often considered incomplete without a comparison to a normal control population, but we are also told that to sedate or expose a normal, healthy child to clinically nonindicated imaging for the sole purpose of securing normative data is unethical and often refused by the local Institutional Review Board. The use of normative data from a population of children undergoing a clinically indicated examination, but who are otherwise ''normal,'' is one logical way around this dilemma. Unfortunately, this practical solution is often snubbed by academic purists who argue, ''How can you ever be sure these children are truly normal if they should happen to have a clinical problem that requires imaging?'' One way around this would be to recruit ''normal'' subjects from among the families of these academic purists, or more practically, we could better define acceptable inclusion criteria for a normal control population that makes it easy to gather such data.

In the current issue of the *AJNR,* Choi et al (page 1354) attempt to deal with one part of this difficult issue by defining a range of values (peak area ratios) using magnetic resonance spectroscopy (MRS) for the allocortex and isocortex in the normal developing human brain (that is the hippocampal formation and the peripheral cortex, respectively). Their intent was to define the range of normal using MRS images from different regions of the developing brain at different ages. Their study consisted of 30 subjects in different age groups, who were defined as normal based on an appropriate developmental history, the absence of identifiable disease, a normal neurologic examination, and normal cross-sectional imaging. Single-voxel MRS using stimulated-echo acquisition mode was used to assess portions of the limbic cortex, often defined as the allocortex, versus parietal or frontal peripheral cortical regions, often referred to as the isocortex. This division was sound, as it is well known that these two regions perform differently both structurally and functionally. They are also regions that are often affected by disease states in the pediatric age group.

Their results revealed a trend of metabolic ratio values, which allowed differentiation of the two regions, and that is in agreement with previous work in this area. The presence of N-acetylaspartate/total Creatine (tCr) was found to be significantly lower in the allocortex compared to the isocortex; amounts of choline/tCr and myo-inositol/tCr were found to be significantly higher in the allocortex compared to the isocortex. These trends give us further insight into the differences between these two distinct regions, and provide normative data, which can be used to characterize a pathologic process when anatomic changes may be absent. Obvious weaknesses do exist in their work. First, the number of subjects enrolled in the study is insufficient, especially when different age groups are taken into consideration. The second weakness is the rather loose documentation of normalcy in their study group, which is a topic we should explore further.

Let me begin by saying the work by Choi et al, in my opinion, is a valid contribution to neuroscience. Despite the two issues I have raised, which are common to many similar studies, this work represents a well-performed study with valid preliminary information toward creating a normative database for MRS in specific regions of the developing brain. How many subjects are sufficient is always a critical issue. Clearly, 30 subjects are

not enough for a normative database that may require hundreds, if not thousands, of observations to reach statistical significance. The real issue is when are subjects really normal? There is, of course, no definitive answer to this question, but some generalizations of practical importance can be made.

Normal for an imaging study must take into consideration both minimal clinical as well as imaging criteria. Clinical issues must be resolved for each subject to assure they fit a profile of clinical normalcy that is acceptable based on observation and examination, perhaps by more than one observer. In the case of children, this must include an adequate assessment of childhood development and achievement. For example, does the child function at an appropriate school level? Have appropriate developmental milestones been on time? While the methods to assess childhood development are complex, and acceptable standards for clinical normalcy remain controversial, no study to create a normative database using brain imaging should fail to provide adequate documentation of normal development. At the very least, such data should always be included for each subject even if it is not used to include or exclude subjects. For the same reason, documentation of a normal general and a normal neurologic examination is also essential, while recognizing that it is difficult to standardize such an examination or overcome interobserver variability in performing the examination.

Finally, what are minimal criteria for normalcy with respect to the imaging examination? Two approaches have some validity as well as pitfalls. The first is to assume that whatever we recognize by imaging is to be considered normal if the child is clinically determined to be normal. The second is to accept minimal criteria for normalcy based on imaging corroborated by a normal clinical assessment. While these two approaches at first sound similar, their outcome and the way subjects are recruited may be quite different. In the first approach, minor abnormalities revealed by imaging often may be found even if the child is considered clinically normal. These may take the form of congenital malformations that are often clinically silent. Such an approach always raises questions with respect to whether such normal control populations are indeed valid. This approach also fails to deal with the dilemma of recruiting normal children to have examinations, which may not be clinically indicated, and therefore cannot be sedated even if they are too young to hold still for the examination. In the second approach, such abnormalities would be excluded because they would fail to meet the criteria for normal imaging as well as a normal clinical examination. Recruitment using this approach allows one to include children undergoing clinically indicated examinations and use them as normal controls. As long as the imaging is normal and the clinical examination is likewise normal, these subjects may well fulfill the needs of a normal control population.

But how are we to deal with cases of structural normalcy with metabolic or functional compromise? This brings me back to my original point. Is it not more appropriate to assume that for the brain to be considered truly normal, it must be normal in form, metabolism, and function? The answer is yes, as one might expect. We cannot assume that the brain is normal based on anatomic definition alone, but the presence or absence of normal metabolism, and perhaps even function, must also be taken into consideration. Normal function may be assumed if the clinical examination is normal, which leaves us only to resolve metabolic issues. The work by Choi et al thus takes on an even more important role as we attempt to define normal control populations. We should begin to look, based on multi-spectral imaging, at what are or are not acceptable criteria for recruitment into a normal control population that does not tie our hands or limit our options. One could argue validly that as long as the clinical examination is normal, and the anatomic and MRS images are normal, a subject might be an acceptable normal control despite any clinical indication for the examination itself. By doing so, we may untie our hands with respect to identifying acceptable control populations that meet minimal standards, but whose data are easily collected in statistically valid numbers, while maintaining our ethical and legal obligations.

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