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esty and accuracy, will not be tolerated by the editorial staff of the *AJNR*.

After the South Korean stem cell scandal, a survey showed that 8 of 10 Korean investigators were not aware of the "Declaration of Helsinki."[6] This declaration reflects the policies of the World Medical Association with respect to research and states that both authors and publishers have ethical obligations that include preservation of the accuracy of the results in any investigation. Because we are an image-driven specialty and journal, we need to abide, in the most rigorous fashion, by the above-mentioned principle if we want to retain our credibility.

Mauricio Castillo
Editor-in-Chief

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EDITORIAL

A New Era in Neuroradiology: Ex Vivo Validation of In Vivo Imaging Research

In an intriguing article in this issue of the *American Journal of Neuroradiology* on diffusion tensor imaging (DTI) and brain abscesses, Gupta et al[1] have elevated the field of neuroradiology to a more sophisticated and erudite level. These authors set new standards for the investigational analysis of novel imaging techniques and their application to patient care. Our attention is directed not only to what lesions DTI and fractional anisotropy (FA) can diagnose and how these techniques can be used in treatment monitoring but also to the molecular basis for this diagnosis and treatment response and the ex vivo validation. These authors show us that we should no longer be content with the use of conventional images to diagnose brain abscesses (by the display of thin ring enhancement in lesions that demonstrate high signal intensity centrally and low signal intensity peripherally on T2-weighted imaging, low signal intensity centrally on T1-weighted imaging, and high signal intensity centrally on diffusion-weighted MR imaging [DWI] with matching low signal intensity on apparent diffusion coefficient [ADC] maps indicative of restricted fluid motion) but that we must also use these latest imaging techniques to expand our understanding of the molecular basis and the tissue microstructure of this pathology.[1,2] This greater comprehension, bolstered by the results of confirmatory ex vivo investigations, should not only increase our confidence in the imaging diagnosis of brain abscess but should also aid clinicians in the development of new treatment strategies.

So just what exactly did these investigators do? They examined by DTI 24 consecutive patients with brain abscesses and then quantified the FA in the central portion of the brain abscess.[1] After sonography-guided neurosurgical aspiration of the pus from the abscess cavity, the neuroinflammatory molecules from the aspirate, including tumor necrosis factor-α, interleukin1-β, lymphocyte function associated molecule-1, and intercellular adhesion molecule-1, were analyzed and quantified. Increased FA was found to be correlated with the presence of these neuroinflammatory molecules, leading the authors to suggest that this increased FA was a reflection of an upregulated inflammatory response in brain abscess.[1] However, these authors did not stop their investigation there. The beauty of their research was that they went 1 step further and confirmed their results through ex vivo assays. They induced neuroinflammatory molecules in Jurket cell lines by exposing them to heat-killed *Staphylococcus aureus*.[1] They then performed DTI and obtained FA measurements at 4 time points (1, 24, 48, and 72 hours) on both *S aureus*–treated as well as nontreated Jurket cell lines and confirmed that increased FA correlated strongly with the presence of these neuroinflammatory molecules.[1] They concluded that the increased FA was due to the structured orientation of neuroinflammatory cells in the abscess cavity, an environment induced by the upregulation of these various adhesion molecules on the inflammatory cells.[1]

This theory certainly seems to make sense if one reviews the mechanism of abscess formation in the brain. As briefly summarized by Gupta et al, [1] it is thought that the presence of a bacterial organism in the brain such as *S aureus* activates glial cells, which then cause proinflammatory molecules to be secreted such as tumor necrosis factor-α and interleukin1-β, which subsequently influence the expression of numerous cell adhesion molecules, known as CAMs, located on the wall of the endothelial cells. Included among the CAMs are intercellular CAMs, vascular endothelial CAMs, and platelet-endothelial CAMs.[1,3-5] The upregulation of these CAMs on endothelial cell walls leads to adherence of inflammatory cells such as neutrophils and to the opening of the blood-brain barrier and subsequent extravasation of these peripheral immune cells, which then target the infected area.[5] A brain abscess develops in this milieu of immune activity and inflammatory response and, as a result, assumes a structured microenvironment due to these immune cells and neuroinflammatory molecules. Although many investigators, using DWI and ADC values, have drawn on this feature of a structured microenvironment to help distinguish bacterial brain abscesses from either cystic necrotic tumors or from fungal or parasitic brain abscesses[2,6-11] and to aid in treatment monitoring,[12] the use of DTI and FA to make these distinctions is just now emerging.[13] Even more novel is the exploration of the rationale behind these distinctions provided by FA.

The authors then are to be congratulated that they have provided us with ex vivo evidence to support their hypothesis relating FA to the upregulation of various adhesion molecules

on inflammatory cells. Yet, as with all good research, the study raises as many questions as it answers and stimulates us to broaden the scope of these authors' initial investigations. For example, one has the feeling that the question of what causes increased FA in brain abscesses may be more complex than this article suggests. Surely the upregulation of neuroinflammatory molecules is not the only factor involved in increased FA in brain abscesses. One notes in the authors' own series that 2 types of signal-intensity distribution were observed on DWI—homogeneously hyperintense and heterogeneously hyperintense—and that most brain abscesses were heterogeneous. This implies that the FA may vary in different parts of the same abscess, a finding that may have an impact on diagnosis and treatment monitoring. Furthermore, if the demonstration of an organized matrix is the key to the establishment of a link between a high FA and the presence of neuroinflammatory molecules and immune cells in brain abscesses, it seems reasonable that the authors should have performed microscopic analyses to confirm this structured environment, which is so critical to FA.

One could also query whether the severity of the initial insult (the bacterial load), the type of organism (ie, *Streptococcus* sp. versus *Staphylococcus* sp. or bacteria versus fungus versus parasite), the status of the patient's immune system (immune intact versus immunocompromised), the time since the inoculation, the use of antibiotics or steroids before diagnosis, or any other modifying events contribute to the FA values. Is the FA elevated to the same degree in different abscesses in the same patient or in different locations in the brain in the same patient? Does the size of the abscess, the location and size of the region of interest, or the use of contrast make any significant difference to FA measurements? If indeed there are additional factors that may alter or contribute to the FA of brain abscesses, can we rely on a high anisotropy value to establish the diagnosis of brain abscess and confirm the integrity of the patient's immune system? Furthermore, would we be able to expand our use of DTI and use FA measurements to reliably differentiate toxoplasma encephalitis from lymphoma in immunocompromised patients? If the FA values in different disease processes are too similar to those described by Gupta et al[1] in bacterial abscesses, how helpful will this technique be to diagnosis if these overlaps are present?

The answers to these questions are yet to be elucidated, but certainly the authors have provided us with a framework on which to build and on which to expand our role as neuroradiologists. Bravo to these investigators for encouraging us not only to detect, diagnose, and therapeutically monitor brain abscesses with these newer imaging techniques but also to broaden our understanding of the molecular basis and tissue microstructure of brain abscesses and to corroborate our understanding through ex vivo experiments!

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