Image of the Month

Functional MRI, single-photon emission computed tomography, PET, and magnetic resonance spectroscopy have identified brain structures activated by pain. These include the primary and secondary somatosensory cortices, the insula, the anterior cingulate, the thalamus, the dorsal lateral prefrontal cortex, and the basal ganglia.

Similar studies have indicated fibromyalgia patients have abnormal activation in these regions, both at baseline and in response to painful stimuli.

Diffusion-weighted imaging (DWI) measures the restriction of water diffusion (the apparent diffusion coefficient or ADC) in the brain. Diffusion tensor imaging (DTI) measures the directional diffusion properties of water (fractional anisotropy or FA), and therefore, the integrity of organized tissue microstructures.

Dr. Pia C. Sundgren and Dr. Daniel J. Clauw, with colleagues at the University of Michigan in Ann Arbor, used DWI and DTI to look for cerebral abnormalities in fibromyalgia patients, versus healthy controls (Acad. Radiol. 2007;14:839-46).

The researchers studied 19 fibromyalgia patients (16 women), aged 20-57 years, and 25 pain-free controls (19 women). All subjects underwent MRI (1.5 T) including pre- and postcontrast enhanced axial and sagittal T1-weighted images, axial T-2 weighted images (with fat saturation), axial fluid attenuated inversion recovery (FLAIR) images, diffusion-weighted images, and postcontrast coronal T1-weighted images. The images were evaluated for brain volume loss, abnormal signal, abnormal contrast enhancement, abnormal diffusion, the presence of hemorrhage or mineralization, or other abnormalities.

First, the researchers developed whole-brain, gray matter–only, and white matter–only ADC histograms for each patient and control. Then histograms by group (fibromyalgia patients and controls) were calculated. ADC and FA maps also were calculated. Both ADC and FA are quantitative, with normal brain values of ADC around 0.7×10^{-3} mm^2/second. FA is a value between 0 (isotropic) and approaching 1 (highly anisotropic).

DTI maps were registered with postcontrast axial T1-weighted images. Standardized 50 mm^3 circular regions of interest (ROIs) were at the amygdala, periaqueductal gray, insular cortex, orbitofrontal cortex, internal capsule, middle thalamus, corpus callosum, dorsolateral prefrontal cortex, cingulate gyrus cortex, parietal white matter, and frontal white matter. Mean ADC and FA values at the ROIs were compared between groups.

Clinical pain was assessed immediately before the DWI and DTI scans using a 10-cm visual analog scale. Pressure pain threshold was assessed before the DWI and DTI scans. Discrete pressure stimuli were applied to the subject's left thumbnail. Pain intensity ratings were recorded. Patients with fibromyalgia also were given the Center for Epidemiologic Studies Depression Scale questionnaire and the Spielberger's State-Trait Personality Inventory anxiety questionnaire. Specific cognitive beliefs about pain and control over pain were assessed using the Beliefs About Pain Control Questionnaire.

FA values were significantly less in the right thalamus for fibromyalgia patients, compared with controls. No differences were found in any other locations.

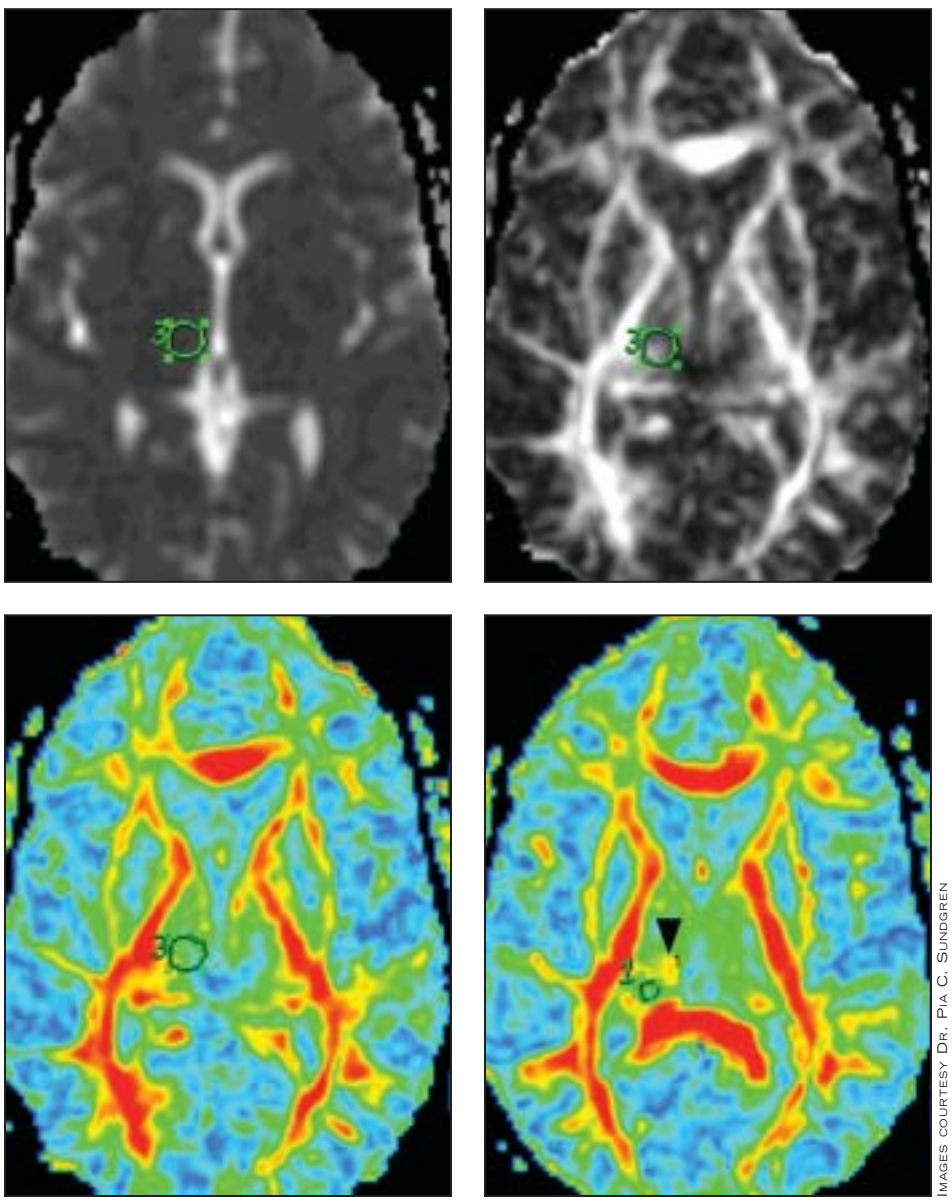
The differences in FA in the thalamus prompted the researchers to examine the relationship between the severity of fibromyalgia and FA within the group. Patients with more severe pain had lower FA values. Fibromyalgia patients tend to attribute their pain to an external event like minor trauma. The investigators found a negative correlation between the belief in an "external" cause of their pain and the FA values. This indicates these low right-thalamic values also were tied to a cognition known to be negatively associated with prognosis in chronic pain. Lower right-thalamic FA values also were tied to greater numbers of tender points, higher levels of depression, and a low pain threshold.

"The abnormalities that we've identified using this technique are actually less pronounced than what you'd find with [functional MRI] or PET or proton spectroscopy or other modalities. All of those modalities identify objective differences between fibromyalgia patients and controls with respect to pain processing regions," said Dr. Clauw. "What you really find with all of those functional imaging techniques—this one included—they all give you different and somewhat complementary information. … There really is something wrong going on in the brains of these patients with fibromyalgia," said Dr. Clauw.

The focal nature of these findings suggest these abnormalities are caused by ongoing demyelination or axonal injury but are rather due to neuronal dysfunction.

"If the tissue is less organized or the axons are dysfunctional, it might be seen as a reduction in the main directionality combined with alterations in the other diffusion directions resulting in a more round and less sphere/ellipsoid appearance of the diffusion directionality as can be seen in a more isotropic environment. This idea can be supported by the normal ADC value found here in the same region," they wrote.

—Kerri Wachter



Images courtesy Dr. Pia C. Sundgren

ADC and FA maps (top left and right) of a fibromyalgia patient: On the same FA map (bottom left), red white matter tracts indicate greater anisotropy. On another FA map (bottom right), there is less anisotropy in the dorsomedial aspect of right thalamus.

Expert Commentary

Pregnancy Registries

BY GERALD G. BRIGGS, B.PHARM., FCCP

Pregnancy registries are valuable sources of information, and for many drugs and vaccines they are the primary source of human pregnancy experience. The strengths of these registries are their prospective nature—women are enrolled before the outcome is known—and enrollment is over a wide geographical area. Typically, two types of pregnancy outcomes are obtained: outcomes with birth defects and outcomes without known birth defects. The latter comprises live births, fetal deaths, and spontaneous abortions.

Registries can identify the early signals of teratogenicity, but they also have several limitations. They depend on voluntary reporting, which results in selection bias, and they are not representative of target populations. Pregnancies that are lost to follow-up may have had different outcomes than those with documented outcomes. Furthermore, registries lack details on elective terminations and fetal deaths without birth defects, and all spontaneous abortions. Finally, with some exceptions, they usually lack control groups.

Because the total number of exposed pregnancies is unknown, data from a registry cannot be used to calculate prevalence of an outcome, but the data can be used to estimate the proportion of birth defects. Some registries also collect data on retrospective reports, which are less representative of the target population because they can be biased toward the reporting of more unusual and severe outcomes. However, they may be helpful in detecting unusual patterns of birth defects.

A complete list of pregnancy registries is available on the Food and Drug Administration Web site, which provides additional details on the registries, such as fax numbers, links to other Web sites, and mailing addresses (www.fda.gov/womens/registries). The registry most relevant to rheumatologists is associated with the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases Study. This registry is seeking women with rheumatoid arthritis, psoriasis, psoriatic arthritis, or ankylosing spondylitis who become pregnant while taking leflunomide (Arava), etanercept (Enbrel), adalimumab (Humira), and abatacept (Orencia). Contact the registry by calling 877-311-8972.

I encourage health care professionals to enroll appropriate patients in these registries whenever possible. ■

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