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EDITORIAL

Exceeding the Limits of the Normal Blood-Brain Barrier: Quo Vadis Gadolinium?

In this issue of the *American Journal of Neuroradiology,* hyperintense CSF in the subarachnoid space is demonstrated on fluid-attenuated inversion recovery (FLAIR) imaging in patients who had gadolinium-enhanced MR imaging (Morris et al). These surprising findings are described in subjects without abnormalities known to disrupt the blood-brain barrier and can occur with or without the presence of renal insufficiency.

Although this finding is reversible and may represent a diagnostic pitfall, there can be important implications. Clinical issues such as drug dosage and administration, toxicity, and contraindications need to be carefully considered. New and useful pathophysiologic information may be obtained from the imaging findings. Mechanisms involving the behavior of the normal and abnormal blood-brain barrier may be further clarified.

Whether gadolinium contrast enters the CSF is presently not in question. In studies of healthy animals and in vitro phantoms, Mamourian et al[1] showed that gadolinium concentration in CSF increased with the administered dose of contrast. The in vitro gadolinium effects were observable on FLAIR images at concentrations 4 times lower than those on T1-weighted images. The amount of visualized CSF signal-intensity change should depend on technical factors such as the dose of contrast, injection speed, and pressure; however, the presence of underlying clinical conditions may also exacerbate this effect. Although the severity of the underlying barrier disruption and the resulting clinical consequences are not fully known, similar CSF signal-intensity changes have been observed with major disruptions of the blood-brain barrier in studies involving neurologic disorders such as ischemic stroke, epilepsy, tumors, and acute brain injuries. In a study of seizures, the high CSF signal intensity on sequential FLAIR images was attributed to high protein levels in CSF, secondary to disruptions of the blood-brain barrier related to seizure activity.[2] More specifically, blood-brain barrier leakage may occur during epileptogenesis and the chronic epileptic phase, contributing to the progression of epilepsy.[3] If free gadolinium is actually released from the chelated complexes, significant neurotoxicity may then occur. Predisposing conditions such as renal dysfunction may lead to elevated free gadolinium in the CSF. In fact, subacute encephalopathy secondary to inadvertent repetitive gadolinium contrast administration did occur in a patient in renal failure.[4] Although this type of complication could be reduced with proper hemodialysis, intrathecal gadolinium has been shown to produce movement disorders and ataxia in animals, with necrosis and myelinolysis. More generally, the phenomenon of CSF signal-intensity change is not just limited to gadolinium because similar results have been observed with iodinated contrast injection. In a series involving patients with acute ischemia treated with intra-arterial thrombolysis, Kim et al[5] noted that sulcal hyperintensity on FLAIR imaging may be caused by iodinated contrast medium. Again, this should not be considered subarachnoid hemorrhage and could be associated with subsequent hemorrhagic transformation.

Where does the leakage actually occur? Presently, the physiologic mechanisms that control the brain environment are collectively known as the blood-brain barrier and consist of an anatomic barrier and a regulatory interface.[6] In the early 1900s, it was observed that dyes injected into the circulation did not stain the CSF, and this led to the idea of a blood-brain barrier. However, the typical morphologic features of the blood-brain barrier are not present in all brain regions. The first component of the blood-brain barrier occurs at the cerebral microvasculature level and is composed of unique cerebral capillary endothelial cells with tight junctions. The lack of permeability of this barrier and the absence of intraparenchymal enhancement on postcontrast scans suggest that it is an unlikely pathway for gadolinium penetration.

A second component is the blood-CSF barrier at the choroid plexus level, first demonstrated by Goldmann in 1913 and further analyzed by Broman in 1941.[6] The blood-CSF barrier is essential in maintaining homeostasis and in the regulating neuronal function. Unlike the blood-brain barrier, the blood-CSF barrier is selectively permeable and therefore could have allowed the passage of gadolinium under certain conditions.

A third component consists of the circumventricular organs, several small regions including the neurohypophysis, median eminence, pineal gland, supraoptic crest, area postrema, and the subfornical and subcomissural organs. Because the blood vessels in the circumventricular organs have increased permeability compared with those in other brain regions, they can allow the free passage of gadolinium. However, the surface area of the circumventricular organs is 5000 times smaller than the blood-brain barrier, compared with either the surface areas of the blood-CSF or blood-brain barriers, which are both of the same order of magnitude. It is thus unlikely that the relative contribution of the circumventricular organs to CSF signal-intensity change is significant, though the effects of regionally increased gadolinium leakage remain unclear. In the future, detailed imaging could perhaps resolve the sites of leakage more accurately.

Although there has been significant research regarding the blood-brain barrier, the mechanisms involving its function and the consequences of its dysfunction are still under investigation. However, present studies indicate that a damaged blood-brain barrier may allow toxins to enter the brain, leading to neurologic conditions, including epilepsy, inflammation, and Alzheimer disease.[7]

With the continued development of improved imaging techniques, there is now an increasing need to evaluate the significance and consequences of greater intravenous contrast use. Our advances in imaging should also lead to a better understanding of the mechanisms underlying blood-brain barrier abnormalities.

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EDITORIAL

Inducing Brain Growth by Pure Thought: Can Learning and Practice Change the Structure of the Cortex?

In this issue of the *American Journal of Neuroradiology* (*AJNR*), the cortical gray matter attenuation in the inferior frontal and parietal regions of mathematicians is found to be increased compared with that of control subjects (Aydin et al). Cortical attenuation also correlates with time spent as an academician, suggesting that this is experience-dependent structural plasticity. The surprising discovery that the brain can actually change its shape within weeks in response to certain mental and physical stimuli differs from the traditional concept that brain morphology must remain unchanged, except as a result of neurologic disorders. Although it was previously known that plasticity leads to functional changes and new connections at the microscopic level, it was not until recently that stimuli-induced macroscopic changes in the brain were observed. A new and powerful technique, voxel-based morphometry, has now made it possible to evaluate changes in brain morphology in vivo and to correlate these changes with experience-related effects and brain function.

Historically, considerable attention has been given to the effect of knowledge and intelligence on brain size and shape, but all of these efforts have been completely unsuccessful. In the 19th century, multiple attempts to map personality attributes by observing bumps on the head (phrenology) were thoroughly discredited. It is only now that researchers have finally demonstrated that certain parts of the brain are function-specific and may grow with learning. Indeed, the expression "la bosse des maths" could now refer to the "bump for mathematics" described in this paper (Aydin et al).

The recent studies using voxel-based morphometry indicate that persons with particular skills developed for years have a thicker cortex. Specific anatomic alterations of the human brain have been observed in functional brain regions in response to various tasks involving music, navigation, language, and activity. In mathematicians, the increased cortical attenuation observed may be a result of their greater skills, but it may also be a cause. The correlation of cortical-attenuation difference with time spent as an academician suggests that this difference is an experience-dependent type of structural plasticity. This form of plasticity generally reflects learning and practice but is not necessarily the type that changes the makeup of the cortex. If the mechanisms producing learning-induced cerebral alterations produce macroscopic changes, what are the corresponding changes at the microscopic level? Moreover, if there are changes at the microscopic level, will they be manifested at the macroscopic level?

In terms of macroscopic changes, previous anatomic studies have reported increased attenuation of synapses, glial cells, and capillaries in the motor cortex. Biochemical studies have also shown that neurotrophic factors can play an essential role in affecting neuronal development. Nerve growth factor and brain-derived neurotrophic factor affect both neuronal survival and activity-related plasticity. Neurogenesis with increased neurons derived from basic stem cells has been documented in the hippocampus. In a study by Maguire et al,[1] increased cortical gray matter was demonstrated in the right posterior hippocampus of London taxi drivers compared with control subjects, and this correlated with time spent as a taxi driver. These changes were thought to be secondary to increased memory storage with internal changes in the hippocampus. However, the additional spatial information associated with increased posterior hippocampal volume was also thought possibly to affect adversely new spatial information in the anterior hippocampus. It has thus been theorized that too much plasticity may not always be good.[2] In a study involving medical students studying for their medical examination, the gray matter in the posterior and lateral parietal cortices was found to be significantly increased.[3] Similarly, changes have been observed in the Broca area and Heschl gyrus of musicians compared with nonmusicians. These results were thought to be use-dependent adaptation caused by musical training.

In terms of microscopic changes, mechanisms such as modulation of synaptic transmission may also lead to brain plasticity. Establishment of new synaptic contacts has been described as a possible neural mechanism mediating long-term cortical reorganization.[4,5] On the other hand, unmasking of existing but latent corticocortical connections could underlie the shorter term reorganization observed after deafferentation.[6] Reduced local inhibition and changes in synaptic efficacy may mediate connectional unmasking, with reduced gamma-aminobutyric acid (GABA)ergic function, possibly contributing to short-term cortical plasticity induced by deafferentation.[6] Although GABAergic-pathway modulation is rapid and short-term, it would not be expected to cause significant learning-related morphologic changes.

Other imaging techniques have also been used to further investigate learning-induced cerebral changes. In a previous issue of the *AJNR*,[7] MR spectroscopy was used to evaluate cerebral metabolite changes in musicians. *N*-acetylaspartate (NAA) concentration in the left planum temporale of musicians was found to be increased compared with that in non-