Enhancing our understanding of white matter changes in early multiple sclerosis

This scientific commentary refers to ‘Permeability of the blood–brain barrier predicts conversion from optic neuritis to multiple sclerosis’, by Cramer et al. (doi:10.1093/brain/awv203).

The cause of multiple sclerosis remains one of the great mysteries of neurology. Despite its clinico-neuropathological characterization almost 150 years ago by Charcot, we continue to gain fundamental knowledge about multiple sclerosis pathology. A major roadblock to the better understanding of multiple sclerosis, and many chronic CNS diseases, is the lack of adequate longitudinal histological analyses of the CNS. These are needed to show the early development of individual lesions as well as the changes in neuropathology over the years.

How do multiple sclerosis lesions begin? Neuroimaging has provided clues by revealing that lesions commence with blood–brain barrier (BBB) breakdown as indicated by gadolinium enhancement. In the BECOME study in which monthly gadolinium-enhanced brain MRIs were performed in 75 subjects with multiple sclerosis for 2 years, more than 95% of new lesions seen on T2-weighted/FLAIR magnetic resonance began with gadolinium enhancement (Cadavid et al., 2009). However, we do not know what precedes BBB breakdown. It is likely that subtle focal or global changes occur prior to gadolinium enhancement within the normal-appearing CNS.

To understand early events in lesion development, investigators often focus on patients who are at the early stages of a single demyelinating event, so-called ‘clinically isolated syndrome’ (CIS). In this issue of Brain, Cramer and co-workers examine patients with CIS limited to the optic nerves to determine whether subtle changes in BBB permeability are also present elsewhere in the CNS (Cramer et al., 2015).

Previous studies have examined such patients with magnetic resonance spectroscopy, finding increases in myo-inositol (Fernando et al., 2004) and reductions in N-acetyl-aspartate within normal-appearing white matter that are predictive of subsequent conversion to multiple sclerosis (Wattjes et al., 2008). Such chemical shifts suggest glial cell activation and neuronal injury at the earliest stages of the disease. Evidence of altered tissue integrity in normal-appearing white matter of patients with CIS has been revealed by magnetization transfer (Fernando et al., 2005) and diffusion tensor imaging (Gallo et al., 2005). Studies using magnetization transfer imaging suggest loss of macromolecules such as myelin, while diffusion imaging measures correlate with injured structural components within the tissue, including axons, myelin, and the tissue matrix. A recent study using PET showed that microglia are globally activated in the normal-appearing white matter and deep grey matter of patients with CIS compared to control subjects (Giannetti et al., 2015), and that the global increase in microglial activation is predictive of earlier development of multiple sclerosis over the next 2 years. This PET study is in accord with studies of autopsied multiple sclerosis tissues that have revealed activated microglia throughout normal-appearing white matter.

Dynamic susceptibility contrast (DSC)-MRI assesses tissue perfusion based upon susceptibility effects on T2-weighted sequences associated with the first pass of gadolinium contrast through the cerebrum. DSC parameters of cerebral blood flow and volume have been shown to increase in the weeks prior to acute lesion development (Wuerfel et al., 2004). Haemodynamic changes as assessed by DSC have varied within normal-appearing white matter across studies. One study observed cerebral blood flow and transit time to be increased within normal-appearing white matter in patients with CIS compared to controls (Papadaki et al., 2012), although this and earlier studies observed a decrease in these parameters in the normal-appearing white matter of patients with established multiple sclerosis.

Dynamic contrast enhanced (DCE) MRI has been utilized to qualitatively evaluate temporal patterns of enhancement (signifying BBB permeability) for lesions in various stages (Gaitán et al., 2011). Newly enlarging lesions often enhance outwards from the centre, but over time, the enhancement appears from the peripheral portion of the lesion towards the centre. This suggests different patterns of permeability associated with lesion outgrowth.

In this issue of Brain, Cramer and co-workers use DCE imaging to estimate subtle differences in gadolinium enhancement throughout the brain in very early stages of CNS demyelination. Previously, this same group has demonstrated by using DCE that patients with established relapsing-remitting multiple sclerosis have higher BBB permeability than controls (Cramer et al., 2014). Not unexpectedly, permeability was greatest in association with relapse. Although still higher than in normal control subjects, DCE was lower among those patients who were receiving disease-modulating therapies.

In the present study, Cramer et al. have applied the DCE-MRI technique to 39 patients with a single acute optic neuritis attack in order to search for BBB permeability changes elsewhere in the CNS, and to determine whether such changes might be predictive of confirmed multiple
sclerosis over the next 2 years. Periventricular permeability within normal-appearing white matter was increased by 50% compared to healthy controls in these patients with a single clinical demyelinating episode of the optic nerve. Among the 44% of patients who met 2010 McDonald criteria for diagnosis of multiple sclerosis during the 2-year follow-up, periventricular permeability was increased by 50% compared to those who did not subsequently meet multiple sclerosis criteria. Those who converted to multiple sclerosis also showed an ~50% increase in permeability in the thalamus compared to both non-converters and controls. Those patients who did not convert to multiple sclerosis over the 2 years showed no permeability differences from controls in either periventricular white matter or thalamus. While having nine or more T2 lesions at baseline was a strong predictor of conversion as established previously, the addition of increased BBB permeability improved the predictive power for development of multiple sclerosis. Moreover, permeability by DCE MRI was not correlated with T2 lesion counts, suggesting that alterations of the BBB leading to increased permeability may also be independent of focal inflammatory plaques.

This study is notable for revealing subtle changes in BBB integrity that support the concept that multiple sclerosis is not just a disease of multiple focal lesions, but affects large regions of the CNS white matter at the earliest disease stages. The present study indicates that, in regions that appear normal based on FLAIR (fluid attenuation inversion recovery) and are located well away from the site of acute optic neuritis, there is nevertheless a global mild alteration in BBB integrity in normal-appearing white matter. The level of increased contrast leakage correlated with elevated CSF levels of the chemokine CXCL10 and of MMP9, and with increased CSF cells. Activated microglia, as well as infiltrating inflammatory cells, may be the source of chemokines and MMP9. Of note, the majority of the converters to multiple sclerosis in the present study had CSF oligoclonal bands (82%), the presence of which indicates that the CNS had already been infiltrated by B cells and/or plasma cells. One interpretation of this study, in the context of previous studies using other imaging techniques, is that in early CIS, there already exists a pervasive underlying CNS pathology that is invisible to many standard imaging modalities.

Future studies should evaluate DCE in a longitudinal setting, in concert with other quantitative imaging techniques. The potential of DCE as a long-term predictor of disease severity would be interesting to assess. The multiple sclerosis disease-modifying therapy natalizumab acts by blocking cellular transmigration into the CNS. Thus, the effect of natalizumab therapy on DCE would be of particular interest to help determine whether increased DCE requires cellular infiltration, which might help address the question of whether multiple sclerosis lesions initiate inside the CNS or are instigated from outside. However, examining CIS may not be early enough. To determine the very earliest events of multiple sclerosis, we may need to perform longitudinal imaging and CSF studies in young people who are at very high risk of developing multiple sclerosis based on genetics and demographics.

Robert T. Naismith and Anne H. Cross
Department of Neurology,
Washington University School of Medicine,
St. Louis, MO 63110, USA

Correspondence to: Anne H. Cross
E-mail: crossa@neuro.wustl.edu
doi:10.1093/brain/awv196

References