Letter to the Editor

Is the disruption of the blood–brain barrier a prerequisite for cellular infiltration in autoimmune encephalitis?

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Sir,

We read with great interest the recent article by Floris et al. (2004) on the application of iron oxide particles as MR contrast medium in experimental autoimmune encephalitis (EAE). Infiltration of iron-labelled inflammatory cells was visualized in vivo by MRI. Most notably, local iron accumulation was present at an early clinical stage of disease, i.e. day 11. For assessment of the integrity of the blood–brain barrier (BBB), the authors applied gadolinium-DTPA (Gd-DTPA). Significant enhancement was also present beginning at day 11 after immunization. The authors estimated the area of signal loss on T2-weighted images as an indicator of local iron accumulation. Moreover, maps of Gd-DTPA enhancement were calculated in predefined regions of interest based on non-enhanced and contrast-enhanced T1-weighted images. The mean percentage signal increase after application of Gd-DTPA was more extensive in certain brain regions (i.e. spinal cord and brainstem) than the percentage of pixels exhibiting a signal loss above 2 SDs of the mean T2 value indicating iron deposition in the area of interest. Therefore, the authors conclude that ‘Gd-DTPA leakage clearly preceded monocyte infiltration as imaged by the contrast agent based on ultra small particles of iron oxide’.

It is an important question whether disturbance of the BBB is a prerequisite for subsequent invasion of inflammatory cells, or whether macrophages independently can gain access to the brain parenchyma in autoimmunity of the nervous system. In our view, the data presented by Floris et al. do not sufficiently substantiate the assumption that alterations of the BBB precede cellular infiltration in EAE due to the following reasons.

(i) The first evidence for enhancement of both contrast agents was day 11. Neither of the positively (Gd-DTPA) or negatively enhancing agents accumulated in the brain before that time point. Thus enhancement of both contrast media occurred synchronously.

(ii) The authors take a more extensive signal intensity increase after Gd-DTPA as evidence for an earlier BBB leakage. The analysis, however, is based on a comparison between a signal intensity increase and a square measure. In our view, a correlation between these two different quantities (which is not exemplified in the statistical analysis) is critical. It would have been more informative to correlate either areas of signal changes or signal intensity differences. However, even in case of an increased area or signal change in the Gd-DTPA group, this would not allow the conclusion that the BBB disturbance precedes cellular infiltration.

(iii) Signal intensity increase after application of Gd-DTPA is not per se an indicator of a disturbed BBB. An increased local concentration of Gd-DTPA may be caused not only by BBB leakage but also by an increase in regional cerebral blood volume (rCBV). An increase of the rCBV has been demonstrated in acute demyelinating plaques (Haselhorst et al., 2000) in multiple sclerosis. Recently, it has been shown that an increase of the rCBV preceded the formation of demyelinating lesions on MRI (Wuerfel et al., 2004). Therefore, it cannot be excluded that an increase in the mean signal intensity after application of Gd-DTPA is caused by local blood volume changes.

Accumulation of iron particles in EAE has also been described in the absence of Gd-DTPA enhancement (Doussset et al., 1999). These authors concluded that a disturbance of the BBB is not a prerequisite for the infiltration of iron-labelled monocytes. We have recently described local accumulation of iron-laden macrophages in experimental...
autoimmune neuritis (Stoll et al., 2004). On MRI, signal loss on T2-weighted images in the cauda equina was present already before onset of clinical symptoms, while enhancement of Gd-DTPA was not present (unpublished data). It appears that further experimental studies with repetitive MR studies are needed to clarify the key question regarding the spatiotemporal relationship between breakdown of the BBB and macrophage infiltration during CNS autoimmunity.

References