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LETTER TO THE EDITORS

Brain perfusion by arterial spin labeling MRI in multiple sclerosis

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Dear Sirs,

The role of MRI in multiple sclerosis (MS) has been well established for decades. Moreover, new MRI techniques have been developed to better understand the complex pathogenesis of this disease, since the use of conventional MRI techniques is partially limited by its weak associations with clinical features and low sensitivity for gray matter (GM) involvement and diffuse damage of white matter (WM) [1]. These limitations become even more significant in the disease shift from the predominantly inflammatory to degenerative phase [1].

MS has been traditionally considered a demyelinating inflammatory disorder of the central nervous system; however, vascular involvement and perfusion abnormalities are recently receiving an increasing interest [2]. Earlier PET and SPECT studies showed metabolic alterations and perfusion deficits in cognitively impaired MS patients, particularly at the cortical level in the left frontal and temporal lobes [3]. Recently, a dynamic susceptibility contrast-enhanced (DSC) MRI showed in MS a globally reduced but regionally mixed cerebral blood flow (CBF). Decreased CBF has been demonstrated in both normal-appearing WM (NAWM) [4–7] and deep GM [6, 7] in relapsing–remitting MS (RRMS) patients, which had also a significantly reduced CBF in the putamen compared to patients with clinically isolated syndrome (CIS) [7]. Interestingly, the greater reduction of NAWM CBF was found in primary-progressive MS compared to RRMS [5, 6], though NAWM CBF was decreased even in CIS patients [7]. A regional increase of CBF has been detected in early lesion stages, up to 3 weeks prior to brain–blood barrier (BBB) breakdown with subsequent contrast enhancement [8]. Furthermore, NAWM CBF was shown to significantly correlate with clinical disability [5], whereas GM CBF correlated with neuropsychological dysfunctions [6].

Due to recent increasing availability of higher field strength scanners, a new MRI technique called arterial spin labeling (ASL) has been proposed as a useful research tool in several neurological diseases. Interestingly, a reduction of GM CBF measured by ASL was confirmed in all MS patients compared to healthy controls while NAWM CBF has been alternatively found decreased in some studies [9–11], or increased in others [12, 13]. The reason for the increased NAWM CBF in few studies could be the incomplete separation between NAWM and both WM and enhanced lesions due to the relatively coarse resolution of ASL and non-use of exogenous contrast. Most T1-hypointense lesions were concentrated in WM regions with lower CBF, whilst the T2-hyperintense lesions were distributed in WM regions with both higher and lower CBF [11]. The negative correlations between the T2-hyperintense lesion volume and regional CBF have been showed in several brain areas [14]. Moreover, cerebral vasoreactivity (CVR) from normocapnic to hypercapnic CBF was found diminished in MS patients compared to healthy controls indicating an impaired CBF regulation [15]. Since decreased GM CVR correlated positively with GM atrophy and negatively with the lesion volume, it was hypothesized that the impaired CBF regulation may cause neurodegeneration due to an insufficient blood supply [15]. Similar to

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DSC technique, regional CBF by ASL has been correlated with clinical measures in MS patients, for example the left centrum semiovale CBF was found to be associated with performance on the spell out PASAT [16].

Initially, decreased cerebral perfusion was attributed to hypometabolism secondary to axonal degeneration, however, the study of both perfusion and diffusion tensor imaging supported the concept of primary ischemia in MS [17], as well as no relationship has been found between reduced CBF and impaired axonal mitochondrial metabolism or astrocytic phosphocreatine metabolism [10]. Hence, the decreased cerebral perfusion could be attributed to inflammatory-related changes according to fluid dynamics. It is known that the NAWM and GM manifest a constant, low-grade inflammation, which could lead to a venular vasodilation with slowing, reduced perfusion. The active lesions, coincident with BBB breakdown even in their early stage, determine a local fluid leakage with increased perfusion. Such lesions are less frequent in the deep GM; thus, it is difficult to see increased perfusion here. The inflammation together with perfusion changes can cause neuronal dysfunction even in absence of degeneration. This might explain the link between perfusion and clinical symptoms.

Therefore, perfusion MRI could provide a new potential outcome measures especially in progressive MS characterized by a more severe decrease in CBF and by a lower accrual of both Gd-enhanced or new/enlarged T2-weighted lesions. Moreover, perfusion MRI might represent a suitable tool to investigate microcirculation abnormalities and provide a more comprehensive measure of inflammation in RRMS.

Although ASL technique has limitations such as the relatively low spatial resolution and the requirement of a careful position of region of interests to prevent partial volume effects with lesions and blood vessels, it provides a sensitive measure of cerebral perfusion without the need of a contrast since it uses the blood as an endogenous contrast agent [13]. Therefore, ASL might become a useful tool to evaluate experimental neuroprotective drugs in proof-of-concept studies and reduce both patients' exposure to gadolinium and the costs of clinical trials requesting serial MRIs.

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Ethical standard All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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