Chapter 7

The contribution of magnetic resonance imaging to the understanding of multiple sclerosis pathogenesis

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Introduction

Magnetic resonance imaging (MRI) is a sensitive tool for diagnosing and evaluating in vivo the dynamics of multiple sclerosis (MS) [1]. However, the low pathological specificity of conventional, T2-weighted MRI inevitably limits its potential for defining the pathophysiology of MS [1], although enhancement on T1-weighted scans after the injection of gadolinium-DTPA (Gd) can be used as a reliable marker of blood-brain barrier (BBB) dysfunction [1].

More recently, the introduction of new strategies for post-contrast imaging and the application of non-conventional techniques [e.g. magnetization transfer imaging (MTI) and magnetic resonance spectroscopy (MRS)] [2, 3] have improved our understanding of the evolution of MS lesions [1]. The present review will outline the major contributions which can be obtained by the use of MRI techniques in the study of MS pathogenesis.

Conventional MRI

Studies both in animals [4] and in human MS brain biopsy specimens [5, 6] demonstrated that Gd enhancement is consistent with histopathological findings of BBB breakdown. Perivascular inflammation appears to be a necessary precondition to the development of enhancement, since non-inflammatory demyelination is unaccompanied by changes in BBB permeability [7]. Longitudinal MRI studies confirm that enhancement occurs in almost all new lesions in patients with relapsing-remitting (RR) or secondary progressive (SP) MS [8]. Focal areas of increased signal on enhanced images can also be detected before the appearance of lesions on unenhanced T2-weighted scans [9]. Enhancement may
reappear in older plaques, with or without a concomitant increase in their size [8], thus suggesting either partial repair of BBB or possible reactivation of BBB abnormalities.

The heterogeneity of BBB changes is reflected by the different morphological patterns of enhancement, i.e. nodular, patchy or ring-like. It has been suggested that nodular enhancing lesions represent small areas of perivascular inflammation either at the edges of established lesions or in areas of formerly normal appearing white matter (NAWM), whereas ring-enhancing areas are probably areas of acute inflammation at the edge of chronic demyelinated lesions [10]. Recently, Bruck et al. [11] and van Waesberghe et al. [12] found that ring enhancement is not restricted to reactivation of older MS lesions, but may be the first manifestation of new activity or the evolution of other enhancement patterns, especially in very large plaques.

Some insights about the various pathological substrates of enhancing lesions are also provided by the evolution of findings visible on unenhanced T1-weighted images. Most of the enhancing lesions show a corresponding area of hypointensity on pre-contrast T1-weighted images [12], whereas some lesions are isointense to the NAWM. On follow-up unenhanced T1-weighted scans, these lesions can be classified into four categories: (a) persistently isointense lesions, (b) temporarily isointense lesions, (c) persistently hypointense lesions, and (d) temporarily hypointense lesions [12]. Since the degree of hypointensity on T1-weighted scans is mainly related to the extent of extracellular oedema and axonal loss [13], pattern (a) may represent purely oedematous or inflammatory lesions, affected by only a minor degree of demyelination. Demyelination associated with mild loss of oligodendrocytes may be the histological phenotype of pattern (d), while persistently hypointense lesions (pattern c) are probably those in which axonal loss plays a relevant role in determining T1 hypointensity. At a 6-month follow-up [12], 75% of ring-enhancing lesions remain hypointense, thus suggesting that this pattern of enhancement may be a feature of lesions with a more severe involvement.

Recent strategies in post-contrast imaging have increased the sensitivity of MRI in the detection of enhancing lesions and have provided some insights about the pathological substrates of enhancing lesions. Using a triple dose (TD) of Gd, it has been shown that there are lesions which can be detected only after the administration of TD [14, 15], either because of the time course of their BBB leakage, implying that these lesions might be detectable only with TD for a part of the inflammatory episode, or because BBB permeability is too restricted for