Imaging Phenotypes in Multiple Sclerosis

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KEYWORDS

• Multiple sclerosis • Genetics • MR imaging • Imaging

KEY POINTS

- Multiple sclerosis is a heterogeneous disease with complex interacting environmental and genetic causative factors.
- Several genes have been associated with multiple sclerosis susceptibility and found to be related to imaging patterns.
- Magnetic resonance imaging can especially contribute to the current research of genetic associations with disease prognosis and severity.

INTRODUCTION

Multiple sclerosis (MS) is a progressive disease of the central nervous system with a usual onset in young adulthood, often leading to severe disability. Patients can experience a wide range of symptoms, including motor and sensory problems, ataxia, fatigue, and cognitive impairment.[1] The disease course similarly varies to a large extent between patients. Nevertheless, a limited number of different clinical phenotypes can be distinguished.[2] Before definite diagnosis, patients who experience an acute clinical attack that is suspect for a demyelinating event can be labeled as clinically isolated syndrome (CIS). Many of these patients subsequently develop a phenotype called relapsing-remitting (RR) MS, in which exacerbations are followed by full or partial remissions. In about two-thirds of patients this disease type is succeeded by secondary progressive (SP) MS, characterized by a gradual worsening without recovery. A small proportion of patients (10%–15%) experience progressive decline from onset, defined as primary progressive (PP) MS. In addition to these disease courses, there are MS variants and diseases that mimic MS clinically and radiologically, such as neuromyelitis optica (NMO).[3]

There are multiple findings indicating that environmental factors have a causative role in MS that may interplay with genetic variables. The risk of MS is strongly influenced by region of residence in early life,[1] and the global prevalence of MS is related to distance from the equator, being highest in northern Europe and southern parts of Australia and New Zealand. Furthermore, women are more often affected than men and in recent years they may be increasingly affected.[4] Environmental factors suspected to be (partly) causative have been infections such as Epstein-Barr virus,[5] vitamin D deficiency,[6] smoking, and other toxins. However, from familial recurrence rates of 15% to 20% it can be assumed that part of the risk for the disease is influenced by genetic variables. Maybe even more interesting are effects that genes have on MS disease course and progression of disability, although twins concordant for the diagnosis of MS can have different disease courses. In this context, magnetic resonance (MR) imaging

Disclosures: S.D. Roosendaal has no conflicts of interest; F. Barkhof has no conflicts of interest; The MS Center Amsterdam is supported by a program grant from the Dutch MS Research Foundation (grant number 09-538d).
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Neuroimag Clin N Am 25 (2015) 83–96
http://dx.doi.org/10.1016/j.nic.2014.09.008
1052-5149/15/$ – see front matter

parameters can be used as more accurate and pathologically representative outcome measures than any other clinical parameter.

This article summarizes genetic and imaging findings in MS, reviews correlations between genetics and MR imaging parameters, and discusses implications for current knowledge. It also proposes future perspective and research strategies.

GENETICS OF MULTIPLE SCLEROSIS

A large part of genetic research in MS has been focused on genetic susceptibility to MS. Many studies have found clues for a genetic role in susceptibility in the familial clustering of MS.[7,8] The risk of developing MS is highest for a monozygotic twin; approximately 20% when the other twin is already affected. The risk decreases with the number of shared genes to approximately 2.5% for siblings and 1.5% when one of the parents has MS.[7] Although a low risk, it is still greater than the prevalence of MS in the general population (0.1%–0.3%).

In the past decade, most associations found by linkage studies and candidate gene studies concentrated on the human leukocyte antigen (HLA) locus on chromosome 6. The strongest of associations have been found with the HLA-DRB1*1501 allele of the HLA-DRB1 gene,[9] which is part of a set of genes involved in self versus nonself immune recognition: the major histocompatibility complex (MHC) class II region. Other alleles in immunity-related genes found in these studies have weaker associations to MS susceptibility (odds ratios that are smaller than 2).[10]

The recent ability to use genome-wide association (GWA) studies by assessing single-nucleotide polymorphisms (SNPs) has allowed the detection of new genetic variations with even smaller effects on susceptibility,[11] although these studies require large groups of patients with MS.[12] The GWA studies have resulted in the notion that MS is a complex multigenetic disease, in which several genes are likely to interplay with each other and with environmental factors.

In addition to the aforementioned hypothesis-generating studies, in several studies specific genes have been subject of investigation; for example, those known to be related to neurodegeneration in general, such as brain-derived neurotrophic factor (BDNF) and apolipoprotein E (ApoE).

IMAGING OF MULTIPLE SCLEROSIS

Focal white matter lesions in the brain can be depicted with T2-weighted and fluid-attenuated inversion recovery (FLAIR) images,[13] representing a combination of inflammation, demyelination, axonal loss, and gliosis. Locations considered to be characteristic for MS are the periventricular and juxtacortical areas (**Fig. 1**), the posterior fossa, and the spinal cord. The appearance of new lesions is considered to be a measure of disease activity, and lesion enhancement on postgadolinium T1-weighted images represents blood-brain barrier leakage in the acute stage of a lesion. These MR imaging features of MS contribute to the most recent diagnostic criteria.[14,15]

Axonal degeneration in MS occurs both in acute and in chronic MS lesions,[16] and when focally extensive it is mirrored by persistent T1 hypointensity (also referred to as T1 black holes [T1BH]). However, widespread axonal loss can also be found outside focal lesions in the normal-appearing and diffusely abnormal white matter, where it can be detected by more advanced quantitative MR imaging techniques (**Box 1**), such as diffusion-weighted imaging (DWI)/diffusion tensor imaging (DTI), magnetic transfer imaging (MTR), and MR spectroscopy.[17,18]

In the last decade, it has come to light that gray matter pathology in MS are abundant and clinically meaningful.[19] Focal gray matter lesions are more difficult to identify with conventional MR imaging than white matter lesions, although their visualization can be improved by a more sensitive MR imaging technique called double-inversion recovery (DIR; see **Fig. 1**) and by using (ultra)high-field MR imaging. Loss of brain volume (BV) over time, or atrophy, can be reliably measured for both white matter and gray matter (**Fig. 2**), and assesses the end-stage of the disease process.[20]

Spinal cord abnormalities, either focal or diffuse, are found in most patients with MS and are strongly related to prognosis.[21,22] They can be accurately depicted with proton density–weighted and T2-weighted imaging. Similar to the brain, quantitative MR imaging measures of the spinal cord are more specific with respect to the underlying pathophysiologic process and correlate well with disability.[23] The extent of spinal cord abnormalities varies greatly between patients with MS and is not strongly related to the extent of brain abnormalities within patients.

MR imaging is able to characterize imaging phenotypes that are more directly influenced than clinical outcome measures by pathophysiologic mechanisms, and therefore can be more straightforwardly linked to genotypes. The use of MR imaging in MS genotype-phenotype studies does not only add an objective and repeatable measure of disease severity, it also allows selection of patient groups based on imaging patterns. The goal of using MR imaging as an intermediate