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GRAY MATTER DAMAGE IN MULTIPLE SCLEROSIS: IMPACT ON CLINICAL SYMPTOMS

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Abstract—Traditionally, multiple sclerosis (MS) is considered to be a disease primarily affecting the white matter (WM). However, the development of some clinical symptoms such as cognitive impairment cannot be fully explained by the severity of WM pathology alone. During the past decades it became clear that gray matter (GM) damage of the brain is also of major importance in patients with MS. Thanks to improved magnetic resonance imaging techniques, the *in vivo* detection of GM pathology became possible, enabling a better understanding of the manifestation of various clinical symptoms, such as cognitive impairment. Using higher field strengths and specific sequences, detection of cortical lesions was increased. However, despite these improvements, visualization of cortical MS lesions remains difficult (only about 30–50% of histopathologically confirmed lesions can be detected at 7 Tesla magnetic resonance imaging (MRI)). Furthermore, more research is needed to understand the exact interplay of cortical lesions, GM atrophy and WM pathology in the development of clinical symptoms. In this review, we summarize the historical background that preceded current research and provide an overview of the current knowledge on clinical consequences of GM pathology in MS in terms of disability, cognitive impairment and other clinically important signs such as epileptic seizures.

Key words: multiple sclerosis, cortical lesions, gray matter atrophy, cognitive impairment, physical disability, epilepsy.

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Abbreviations: 2D-T2WFSE, two-dimensional T2-weighted fast spin echo; 3D-SWI, three-dimensional susceptibility-weighted imaging; 9HPT, 9-hole peg test; BDNF, brain-derived neurotrophic factor; CIS, clinically isolated syndrome; CSF, cerebrospinal fluid; DIR, double inversion recovery; EAE, experimental allergic (autoimmune) encephalomyelitis; EDSS, expanded disability status scale; EEG, electro-encephalography; FLAIR, fluid-attenuated inversion recovery; fMRI, functional-magnetic resonance imaging; GM, gray matter; MEG, magnetic encephalography; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, multiple sclerosis functional composite; PPMS, progressive multiple sclerosis; PSIR, phase-sensitive inversion recovery; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; T25FW, timed 25-foot walk test; WM, white matter.

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BACKGROUND: WHITE AND GRAY MATTER PATHOLOGY

Since the first publication of Charcot in the 19th century about ''*sclérose en plaques*'', multiple sclerosis (MS) has generally been considered a pure white matter (WM) disease in which lesions are the result of demyelination following focal inflammation (Charcot, 1868a,b). However, sclerotic plaques at the border of the gray matter (GM) and WM (Sander, 1898), or in the cerebral cortex (Dinkler, 1904) were also reported, and possible underlying pathophysiological processes were

described (Schob, 1907). These preliminary studies on the potential role of GM pathology were initially largely ignored due to suboptimal histological staining techniques that limited the study of the cortical GM.

In the second half of the 20th century, it became clear that some clinical signs of MS, such as cognitive impairment (Benedict et al., 2004, 2005; Morgen et al., 2006) and epileptic seizures (Ghezzi et al., 1990; Thompson et al., 1993; Truyen et al., 1996; Moreau et al., 1998; Sokic et al., 2001; Gambardella et al., 2003; Poser and Brinar, 2003; Uribe-San-Martin et al., 2014), could not be explained with WM pathology alone. Development of more advanced histopathological and magnetic resonance imaging (MRI) techniques subsequently led to more insights into GM pathology in MS. It appeared that GM pathology could be extensive, involving both demyelination (lesions) and neuroaxonal loss. Cortical pathology was found in up to 70–80% of MS patients (Calabrese et al., 2009; Nelson et al., 2011). With these developments in mind, the question may rise to what extent lesions and atrophy of the GM are related to clinical symptoms. To answer this question, we reviewed the currently available literature, starting with pathological changes in the GM of MS patients, and shifting from post-mortem to *in vivo* MRI, toward a relationship between GM pathology and clinical symptoms.

UNDERLYING MECHANISMS OF GRAY MATTER PATHOLOGY

Cortical lesions in the neo-cortex

The introduction of immunohistochemical staining techniques improved the visualization of GM pathology and made it possible to categorize cortical demyelination into four distinct lesion types according to their cortical involvement (see Fig. 1) (Bo et al., 2003a,b; Brink et al., 2005; Wegner et al., 2006). Type I lesions involve the deeper layers of the GM as well as the adjacent WM (and are thus "*mixed lesions*"). The other lesion types are purely intracortical: type II lesions are often small and confined within the cortex; type III lesions account for the majority of all cortical lesions and extend from the pial surface into the cortex, most often reaching to cortical layers 3 or 4 (and are therefore referred to as "*subpial lesions*"). When these lesions involve the entire width of the cortex (without entering the subcortical WM), they are defined as type IV lesions. Although cortical demyelination is a widespread process, the frontal and temporal lobes are probably slightly more affected than the occipital and parietal lobes (Bo et al., 2003a; Albert et al., 2007).

At autopsy, cortical lesions are characterized by a paucity of cell infiltration and by an intact blood–brain barrier (Peterson et al., 2001; Bo et al., 2003b; Brink et al., 2005; Vercellino et al., 2005; Wegner et al., 2006; van Horssen et al., 2007). Although overt neuronal loss (atrophy) in cortical lesions is limited compared to neurodegenerative diseases such as Alzheimer's disease, a reduction in neuronal density of 18–23% was reported (Vercellino et al., 2005). Other signs of pathology, such as loss of glia cells (−36%) and synapses (−47%), were also seen (Wegner et al., 2006). Degeneration of the cortex in MS was found to be largely unrelated to the presence of cortical lesions in the chronic MS brain (Vogt et al., 2009; Klaver et al., 2015).

Although most findings point to a predominant non-inflammatory nature of cortical lesions, some studies did find signs of inflammation. In biopsy studies of patients with a clinically fulminant disease course, cortical and meningeal inflammation (i.e. T-cells and macrophage infiltration) were associated with cortical demyelination (Lucchinetti et al., 2011). Some post-mortem studies also found signs of inflammation. One study found rims of

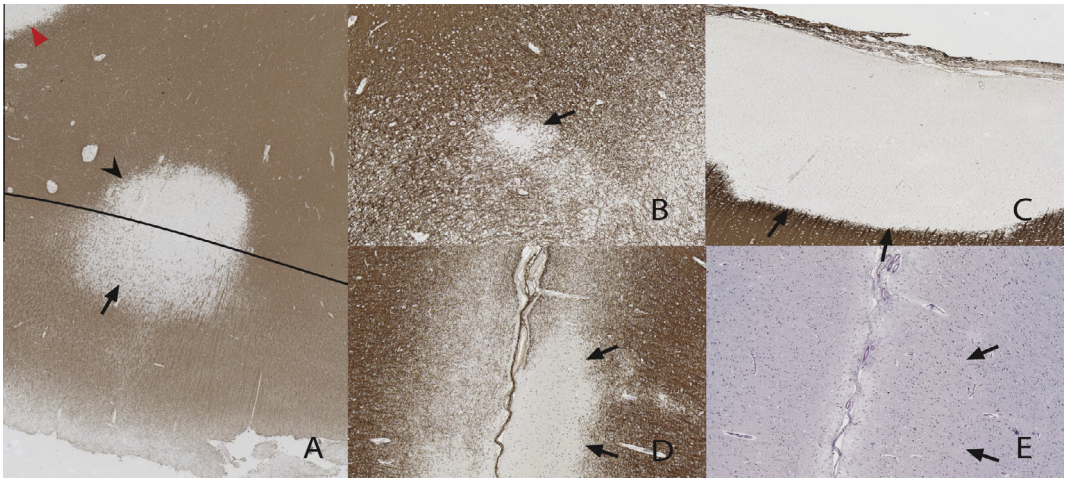

Fig. 1. Cortical lesion classification according to Bo et al. (2003a). (A) *Type I lesions* are located at the border of WM and GM (black line), and are thus mixed-lesions. The GM compartment is indicated with an arrow, and WM with an arrowhead. The red arrowhead indicates a lesion in the WM. (B) *Type II lesions* are purely intracortical lesions. (D and E) *Type III lesions* are confined to the area directly beneath the pia mater. (C) *Type IV lesions* extend throughout the entire width of the cortex. While images (A)–(D) are immunohistochemically stained with myelin basic protein antibodies, image E is stained with the conventional histochemical stain Luxal Fast-Blue. The demyelinated type III lesion is visible with immunohistochemical staining, and invisible with conventional staining. Reproduced from Klaver et al. with permission from Landes Bioscience (Klaver et al., 2013).