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Grey matter lesions in MS
From histology to clinical implications

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Although multiple sclerosis (MS) is a chronic inflammatory-demyelinating disease of the white matter (WM) of the central nervous system, several pathological and magnetic resonance imaging (MRI) studies have shown that a large amount of lesions are located in the cortical and deep gray matter. The histopathological and immunological characteristics of cortical lesions differ significantly from those located in the WM, which suggests a location-dependent expression of the MS immunopathological process. More recently, the availability of not-conventional MRI sequences having higher sensitivity for the gray matter has allowed to depict in vivo a portion of such lesions. The available MRI data obtained on large cohorts of patients, having different clinical forms of the disease, indicate that cortical lesions can be detected early in the disease course, sometimes even before the appearance of WM lesions, and correlate with the severity of physical disability and cognitive impairment, and with the evolution of the disease toward the secondary progressive phase. This review provides a summary of the main histopathological and MRI findings of cortical lesions in MS and discusses their possible clinical implications.

Introduction

Multiple sclerosis (MS) is an autoimmune, chronic and disabling disease of the human central nervous system, histologically characterized by multifocal areas of inflammatory demyelination within white matter (WM). For this reason MS has been traditionally considered a "pure" WM disease. However, several recent neuropathological studies disclosed a relevant, extensive and irreversible "neurodegenerative" process involving the gray matter (GM)[1] and the occurrence of focal inflammatory lesions not only in the WM, but also within the cortex and deep GM.[2,3]

Over the past 10–15 years, quantitative magnetic resonance imaging (MRI) studies have confirmed that focal GM damage and subsequent tissue atrophy are already present at early stages of MS[4] and evolve faster than WM pathology.[5] In addition, GM damage has been correlated with physical disability and cognitive dysfunction more convincingly than either WM T2 hyperintense or T1 hypointense lesion load.[4] So far, GM and WM damages appear to be two simultaneous components of the disease, both observable at its onset and at least partially dissociated from each other. While the relationship between WM lesions and cortical atrophy remains indefinable, it is unlikely that regional changes in cortical volume are the consequence, via retrograde degeneration, of ongoing tissue axonal transection in subcortical WM lesions. On the contrary, they seem to be more depending on local (cortical) inflammation.

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Focal Grey Matter Pathology: The Cortical Lesions

Classification and topographical distribution. Neuropathological studies have described a consistent number of "demyelinating" lesions in cortical and deep GM of the MS brain.[6-14] In the early 1960s, Brownell and Hughes,[15] in a material from 22 MS brains, described that 26% of the MS lesions affected GM and 77% of the cortical lesions (CLs) involved the subcortical WM. In a study of 60 MS cases, Lumsden[16] found that 93% had a cortical involvement of varying degree, with some cases showing only a few CLs, but others having up to 465 gyral plaques. Indeed, in 10 cases, 290 lesions (59% of all hemisphere lesions) were seen to involve the cortex. Both studies showed that the demyelinating lesions involving the cortex were predominately located at the leuco-cortical junction (i.e., cortical/juxtaCL).

The currently accepted histological classification of CLs draws a distinction among four lesion subtypes (**Fig. 1**): Type I lesions are combined WM/GM lesions (cortical/juxta-CLs); Type II lesions are entirely located within the cerebral cortex, they are not in direct contact with subcortical WM or pia mater, and are in general small and perivascular; Type III lesions are subpial areas of demyelination, usually confined within the layers 3 and 4 of the cortex; Type IV lesions comprise the entire width of the cortex, without spreading in subcortical WM, and can extend like large sheaths over several gyri or entire lobes.[6,7]

Demyelination has been reported to vary significantly among the different cortical areas, being the cingulate gyrus (up to 44%), the hippocampus (up to 30%, **Fig. 1B**) and the temporal and frontal cortices (up to 28%) the most affected.[7-9] A smaller portion of demyelinated areas was noted in other cortical areas, including the paracentral lobule (11.5%), occipital lobe (8%) and primary motor cortex (3.5%).[7] Interestingly, a high percentage of demyelination was found in the cerebellar cortex,[10,14] where up to 80% of the CLs are purely intracortical. Finally, focal

demyelinating lesions have been described in spinal cord GM,[17,18] sometimes prevailing on local WM lesions. Thus, inflammatory demyelination occurring within cortical, deep and spinal cord GM is a relevant aspect of the immunopathological process taking place in MS.

Only weak to no correlation between the extent of GM and WM demyelination has been observed,[19] suggesting that the inflammatory process affecting the GM probably occurs, at least partly, independently of WM inflammation. The question whether this finding can be accounted for by a bias in the selection of the analyzed brain specimens needs to be clarified. Nevertheless, although in one study cortical demyelination was largely restricted to progressive forms of MS,[9] a more recent study identified recurrent cortical demyelination with clear inflammatory profile even in the early stages of the disease.[3]

Immuno-histological aspects. Some significant immunohistological differences between CLs and subcortical WM lesions have been described. Although CLs are well-demarcated areas of demyelination, with significant oligodendrocyte and axonal loss,[6,11] they differ substantially from WM lesions in degree and type of inflammation, which appears for some aspects location-dependent. Compared with WM lesions, pure intracortical lesions are characterized by a lower extent of lymphocyte infiltration[6] that might however depend on the patient population. In patients with long-lasting disease, perivascular infiltrates were rarely found within the cortex, and the density of infiltrating lymphocytes was very similar in pure CLs and in the so-called normal-appearing GM. Indeed, when compared with WM lesions, CLs contained 13 times fewer $CD3^+$ lymphocytes and 6 times fewer $CD68^+$ cells of the microglia/macrophages lineage.[6] In a recent neuropathological study on brain specimens from patients with early relapsing remitting MS,[3] CLs containing foamy macrophages, indicating ongoing demyelination, were detected in 66% of patients. The presence of B cells in perivascular cortical inflammation was observed in 27% of CLs, while perivascular $CD3^+$ T lymphocytes were observed in 82% of cortical plaques, 77% of which contained $CD8^+$ T cells. Although leukocortical lesions were the most inflamed, the majority of intracortical and subpial plaques contained perivascular $CD3^+$ and $CD8^+$ T-cell infiltrates that were moderate to marked in almost 23% of subpial lesions. The authors concluded that cortical demyelination is common even in early disease stages and differs substantially from that seen in chronic multiple sclerosis. These data suggest that cortical inflammation is a frequent, transient phenomenon in early relapsing-remitting phase but rarely observed in its completeness in chronic MS patients or in very late stages of the disease.

Notes on the pathogenesis of cortical lesions. Although the pathogenesis of CL is only partially understood, several recent neuropathological studies have pointed out the role of meningeal inflammation.[3,20-22]

The presence of a widespread subpial demyelination, the lack of any significant leakage of plasma proteins, thus suggesting a normal blood-brain barrier function,[23] and the absence of any significant signs of complement activation,[24] seem to preclude that a perivascular inflammation play a major role in the pathogenesis of GM pathology. On the other hand, diffuse inflammatory cell infiltrates and ectopic lymphoid-like structures have been consistently found in the meninges, especially in the deep sulci of frontal, temporal, cingulate and insula cortex and thus topographically associated with cortical demyelination.[3,20-22] Accordingly, when secondary progressive MS patients having B-cell follicle-like structures in the inflamed meninges were compared with those without these structures, a substantial gradient of neuron, astrocyte and oligodendrocyte loss was found, thus suggesting the possible pathogenetic role of some soluble factors diffusing from inflamed meninges.[21]

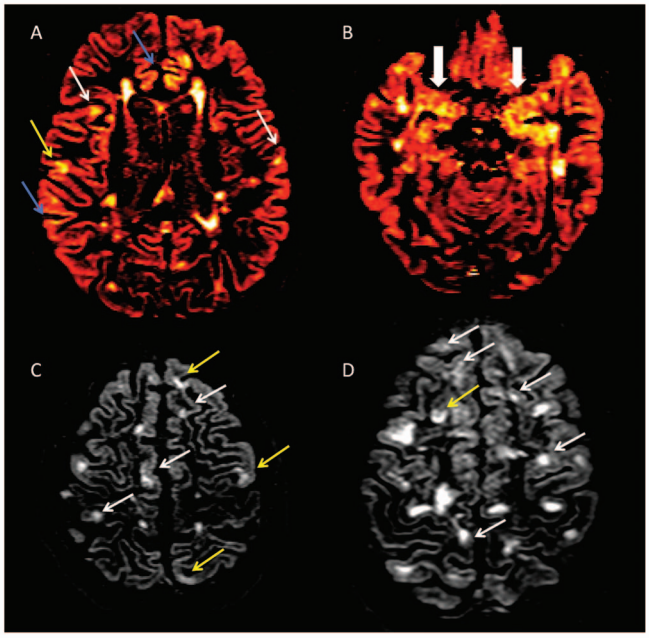

Figure 1. (**A–D**) Axial double inversion recovery from four patients suffering from relapsing-remitting multiple sclerosis. Several Type II (white arrows), Type III (blue arrows) and Type IV (yellow arrows) are detectable (**A**), some of which involving the hippocampus (**B**). Two patients (**C and D**) having a very high cortical lesion load suffer also from epilepsy and from a significant cognitive dysfunction.

Patients with B-cell follicle-like structures also showed a significant increase in MHC class II^+ activated microglial cells, pointing out their potential role in MS cortical pathology.[21] In GM lesions, indeed, the majority of phagocytic cells were described to have the morphology of activated microglia, with only a minority having a phagocytic macrophage appearance.[6] VCAM-1^+ (vascular cell adhesion molecule-1^+) cells in MS lesions, as defined by dual-label immunohistochemistry, were considered as derived from the monocyte/macrophage lineage and were found to be numerous at lesion edges, in coincidence with regions of oligodendrocyte injury.[25] Activated microglia within CLs contained elevated levels of myeloperoxidase, indicating that reactive oxygen species may contribute to GM lesion pathogenesis.[26] In a study aimed at comparing MS and Alzheimer disease cortical pathologies, profound microglia activation, determined by a wide spectrum of immunological and biochemical markers, was found in both MS and Alzheimer disease cortices, and the patterns of

microglia activation were closely similar.[27] However, microglia activation in MS cortices, in contrast with that in Alzheimer disease and control cortices, was clearly correlated with lymphocyte and plasmacell infiltrates in the meninges.[27] Unfortunately very few studies on molecular mechanisms by which neurons degenerate within cortical lesions have been performed, yet the hypothesis of an oxygen- and nitric oxide radical-induced mitochondrial injury and energy failure as the origin of neuronal degeneration is appealing.[28] Indeed the recent observation of oxidized phospholipids and DNA even in neurons within GM lesions seems to confirm the role of mitochondrial injury as a major factor driving GM tissue injury.[29]

Neuroimaging aspects. Although the above described pathological data suggest widespread cortical involvement, especially in patients with long-lasting disease duration, only a few studies have assessed the contribution of cortical pathology to clinical MS symptoms in vivo. This is mainly due to the fact that routinely available MRI techniques, especially T1-weighted and T2-weighted sequences, only rarely allow for identification of purely intracortical lesions. Indeed, among the four types of CLs described by pathologists, FLAIR sequence can usually detect just Type I (leuko-cortical) lesions located at the interface between cortex and WM. Several factors hamper the possibility of demonstrating CLs by means of conventional T2/FLAIR sequence, and they are mostly related to the pathophysiology of cortex and CLs. The lower inflammatory profile of CLs (compared with WM lesions),[6] the absence of significant blood-brain barrier damage within CLs,[23] the low myelin density in upper cortical layers, as well as technical constraints, such as partial volume effects resulting from the proximity of CLs to the cerebrospinal fluid (CSF),[30-32] may help explain why in vivo CLs identification remains a challenge.

In a study comparing the number of CLs detected by histopathology and post-mortem MRI, applying dual-echo T2-weighted spin-echo images and 3D-FLAIR, detection rates of 3D-FLAIR images were of only 5% for pure CLs and 41% for leuko-cortical lesions.[32] A significant improvement in the detection rate of CLs and in the delineation of GM structures was obtained by applying 3D double inversion recovery (DIR) sequences. The use of DIR imaging showed an average increase of 152% in CL detection per patient when compared with detection by means of 3D FLAIR sequence. Moreover, in comparison with T2-weighted spin echo (SE) imaging, DIR imaging showed a 500% increase in detection of CLs.[33,34] The major limitation of DIR sequences is the low sensitivity in detecting CLs, especially subpial ones, when compared with histology.[35] Recent comparative histological/MRI studies have however demonstrated that the "tip of the iceberg" detected by MRI and its "bulk" differ only in size, and that the number of CLs detected well correlates with their total number and with the overall percentage of cortical demyelination.[36] Thus, although further improvement in CL detection shall be achieved perhaps by combining different MRI sequences as phase sensitive inversion recovery[37,38] and 3D magnetization-prepared rapid acquisition with gradient echo (MPRAGE),[39] we feel that DIR-based findings can be considered an acceptable assessment of focal GM pathology.

Focal Grey Matter Pathology: Clinical Implications

Cortical lesions and disability progression in patients with MS. Data from several neuroimaging studies indicate a primary role of CLs in determining clinical dysfunction and disability progression in MS. In a study conducted on a large patient population, CLs could be detected by DIR in the majority (64%) of patients with relapsing remitting (RRMS) and secondary progressive (73%) MS (SPMS), as well as in more than one-third (36.8%) of patients with clinically isolated syndromes (CIS) suggestive of MS.[40] In the same study, CL load modestly correlated with Expanded Disability Status Scale (EDSS) score ($r = 0.48$), WM T2 lesion volume ($r = 0.38$), and brain parenchyma fraction ($r = -0.47$) and patients with CLs showed higher EDSS score ($p = 0.004$), greater WM T2 lesion volume ($p = 0.008$) and smaller brain parenchyma fraction ($p = 0.009$) compared with patients without CLs. A 3-year longitudinal follow-up study[41] disclosed that CL accumulation was significantly higher in MS patients showing clinical worsening compared with those clinically stable. CL volume at baseline well correlated with baseline EDSS ($r = 0.36$) and even better with EDSS changes over time ($r = 0.51$). In the same study RRMS and SPMS patients were found to accumulate new CLs at similar rates (0.8/year in RRMS vs. 1.0/year in SPMS), suggesting that, in relapse-onset MS, the medium-term dynamics of CL evolution may not be influenced by the stage of the disease. The greater number of CLs observed in SPMS compared with RRMS patients could therefore be the consequence of the longer disease duration of the former subgroup. Indeed, post-mortem studies[9] showed that GM demyelination and axonal damage are already present in the relapsing-remitting phase but become more prominent in the chronic stages. Alternatively, the fact that cortical demyelination is more extensive in progressive than in early MS could be explained by the faster and more efficient remyelination of CLs in early disease stage.[11]

Finally, patients with CLs show higher frequency of CSF IgG oligoclonal bands[40] and higher level of intrathecal synthesis of Ig (IgG and IgM)[42] compared with patients without CLs. The combination of intrathecal Ig synthesis with the presence of CLs allowed the early identification of RRMS patients having the highest risk of disease activity and the worse clinical evolution over a 3-year follow up.[41] This would be in line with recent neuropathological studies[3,20,22] showing association between the B-cell enriched meningeal inflammation and the subpial demyelination described in MS, thus suggesting a possible pathogenetic role of soluble factors (immunoglobulins included) diffusing from inflamed meninges into subarachnoid space. It's interesting to notice that, although meningeal inflammation has been identified even in the early stages of the disease,[3] ectopic B-cell follicle-like structures have been more frequently detected in SPMS patients with an accelerated clinical course.[20] These findings, along with the evidence of cortical demyelination in early MS and consequent loss of oligodendrocyte, axonal and neuronal injury in the chronic phase of the disease, suggest that disability progression could be the result of neurodegeneration running on a background of inflammation. Further studies aimed at investigating the potential role of CLs in predicting the entrance in

Table 1. Selected works studying gray matter lesions in MS and their diagnostic and prognostic relevance (physical and cognitive disability)

Study	Patients	Follow-up	Parameters evaluated	Main outcome
Filippi et al. 2010	80 CIS	4 y	CLs, T2-WM lesions, Gad^{+} lesions	The accuracy of MRI diagnostic criteria for MS is increased when considering the presence of CLs on baseline scans from patients at presentation with CIS suggestive of MS.
Calabrese et al. 2012	86 patients with CIS	3 y	CL and WM lesion number, new MRI activity, CSF examination.	The association of intrathecal Ig synthesis and CLs is highly predictive of an earlier CIS conversion to MS as well as of a higher disease activity.
Popescu et al. 2011	One RRMS	Case Report	MRI, CSF and histological examination.	Pathologic evidence of RRMS patient presenting with inflammatory solitary cortical enhancing lesion.
Calabrese et al. 2009	4 RRMS	Case Report	CLs and T2-WM lesions	CLs were observed by DIR before the MRI evidence of inflammatory lesions in the white matter.
Absinta et al. 2012	32 patients with migraine, 15 RRMS, 20 healthy controls	Cross-sectional	T2-WM lesion and CL count and volume	No CLs identified in migraine patients. The application of DIR imaging seems to be useful in the diagnostic workup of patients with WM hyperintensities of unknown etiology, including those with migraine.
Giorgio et al. 2011	15 radiologically isolated syndrome	Cross-sectional	T2-WM lesion and CL count and volume, normalized brain and cortical volume	CLs are identified in subject with RIS (40%) and are frequent in subjects with IgOBs and dissemination in time. CLs are therefore associated with important markers of evolution to MS.
Popescu et al. 2011	19 autopsied NMO patients	Cross-sectional	Histological examination	Lack of cortical demyelination in patients with NMO is a feature that might help distinguishing NMO from MS.
Calabrese et al. 2012 (in press)	30 NMO patients, 30 RRMS patients, 30 healthy controls	Cross-sectional	CL and T2-WM lesion count, global and regional cortical thickness	No CLs identified in patients with NMO and no significant differences found in cortical thickness between NMO a controls. MRI analysis of the cortex may be a potential diagnostic tool, especially in ambiguous cases.
Absinta et al. 2011	24 pediatric and 15 adult MS	Cross-sectional	WM lesion and CL number and volume, GM and WM volumes	CLs are rare in patients with MS in comparison with adult patients.
Calabrese et al. 2010	76 RRMS, 31 SPMS	3 y	CL and T2-WM lesion number and volume, T2-WM lesion volume, GM volume	CL volume correlates with EDSS and EDSS changes over time and it is an independent predictor of EDSS accumulation and GM volume change in SP and RRMS patients.
Calabrese et al. 2009	48 benign MS, 96 early not disabling RRMS	1 y	CL and T2-WM lesion number and volume	Benign MS have lower CL number compared with early RRMS patients. At 1 year follow-up a significant increase of CL number and volume is observed only in early patients with RRMS.
Calabrese et al. 2012	35 pediatric and 57 adult MS	3 y	CL and T2-WM lesion number and volume, GM volume	Focal (CLs) and diffuse (atrophy) GM damage are strictly associated with the biologic onset of MS, and proceed linearly and partly independently of WM pathology.
Calabrese et al. 2012	32 RRMS with epilepsy, 60 RRMS without epilepsy	3 y	CL and T2-WM lesion number and volume, regional cortical thickness, new CLs and WM lesions; neuropsychological evaluation	Cortical pathology, psysical and cognitive decline are more severe and evolving in MS patients with epilepsy compared with patients without epilepsy.
Roosendal et al. 2009	9 RRMS, 4 SPMS, 7 healthy controls	3-y	CL and T2-WM lesion number and volume, neuropsychological evaluation	CLs increase significantly over a 3 y time period, are most frequent in SP patients and are associated with cognitive impairment.
Mike et al. 2011	20 RRMS, 20 SPMS	Cross-sectional	CLs number and volume, T2-WM volume, EDSS, cognitive testing	Routinely detectable cortical lesions were related to physical disability and cognitive impairment better than T2-WM lesions.
Calabrese et al. 2009	70 RRMS	Cross-sectional	CL and T2-WM lesion number and volume, GM volume; neuropsychological evaluation	Cognitively impaired patients have a higher CLs number and volume, decreased normalized cortical volume compared with cognitively preserved patients.

Abbreviations: CLs, cortical lesions; CSF, cerebro-spinal-fluid; DIR, double inversion recovery; Gad*, gadolinium enhancing lesions; GM, gray matter; IgGOB, IgG oligoclonali bands; MRI, magnetic resonance imaging, MS, multiple sclerosis; NMO, neuromyelitis optica; RIS, radiologically isolated syndrome; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; T2-WM, T2 white matter; WM, white matter.

the progressive phase of the disease could have remarkable clinical rebounds in terms of prognostic stratification of patients and optimization of available therapies.

Cortical lesions in different MS phenotypes. Additional data on possible clinical implications of CLs come from studies on specific phenotypes of MS (**Table 1**).

CLs were observed in up to 80% of patients suffering from primary progressive form of MS (PPMS).[43,44] Interestingly, when a lesion probability map was delineated, similarities rather than differences were found between RR and PPMS patients: similarities include the total number of CLs, their volume and their topographic distribution on cortical lesion probability map. In the PPMS population, as in RRMS patients, CL load correlated significantly with disease duration, EDSS score and EDSS increase after 1-year follow up.

On the contrary, patients with "benign" MS course (EDSS < 3.0 after 15 years from clinical onset and no cognitive dysfunction)[45] showed significantly smaller CL load compared with early RRMS having the same degree of disability, but much shorter disease duration.[46] After 1-year follow-up, "benign" MS did not show an accumulation of CLs compared with early RRMS patients; again, multivariate analysis indicated that CL load at study entry and its increase over time were associated to the "benign" clinical status.[47] The relative sparing of the cortex in benign MS might therefore be considered as an in vivo feature of this disease subtype, with consequent important implications on clinical grounds: the lack of CL detection during the early RRMS stage may indeed contribute to identify MS patients with a more favorable prognosis.

MS patients with epilepsy constituted another interesting subgroup of subjects (**Fig. 1C and D**). As previously observed, epileptic seizures are more frequent in MS than in the general population[47,48] and the association between epilepsy and MS has been demonstrated not to be mere coincidence.[49,50] In a series of 20 RRMS patients who had epileptic seizures during the course of the disease, CLs were detected in 18/20 (90%) compared with only 48% of not epileptic RRMS ($p = 0.001$).[49] Cortical pathology was quite extensive in epileptic RRMS, inasmuch as they showed five times more CLs compared with not epileptic RRMS, and had a total CL volume that was 6 times greater. Meanwhile, no significant difference between epileptic and not epileptic RRMS was observed with regard to the number and volume of juxta-cortical lesions and T2WM lesion volume. A 3-year longitudinal study on 32 RRMS patients with epilepsy revealed greater accumulation of new CLs and faster progression rate of cortical atrophy compared with 60 matched RRMS patients without epilepsy, while no difference was observed in the number of new WM or Gad^+ lesions.[51] As expected, these patients showed a significantly worse clinical evolution, characterized by faster decline in cognition and greater EDSS increase. This suggests that these patients constitute a peculiar subgroup of MS patients, having a more pronounced and selective involvement of the GM and a severe (cortical) clinical picture.

Finally, observation of CLs even in the pediatric MS population[52] supports the hypothesis that GM pathology is a very early phenomenon in MS, being strictly associated with the biologic disease onset. This result was further confirmed by a 3-year longitudinal study[53] in which atrophy and CL load showed the same rate of progression in both pediatric and adult onset MS. The greater CL load characterizing adult onset MS appear to be likely the consequence of the longer interval of time between biologic and clinical onset in these patients.

Diagnostic relevance of CL. CLs have been noticed in the MS brain months/years before the appearance of inflammatory lesions in subcortical WM,[54,55] strongly indicating that, at least in some patients, the pathological process underlying MS could start in the cortex. While they have been observed by DIR in more than 30% of patients presenting with CIS suggestive of MS[40] as well as in asymptomatic subjects with radiologically isolated syndrome (RIS),[55] CLs are a frequent phenomenon in MS being present in almost 70% of RRMSpatients.[40] On the basis of these observations, the predictive role of CLs in patients with CIS suggestive of MS was assessed in a recent 4-year longitudinal MRI study[57] and compared with the available McDonald-Polman[58,59] and Swanton[60] diagnostic criteria for dissemination in space of lesions. Regression analysis showed that presence of at least one cortical ($p < 0.001$), one infratentorial ($p = 0.03$), one Gad enhancing and one spinal cord ($p = 0.004$) lesion were independently associated to the conversion to definite MS, while the presence of at least two of these variables resulted to be the best criterion for "dissemination in space of the lesions." Furthermore, the combination of the intrathecal Ig synthesis with the presence of CLs identified a subgroup of CIS patients having a high risk of developing definite MS in the following 3 years.[42] This indicates that the accuracy of MRI diagnostic criteria for MS could be increased with the integration of CLs in the diagnostic paradigm, by detection of CLs in patients suspected to be affected with MS. Interesting, cortical changes resembling CLs have been observed in other neurological disorders such as tuberous sclerosis,[61] epilepsy,[62,63] hepatic encephalopathy[64] and neoplastic condition,[65] but not in other inflammatory pathologies such as neuromyelitis optica (NMO)[66,67] and migraine[68] that may enter in differential diagnosis with MS. Therefore, CLs might represent a useful diagnostic element addressing to MS in patients with WM hyperintensities of uncertain etiology.

CL as a major substrate of cognitive dysfunction. Cortical pathology has a significant impact even on cognitive dysfunction observed early in MS course,[69] with dramatic effects on personal, social and occupational functioning. Although the relationship between cognitive impairment and subcortical WM pathology remains controversial,[69-72] there is increasing evidence of a primary role of cortical pathology in determining cognitive disability.[73-75] Neocortical volume loss was observed to correlate with cognitive dysfunction better than whole brain atrophy.[73,74] In addition, RRMS patients having cognitive dysfunctions showed widespread cortical atrophy involving almost all cortical regions, while in cognitive unimpaired RRMS patients, a thinning confined in the fronto-temporal cortical was observed.[75-77]

Beyond this evidence on the relationship between cognitive dysfunction and diffuse GM damage, even the focal damage has been related to the decrease in cognitive performance. In a 3-year follow up study, Roseendaal, et al.[78] found that CL number were

higher in SPMS, tended to accumulate over time and was associated with a worse performance on neuropsycological measures at follow up. Furthermore, CL load was significantly heavier in cognitively impaired patients (**Fig. 1C and D**) compared with cognitively preserved ones[77] and, together with normalized cortical volume ratio, resulted to be an independent predictor of the composite cognitive score, suggesting that focal cortical damage may be considered one of the major substrates of cognitive impairment in MS.

Conclusions

In summary, CLs appear to be quite peculiar inflammatory and demyelinating lesions. They differ from WM lesions for several quantitative and qualitative aspects of the cellular inflammatory network, for the lack of a clear evidence of local blood-brain barrier dysfunction, and for the critical role that seems to be played by reactive microglia cells, thus suggesting different underlying (immuno)pathogenetic mechanisms. Accumulating data suggest a pivotal role of CLs in physical and cognitive decline in MS, but longitudinal studies are needed to explore in detail their clinical implication. The available data, however, are particularly worth of interest and urge us to develop more sensitive MRI technologies to increase our capacity to detect and analyze cortical pathology in MS.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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