TURUN YLIOPISTO

Association between choroid plexus volume, brain atrophy and lesion load measures in multiple sclerosis

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Abstract

Multiple sclerosis (MS) is the most common chronic neuroinflammatory disease affecting young adults, leading to neurological disability and cognitive impairment. Pathologically, MS is characterized by demyelinating white matter lesions (WMLs), gliosis and neuroaxonal loss within the central nervous system (CNS), facilitated by immune cell infiltration into CNS. The number and location of WMLs determine the symptoms experienced by individuals, as well as the severity of clinical disability.

Recent studies have reported that choroid plexus (CP) volume is significantly larger in people with MS (pwMS) compared to healthy controls (HCs). CP is a highly vascularized tissue located within the brain ventricles and is primarily responsible for the production and secretion of cerebrospinal fluid (CSF). It has also been suggested to serve as a pathway for immune cell entry into the CNS, playing a vital role in MS pathology. CP has shown several structural and functional alterations in MS, leading to abnormal CSF production and impaired glymphatic function, as well as increased microglial activity and release of pro-inflammatory cytokines.

Interest in the relationship between CP enlargement and MS has increased in recent years. CP enlargement has been associated with increased lesion load and greater brain atrophy in pwMS, particularly in periventricular regions. Furthermore, CP enlargement has been correlated with greater clinical disability and cognitive impairment in pwMS. Taking these observations together, enlargement of CP has been suggested to enhance chronic, smouldering inflammation within the CNS. This review will discuss the association between CP volume, brain atrophy and lesion load measures in MS, as well as their relationship to chronic neuroinflammation.

Key words: multiple sclerosis, choroid plexus, white matter lesions

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1 Introduction

Multiple sclerosis (MS) is a chronic neuroinflammatory and neurodegenerative disease of the central nervous system (CNS), pathologically characterized by inflammatory cell infiltration, demyelination, gliosis, and neuroaxonal loss.[1,2] MS is the most common neurological disabling disease among young adults.[3] The disease course varies considerably between individuals, ranging from relapsing–remitting to progressive forms, leading to clinical disability and cognitive impairment.[2,4] Symptom presentation depends on the location and extent of demyelinating lesions within the CNS.[4,5] The common clinical manifestations during the first episode of MS include optic neuritis, partial myelitis, as well as brainstem and spinal cord syndromes. The most common cerebral symptoms include motor or sensory hemiparesis and cognitive dysfunction, such as difficulties with memory or concentration.[4,5]

The diagnosis of MS is guided by the McDonald criteria, which integrate clinical features with radiographic evidence such as Magnetic Resonance Imaging (MRI) detected lesions, and supportive laboratory findings including cerebrospinal fluid (CSF) specific oligoclonal bands.[4,5] The precise etiology of this demyelinating disease remains unclear; however, it has been suggested that a combination of genetic susceptibility and environmental risk factors contributes to the development of MS.[3,4,6,7] The general risk factors include Epstein-Bar virus (EBV) infection, smoking, female gender, obesity during adolescence and low vitamin D levels.[3,4,6,7]

Pathologically, immune cell infiltration into the CNS induces cascades that lead to development of MS.[8,9] It has been suggested that choroid plexus (CP), which is a highly vascularized tissue within each of the brain ventricles, may be one of the many pathways for immune cells to entry the CNS.[8,9] CP has been shown to undergo several structural and functional alterations during the development and progression of MS.[10,11] Furthermore, multiple studies have reported significant CP enlargement in people with MS (pwMS).[10–16] CP enlargement has further been associated with lesion load[17–20] and brain atrophy[21–24] as well as greater clinical disability and worse cognitive function.[17,19,25,26] These associations will be discussed in greater detail in this review.

2 Literature review

2.1 Clinical features of MS

Evidence suggests that several years before a formal MS diagnosis is made, many individuals experience a range of nonspecific symptoms, including fatigue, insomnia, pain, and urinary or gastrointestinal disturbances.[27] These are often referred to as prodromal symptoms.[27] In contrast, some individuals demonstrate MS-specific MRI abnormalities in the absence of neurological manifestations, known as radiologically isolated syndrome (RIS).[28,29] In a couple of recent studies 20-50 % of individuals with RIS convert to a diagnosis of MS during a five years follow-up.[28,29]

At disease onset, patients can present with clinically isolated syndrome (CIS), in which neurological symptoms are evident but the diagnostic criteria for MS are not yet fully met.[27–29] Both CIS and MS episodes are characterized by the acute or subacute onset of symptoms with demyelinating lesions in the CNS, persisting for a minimum of 24 hours, and not associated with fever or an underlying infection.[27–29] Once an individual experiences a second attack and repetitive lesion formation is detected, the diagnosis of MS can be confirmed.[27–29] Typical manifestations of CIS include optic neuritis, a focal brain syndrome, myelitis, or a brainstem syndrome with symptoms such as diplopia, vertigo, facial weakness, or sensory disturbances.[30,31] The risk of CIS developing to MS is influenced by baseline factors, with a higher likelihood observed in patients with multiple MRI lesions, spinal cord involvement, or CSF specific oligoclonal bands in CSF samples.[32,33] Long-term studies indicate that up to 80% of CIS patients with MRI abnormalities progress to MS within 20 years, whereas those with a normal baseline MRI have a remarkably lower risk.[34–36]

The most prevalent type of MS is relapsing-remitting MS (RRMS).[29,37] In RRMS, individuals experience relapses, followed by a period of complete or near-complete recovery, known as remissions.[29,37] Clinical relapses represent acute inflammation in the CNS causing axonal myelin loss, which is considered the primary pathophysiological mechanism of MS.[38] The symptoms an individual experiences

depend on the location of the lesions in the CNS.[38] The most common symptoms include cognitive dysfunction, loss of balance, sensory changes such as numbness in hands or feet, muscle weakness, fatigue, problems with vision, and bladder or bowel dysfunction.[4,39–41]

As the disease progresses, RRMS can transform into secondary-progressive MS (SPMS).[42] One retrospective study reported that approximately 50 % of patients with RRMS eventually experience secondary progression within 20 years follow-up.[43] In a minority, approximately 10% to 15%, of pwMS, relapsing-remitting phase is bypassed, and patients experience disease progression already from the onset, known as primary-progressive MS (PPMS), which is associated with a worse clinical prognosis.[44]

Recent studies indicate that many pwMS experience clinical progression despite remaining relapse-free.[45–49] Clinical disability may accumulate either through relapse-associated worsening (RAW) or progression independent of relapse activity (PIRA).[45–49] PIRA can occur alongside relapse-activity and contribute to disease progression from the early onset of the disease.[48] One recent study reported that up to 50 % of disease progression in individuals with RRMS occurred without clinical relapses.[45] Another study showed that even 80 % to 90 % of disability in pwRRMS was accumulated independently from relapses.[46] Among patients with PPMS or SPMS, PIRA appears to be the primary driver of disability accumulation.[45] While high-efficacy therapies have effectively reduced RAW, PIRA has emerged as a contributor to disability progression regardless of the disease modifying therapy.[46,50–52] PIRA is associated with smouldering neuroinflammation within the CNS and is thought to be largely driven by persistent microglial and macrophage activity, particularly within chronic active lesions (CALs), which will be discussed below.[47]

2.2 Pathophysiology of MS

White matter lesions (WMLs) in the brain and spinal cord are a hallmark of MS, signifying neuroinflammation, demyelination, gliosis, and neuroaxonal degeneration in the CNS.[53] Clinical relapses in RRMS result from the formation of new WMLs or the activity and/or enlargement of old WMLs.[54] Histologically lesions have traditionally been

classified into following subtypes: early active, late active, chronic active (smouldering), inactive and remyelinated lesions.[54] Early active WMLs are associated with relapses and feature blood-brain barrier (BBB) breakdown, with peripheral immune cells penetrating the CNS.[55] Acute lesions can develop into CALs, chronic inactive lesions, or they may undergo remyelination.[55–57] Different lesion subtypes cannot be distinguished on conventional MRI.[57–59]

Inflammatory lesions are characterized by the infiltration of the autoreactive immune cells into the CNS, where T- and B-cells penetrate the CNS through an impaired BBB and potentially via the CP, which will be examined later in this review.[8,9] In the CNS, T- and B-cells induce an inflammatory response by releasing pro-inflammatory cytokines, which in turn activates lymphocyte-mediated macrophage and microglial responses.[60] Both macrophages and microglial cells are present in and around MS lesions, especially in acute lesions and CALs, and are considered key mediators of smouldering neuroinflammation.[61,62] By contrast, inactive lesions contain significantly fewer macrophages and microglia, reflecting the reduced inflammatory activity in these regions.[61,62] In CALs, activated microglia and macrophages can be distributed throughout the lesion, known as homogenously active lesions, or localize to the lesion border, while the lesion center is typically hypocellular.[17,58] Lesions characterized by a peripheral rim of iron-accumulating innate immune cells are generally termed paramagnetic rim lesions (PRLs).[17,58] (Figure 1)

Macrophages and activated microglia together with reactive astrocytes produce reactive oxygen species (ROS).[60] ROS promote oxidative injury and mitochondrial dysfunction, which in turn drive inflammatory demyelination and contribute to axonal damage in MS lesions.[60] It is suggested that mitochondrial and oxidative injury represent central mechanisms in the pathogenesis of MS, linking chronic neuroinflammation to progressive neurodegeneration.[63–65]

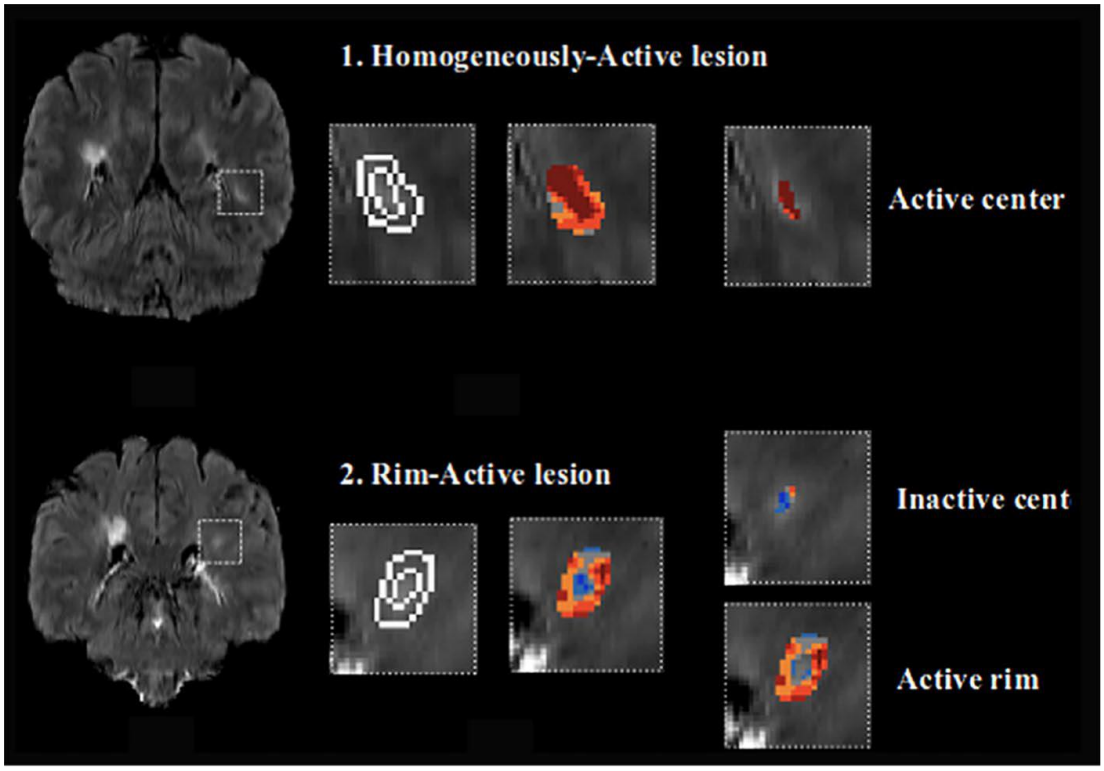

Figure 1. CALs can be identified using Positron emission tomography (PET) -imaging with translocator protein (TSPO) radioligands, where TSPO-PET signal reflects activated microglia and macrophage density. White boxes on the coronal FLAIR MRI slices indicate WMLs of interest. Hot colors denote increased inflammatory activity within CALs, distinguishing homogenously active lesions with active centers from rim-active lesions, or PRLs, with inactive center and active rims.[17]

2.3 Choroid plexus

CP is an extensively vascularized tissue in each of the brain ventricles, located along the floor of lateral ventricles and on the roof of the third and fourth ventricles (Figure 2A).[9,66–68] The CP is primarily responsible for the production and regulation of CSF composition, with up to 80 % of CSF produced and secreted via CP.[68] CP also plays a key role in maintaining brain homeostasis and mediating signalling within the CNS.[9,66,67]

The CP consists of looped vessels surrounded by stromal tissue, which is covered with a single monolayer of polarized cuboidal epithelial cells.[68–72] (Figure 2B) Epithelial cells are specialized for producing and secreting CSF.[68,73] In the CP stroma, immune cells, particularly antigen-presenting cells, support immunosurveillance and help preserve brain homeostasis.[67] Tight junctions (TJs), located at the apical surface of CP epithelial cells, seal the intercellular space and regulate paracellular transport between the blood

and CSF, forming the blood-CSF barrier (BCSFB).[68,72,73] Additionally, microvilli extend the apical surface area, enhancing exchange and secretory functions.[66,73]

BCSFB protects the brain from adverse peripheral substances and provides selective transport for peripheral signals and small molecules.[70] It has been suggested that lymphocyte trafficking into the CNS is mainly regulated by the brain's barriers, including BCSFB.[12] In some inflammatory situations, such as MS, alterations in CP function serve as a gateway for peripheral immune cells to enter the CNS.[12,70]

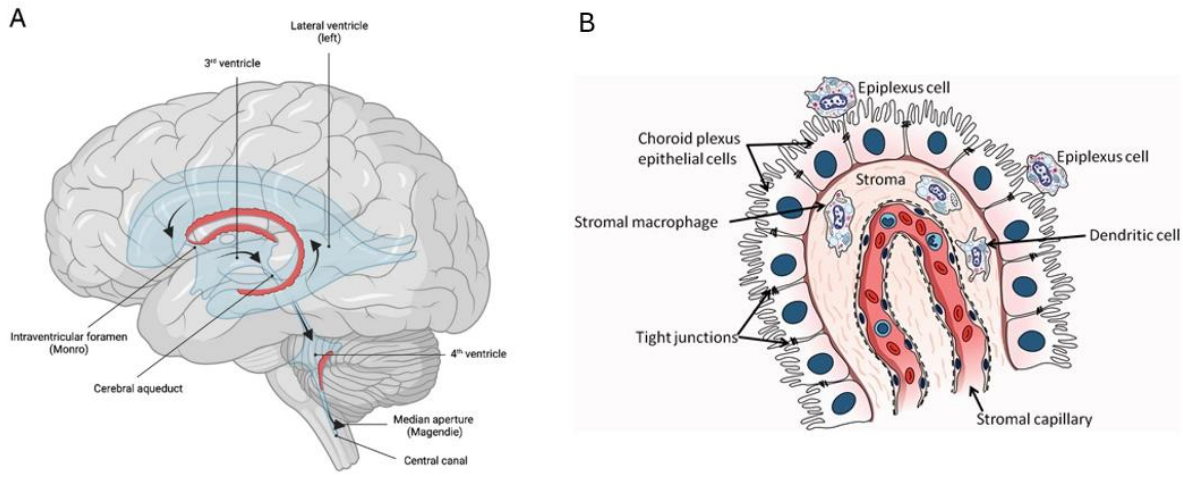

Figure 2. A Schematic illustration of the brain showing the ventricular system (pale blue) and the CP (red). Modified from ref.[72] B Schematic model of the CP microstructure. Cuboidal epithelial cells with apical microvilli overlie a loose stromal tissue containing stromal capillaries. The stroma includes perivascular macrophages and dendritic cells involved in antigen presentation and modulation of inflammatory responses. Tight junctions between epithelial cells form the BCSFB and participate in molecular and cellular exchange between blood and CSF.[12]

2.4 Association between CP and MS

Recent studies have shown alterations in the CP in pwMS.[74,75] It is indicated that there are more antigen-presenting cells, such as macrophages and dendritic cells, in the CP stroma in pwMS than in HCs.[75] It has also been suggested that infiltration of peripheral lymphocytes through the BCSFB is increased in pwMS, contributing to autoinflammatory processes within the CNS.[76]

TJs play a crucial role in maintaining brain homeostasis.[67] Well-known TJ proteins are claudins and junctional adhesion molecules.[67] It has been shown in postmortem MS

tissue that the expression of one TJ protein, claudin-3, is decreased in the CP, leading to reduced barrier integrity, which increases permeability to peripheral molecules and immune cells.[67,77] This enables peripheral immune cells to penetrate the CNS.[18,67,70,77]

Alterations in the CP, as well as hypoxic conditions in MS brain and in CP, can lead to abnormal CSF production and secretion.[74] Dysregulation of CSF composition involves changes in ion balance, growth factors, cytokines, and metabolites.[12,78–80] Such alterations may enhance microglial activation and impair glymphatic system function, leading to disrupted waste clearance in the brain, which can further lead to increased degree of inflammation in brain tissue.[81] In addition, pro-inflammatory factors within the CSF may further contribute to neuronal injury.[81]

Several studies have shown that CP volume is significantly larger in pwMS compared to HCs.[11,13,15,16,19] (Figure 3) CP is enlarged from the earliest stages of the disease and shows a gradual increase as the disease progresses.[24] CP volume has been reported to be approximately 30 % larger in pwMS compared to HCs.[13,19] One recent study reported that CP volume can be up to 35 % greater in pwMS, particularly among those with RRMS.[11] Enlarged CP in MS is linked to more severe clinical disability and cognitive impairment, greater global and central brain as well as white matter (WM) atrophy, increased lesion load, impaired glymphatic function and greater demyelination.[10,20] CP enlargement has also been shown to associate with a lower probability of successful remyelination within MS lesions.[82]

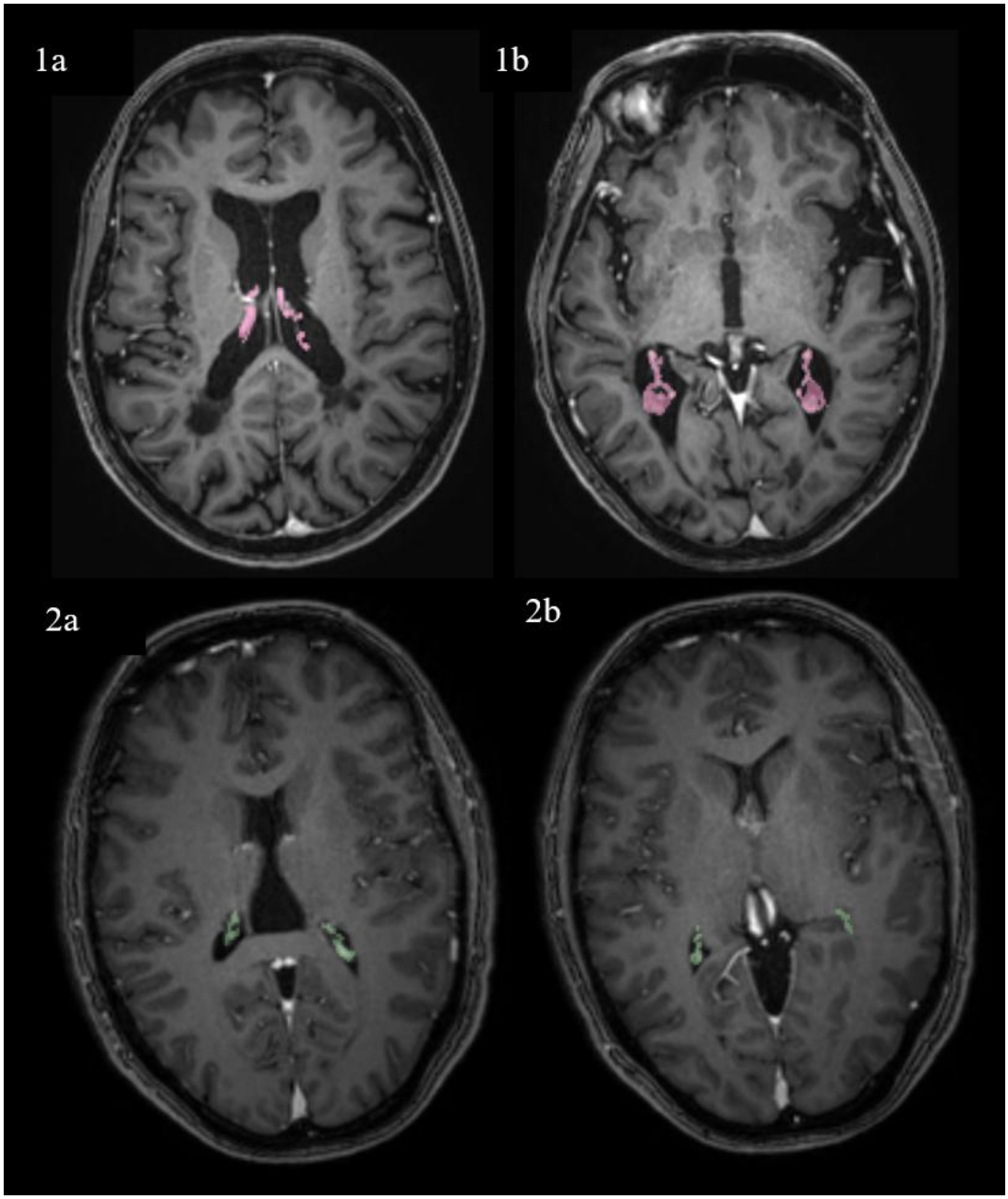

Figure 3. CP volume images from two patients with MS. Images 1a and 1b (CP represented in pale pink) depict a 48-year-old female pwRRMS with a disease duration of 12 years, while images 2a and 2b (CP represented in pale green) correspond to a 43-year-old female HC. The CP volume is markedly greater in the RRMS patient (4.6 cm^3) compared to the HC (1.6 cm^3).

2.5 Association between CP volume and brain atrophy

Several studies have demonstrated that CP enlargement correlates with central and total brain atrophy,[21–24] as well as atrophy in white and deep gray matter.[22,24] Enlargement of the CP has also been associated with reduced cortical thickness and with greater cortical atrophy observed in sulcal regions compared to gyral regions.[21]

Recent studies indicate that CP enlargement in MS is particularly associated with central brain atrophy, which can be assessed by change in brain ventricular volume. [23,24] In these studies, CP volume was correlated with total intracranial volume and adjusted for age, gender, and disease duration. Central brain atrophy has been shown to have a stronger association with CP volume than other forms of brain atrophy.[23,24] One recent longitudinal study reported an annual central brain volume loss of 2.68 %, whereas total brain atrophy loss was only 0.23 % per year.[24] In this study, disease duration had a significant effect on both central and total brain atrophy. Greater changes in central brain volumes suggest that inflammatory changes in the brain may be driven primarily by the periventricular brain region rather than the cortical or peripheral regions.[23] Furthermore, central brain atrophy appears to be more closely related to periventricular WM atrophy than to alterations in GM.[23]

CP enlargement has been found to correlate with greater WM atrophy in pwMS, both with RRMS and SPMS, compared to HCs.[20,21,24,81] One recent study reported a significant reduction in cerebral WM volume in pwMS compared to HCs.[20] Greater WM atrophy was further associated with CP enlargement, even after adjusting for lateral ventricle volumes.[20] In contrast, CP volume showed no correlation with GM atrophy.[20] Another study reported that enlargement of CP is linked to periventricular WM and GM atrophy and suggested that ventricular enlargement in MS may result from neurodegeneration in the surrounding periventricular region.[83]

While the correlation between increased CP volume and WM atrophy has been consistently reported, findings regarding the relationship between CP enlargement and gray matter (GM) volume reduction have been more variable.[19–21] It is also unclear whether GM atrophy predominantly affects deep or cortical regions, with deep GM atrophy typically involving the thalamus, caudate, putamen and globus pallidus.[13,19] It has further been suggested that distinct mechanisms underline deep and cortical GM volume loss.[84]

Deep GM atrophy in MS has been widely reported and is associated with more severe clinical disability in pwMS.[85–87] A recent cross-sectional study demonstrated a

significant correlation between increased CP volume and both deep GM and total GM atrophy, with the most pronounced deep GM atrophy observed in the thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens in patients with RRMS.[19] In comparison, another cross-sectional study found that CP enlargement was associated with cortical GM loss in RRMS patients but not in those with PPMS.[13] Conversely, other studies have reported no significant association between CP enlargement and GM atrophy.[14,15,20] In one study, after adjusting for lateral ventricular volume, multivariable models revealed no correlation between CP enlargement and GM atrophy.[20] The authors suggested that while GM atrophy is evident and primarily responsible for total brain atrophy in pwMS, it may be mainly driven by neurodegeneration rather than CP-related processes, with CP enlargement reflecting neuroinflammatory rather than neurodegenerative activity.

2.6 Association between CP volume, lesion load and lesion expansion

Recent studies show that increased CP volume correlates with a higher volume of WMLs,[19,20] as well as with the expansion and severity of CALs, particularly those located in close proximity to the brain ventricles [17–20]. In contrast, CP volume does not appear to be associated with the formation of new WMLs. [23,24]

CP enlargement showed a significantly positive correlation with T2-weighted WML volume detected on conventional MRI in pwMS.[16,19,22] One cross-sectional study reported that CP enlargement was associated with both greater T2 lesion number and volume.[88] This study indicated that each T2 lesion increased CP volume by approximately 4.4 microliters, after adjusting for age, sex, total intracranial volume and other significant clinical parameters. As T2 lesions are linked to focal inflammation within the CNS, the authors of this study suggested that CP may be directly associated with inflammatory activity in MS. Furthermore, in a recent longitudinal study, baseline CP enlargement was associated with increased T2 lesion accumulation at 5.5 years follow-up in both RRMS and PMS patients, suggesting that CP may play a significant role in neuroinflammatory process in pwMS.[83]

Increasing evidence suggests that disease progression in MS is primarily driven by CALs rather than the formation of new lesions.[23,24,89] CALs can be identified in vivo by MRI or PET based methods.[17] Smouldering inflammation at the edge of CALs, corresponding to lesion expansion on MRI, may represent a primary mechanism driving disease progression, including progressive neurodegeneration, brain atrophy and worsening disability, and is considered a key mediator to PIRA.[17] It has been suggested that CP may sustain low-grade inflammatory processes at the periphery of CALs, particularly within the periventricular region.[24] CP enlargement has been associated with a higher presence of CALs in pwMS, reflected by both lesion expansion[23,24] and paramagnetic rim lesions (PRLs),[18,19] which will be discussed in greater detail later in this chapter.

It has been demonstrated that immune cell activation in MS is highest near the ventricular border and decreases with increasing distance from the ventricles.[90] Consistent with this observation, the greatest lesion expansion has been detected in periventricular regions, suggesting that CSF-related factors, including the secretion of pro-inflammatory cytokines, may contribute to neuroinflammation and tissue injury in these areas.[91] Activation of macrophages and microglia is considered the main factor in this inflammatory process.[90,91] Reactive microglia and macrophages at the lesion edge, as well as associated lesion expansion,[92,93] have been further linked to increased CP volume.[23,24] It has been suggested that CP enlargement may predict future periventricular neurodegeneration.[83] Conversely, recent studies have not found an association between CP enlargement and the development of new WMLs, supporting the notion that CP enlargement is more closely related to chronic, or smouldering inflammation rather than acute MS pathology.[23,24] Nevertheless, it was suggested that there may be a potential correlation between increased CP volume and the activation of pre-existing WMLs, requiring further investigation.[24]

Paramagnetic rim lesions (PRLs), that represent a subset of lesions histologically categorized as smouldering lesions, can be identified by susceptibility sensitive MRI sequences.[19] PRLs have been linked to CP enlargement, particularly in pwPPMS and SPMS, suggesting a potential relationship between CP enlargement and chronic active inflammation within the CNS.[18] A recent cross-sectional study reported CP volumes to

be approximately 20 % larger in patients with PRLs compared to those without.[19] As activated, iron containing microglia is a defining feature of PRLs and strongly associated with CP enlargement, these findings further support the link between CP enlargement and chronic neuroinflammation.[19] In contrast, a study using PET-imaging and the radioligand [^{18}F]DPA-714 to phenotype chronic MS lesions, found that increased CP volume was associated with a higher proportion of homogenously active lesions, but not with rim-active or nonactive lesions.[17] The study further reported that the association was stronger in the periventricular WM, which enforces the notion that neuroinflammation may be primarily driven by periventricular regions and suggests a potentially impaired function at the BCSFB level. Equal to PRLs, homogenously activated lesions were linked to increased presence of activated microglia, as [^{18}F]DPA-714 binding results from increased presence of proinflammatory cells, mainly microglia and in smaller proportions of inflamed astrocytes.[94]

In addition to increased inflammatory activity at the lesion rim, progressive tissue loss within slowly expanding WMLs, or CALs, has been reported.[89,95,96] Slowly expanding WMLs demonstrate lower signal density on MRI compared with non-expanding lesions, suggesting progressive accumulation of demyelination and axonal loss within the lesion core in slowly expanding lesions.[23,89,97] Furthermore, a recent study found an association between CP enlargement and WM tissue loss in slowly expanding WMLs.[23] Another study, using ^{11}C-PiB PET to assess myelin content change within MS lesions, reported that failure of remyelination in WMLs in periventricular area positively correlated with CP enlargement in pwMS.[82] However, the relationship between chronic demyelination at the center of CALs, activated microglia and macrophages at the lesion edge, and CP volume remains incompletely understood and requires further investigation.

2.7 Association between CP volume and clinical aspects

Enlarged CP has been linked to more severe clinical disability and cognitive impairment in pwMS.[19,25,26] Larger CP volume has been associated with higher EDSS (expanded disability status scale) scores[19,25] as well as lower MoCA (Montreal cognitive assessment)[19,26] and SDMT (symbol digit modalities test) scores,[19,25,26] suggesting that greater CP volume is associated with greater disability and worse cognitive

performance in pwMS.[19,25] However, in one cross-sectional study, the association between CP volume and clinical status scores lost statistical significance after adjusting for brain lesion volume and brain atrophy.[19] This study suggested that the relationship between CP enlargement and clinical disability may be indirectly mediated by increased lesion load and brain atrophy.

Another recent cross-sectional study demonstrated that patients with cognitive impairment showed a significantly larger CP compared to patients without cognitive impairment.[26] The authors suggested that structural and secretory changes of the enlarged CP, including the release of proinflammatory cytokines and increased immune cell entry into the CNS, may contribute to a chronic proinflammatory state in the brain. The authors further suggested that this may promote not only demyelination and neuroaxonal loss but also impaired synaptic function, which may play a vital role in disease progression and cognitive impairment.[26]

Furthermore, one longitudinal study found that pwMS with greater clinical disability at baseline, as measured by EDSS scores, showed a greater increase in CP volume after a 2-year follow-up.[25] Conversely, worse cognition at baseline, as measured by SDMT scores, was not significantly correlated with CP volume changes during the same 2-year follow-up. No correlation was observed between baseline CP volume and disability or cognition worsened over a 2-year follow-up period either. However, manually segmented CP volume at baseline was associated with disability worsening over a 5-year follow-up, but this association lost statistical significance when automatic segmentation was used.

Fatigue is a common symptom in pwMS, with up to 80 % of patients experiencing MS-related fatigue.[98] Fatigue is difficult to treat and to prevent with modern disease-modifying treatments.[99] Recent studies have shown no correlation between WM lesion burden, brain atrophy, and fatigue experienced by pwMS.[26,98] Interestingly, more severe MS-related fatigue has been significantly associated with higher CP volume.[26,98] These studies suggested that the chronic proinflammatory state potentially induced and sustained by enlarged CP may contribute to fatigue in pwMS. In addition, although more

severe disability and a progressive disease course may exacerbate MS-related fatigue, fatigue can also occur independently of disability status and disease duration.[26] As both CP enlargement and fatigue can be present in the early stages of the disease, these observations suggest that CP enlargement may be a key facilitator of a process contributing fatigue in pwMS.[26]

3 Conclusions

MS is the most common neurodegenerative disorder among young adults. The disease course varies from relapsing-remitting to progressive forms of MS. Progression can also be experienced without relapses, known as PIRA, which is considered the key mediator of disability accumulation in pwMS. Autoreactive immune cells enter the CNS via an impaired BCFSB and potentially via the CP, which has been shown several alterations in pwMS.

Multiple studies have reported CP volume being significantly larger in pwMS compared to HCs. CP enlargement in MS has been linked to increased microglial and macrophage activity, as well as increased release of proinflammatory cytokines in the CNS. Furthermore, CP enlargement has been associated with greater total and central brain atrophy, the latter being more significant than other forms of brain atrophy. CP enlargement has also been linked to greater WM atrophy, particularly in the periventricular region, suggesting increased neuroinflammatory activity near the ventricles. GM atrophy is widely reported in pwMS, but its relationship with CP enlargement remains unclear. It has been suggested that GM atrophy is mainly driven by neurodegenerative processes whereas WM atrophy is more closely associated with smouldering neuroinflammation in the CNS.

Higher CP volume has been linked to increased number and volume of WMLs. Interestingly, CP enlargement has been further significantly associated with a higher presence of CALs, which is reflected by both PRLs and lesion expansion. As activated microglial cells and macrophages are present CALs and have also been linked to CP enlargement, these findings suggest that CP may be one of the key mediators driving smouldering neuroinflammation. In line with this, lesion load and expansion, together with brain atrophy, has been shown to be greater near the brain ventricles than in the brain periphery. This suggests that chronic neuroinflammation may follow a periventricular gradient, which may result from dysfunction at the BCSFB level.

Lastly, enlarged CP has been strongly associated with MS-related fatigue and together with increased lesion load has been shown to predict more severe clinical disability and cognitive impairment in pwMS. These findings further support the notion that CP may play a crucial role, or even drive, smouldering neuroinflammation in pwMS. However, more longitudinal studies are required to examine these associations.

References

1. Haki, M., AL-Biati, H. A., Al-Tameemi, Z. S., Ali, I. S. & Al-hussaniy, H. A. Review of multiple sclerosis: Epidemiology, etiology, pathophysiology, and treatment. *Medicine* **103**, (2024).

2. Oh, J., Vidal-Jordana, A. & Montalban, X. Multiple sclerosis: clinical aspects. *Curr. Opin. Neurol.* **31**, (2018).

3. Dobson, R. & Giovannoni, G. Multiple sclerosis – a review. *Eur. J. Neurol.* **26**, 27–40 (2019).

4. McGinley, M. P., Goldschmidt, C. H. & Rae-Grant, A. D. Diagnosis and Treatment of Multiple Sclerosis: A Review. *JAMA* **325**, 765–779 (2021).

5. Katz Sand, I. Classification, diagnosis, and differential diagnosis of multiple sclerosis. *Curr. Opin. Neurol.* **28**, (2015).

6. Karussis, D. The diagnosis of multiple sclerosis and the various related demyelinating syndromes: A critical review. *J. Autoimmun.* **48–49**, 134–142 (2014).

7. Olsson T, Barcellos LF & Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nat Rev Neurol. 2017 Jan;13(1):25-36. doi: 10.1038/nrneurol.2016.187. Epub 2016 Dec 9.* (2016).

8. Ortiz, G. G. *et al.* Role of the Blood–Brain Barrier in Multiple Sclerosis. *Arch. Med. Res.* **45**, 687–697 (2014).

9. Haschek, W. M., Rousseaux, C. G. & Wallig, M. A. Nervous System. *Fundamentals of Toxicologic Pathology* 377–410 (2010) doi:10.1016/B978-0-12-370469-6.00013-1.

10. Kolahi, S. *et al.* Choroid plexus volume changes in multiple sclerosis: insights from a systematic review and meta-analysis of magnetic resonance imaging studies. *Neuroradiology* **66**, 1869–1886 (2024).

11. Ricigliano, V. A. G. *et al.* Choroid plexus enlargement in inflammatory multiple sclerosis: 3.0-T MRI and translocator protein PET evaluation. *Radiology* **301**, 166–177 (2021).

12. Kaur, C., Rathnasamy, G. & Ling, E.-A. The Choroid Plexus in Healthy and Diseased Brain. *J. Neuropathol. Exp. Neurol.* **75**, 198–213 (2016).

13. Krieger, B. *et al.* Relevance of choroid plexus volumes in multiple sclerosis. *Fluids Barriers CNS* **22**, 47 (2025).

14. Wołos, J., Grodzka, O., Kochanowski, J. & Domitrz, I. Choroid plexus imaging in multiple sclerosis management-a systematic review. *Polish Journal of Neurology and Neurosurgery* **2024**, 233–244 (2024).

15. Moases Ghaffary, E. *et al.* Choroid plexus volume in multiple sclerosis: a systematic review and meta-analysis of an emerging imaging biomarker. *Eur. J. Med. Res.* **30**, 762 (2025).

16. Chen, W., Zeng, K., Chen, H., Li, Z. & Lin, A. Choroid plexus enlargement in Chinese multiple sclerosis is independent of oligoclonal band status and associated with thalamic atrophy: A 7T MRI study. *Mult. Scler. Relat. Disord.* **104**, 106852 (2025).

17. Hamzaoui, M. *et al.* Positron Emission Tomography with [18F]-DPA-714 Unveils a Smoldering Component in Most Multiple Sclerosis Lesions which Drives Disease Progression. *Ann. Neurol.* **94**, 366–383 (2023).

18. Reeves, J. A. *et al.* Paramagnetic rim lesions are associated with choroid plexus inflammation and expansion over 5 years in people with multiple sclerosis. *J. Neurol.* **272**, 585 (2025).

19. Wang, X. *et al.* Enlarged choroid plexus related to iron rim lesions and deep gray matter atrophy in relapsing-remitting multiple sclerosis. *Mult. Scler. Relat. Disord.* **75**, 104740 (2023).

20. Akaishi, T., Fujimori, J. & Nakashima, I. Enlarged choroid plexus in multiple sclerosis is associated with increased lesion load and atrophy in white matter but not gray matter atrophy. *Mult. Scler. Relat. Disord.* **82**, 105424 (2024).

21. Chen, X. *et al.* Enlarged choroid plexus related to cortical atrophy in multiple sclerosis. *Eur. Radiol.* **33**, 2916–2926 (2023).

22. Preziosa, P. *et al.* Glymphatic System May Mediate the Relation Between Choroid Plexus and Brain Damage in Multiple Sclerosis. *Neurology Neuroimmunology; Neuroinflammation* **12**, e200414 (2025).

23. Klistorner, S. *et al.* Choroid plexus volume in multiple sclerosis predicts expansion of chronic lesions and brain atrophy. *Ann. Clin. Transl. Neurol.* **9**, 1528–1537 (2022).

24. Klistorner, Samuel *et al.* Longitudinal enlargement of choroid plexus is associated with chronic lesion expansion and neurodegeneration in RRMS patients. *Multiple Sclerosis Journal* **30**, 496–504 (2024).

25. Wang, X. *et al.* Enhanced choroid plexus segmentation with 3D UX-Net and its association with disease progression in multiple sclerosis. *Mult. Scler. Relat. Disord.* **88**, 105750 (2024).

26. Preziosa, P. *et al.* Chronic Active Lesions and Larger Choroid Plexus Explain Cognition and Fatigue in Multiple Sclerosis. *Neurology Neuroimmunology; Neuroinflammation* **11**, e200205 (2025).

27. Disanto, G. *et al.* Prodromal symptoms of multiple sclerosis in primary care. *Ann. Neurol.* **83**, 1162–1173 (2018).

28. Jakimovski, D. *et al.* Multiple sclerosis. *The Lancet* **403**, 183–202 (2024).

29. Lorenzut, S. *et al.* Exploring the Pathophysiology, Diagnosis, and Treatment Options of Multiple Sclerosis. *J Integr Neurosci. 2025 Jan 21;24(1):25081. doi: 10.31083/JIN25081* https://www.imrpress.com/journal/JIN/24/1/10.31083/JIN25081/htm (2025).

30. Thouvenot, É. Update on clinically isolated syndrome. *Presse Med.* **44**, e121–e136 (2015).

31. Yang, Y. *et al.* Cerebellar and/or Brainstem Lesions Indicate Poor Prognosis in Multiple Sclerosis: A Systematic Review. *Front Neurol. 2022 Apr 29;13:874388. doi: 10.3389/fneur.2022.874388. PMID: 35572921; PMCID: PMC9099189.* (2022).

32. Miller, D., Barkhof, F., Montalban, X., Thompson, A. & Filippi, M. Clinically isolated syndromes suggestive of multiple sclerosis, part I: Natural history, pathogenesis, diagnosis, and prognosis. *Lancet Neurology* **4**, 281–288 (2005).

33. Tintoré, M. *et al.* Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis? *Neurology* **70**, 1079–1083 (2008).

34. Young, J., Quinn, S., Hurrell, M. & Taylor, B. Clinically isolated acute transverse myelitis: Prognostic features and incidence. *Multiple Sclerosis* **15**, 1295–1302 (2009).

35. Tintore, M. *et al.* Brainstem lesions in clinically isolated syndromes. *Neurology* **75**, 1933–1938 (2010).

36. Fisniku, L. K. *et al.* Disability and T2 MRI lesions: A 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain* **131**, 808–817 (2008).

37. Marcus, R. What Is Multiple Sclerosis? *JAMA* **328**, 2078 (2022).

38. Kuhlmann, T. *et al.* Multiple sclerosis progression: time for a new mechanism-driven framework. *Lancet Neurol.* **22**, 78–88 (2023).

39. Barrett, A. *et al.* Understanding the Symptoms and Impacts Experienced by People with Relapsing–Remitting MS: A Qualitative Investigation Using Semi-Structured Interviews. *Neurol. Ther.* **13**, 449–464 (2024).

40. Ziemssen, T. Symptom management in patients with multiple sclerosis. *J. Neurol. Sci.* **311**, S48–S52 (2011).

41. Gelfand, J. M. Multiple sclerosis: diagnosis, differential diagnosis, and clinical presentation. *Handb. Clin. Neurol.* **122**, 269–290 (2014).

42. Brieva, L., Calles, C., Landete, L. & Oreja-Guevara, C. Current challenges in secondary progressive multiple sclerosis: diagnosis, activity detection and treatment. *Front. Immunol.* **16**, (2025).

43. Barzegar, M. *et al.* Early predictors of conversion to secondary progressive multiple sclerosis. *Mult. Scler. Relat. Disord.* **54**, 103115 (2021).

44. Amezcua, L. *Progressive Multiple Sclerosis*. (2022).

45. Lublin, F. D. *et al.* How patients with multiple sclerosis acquire disability. *Brain* **145**, 3147–3161 (2022).

46. Kappos, L. *et al.* Contribution of Relapse-Independent Progression vs Relapse-Associated Worsening to Overall Confirmed Disability Accumulation in Typical Relapsing Multiple Sclerosis in a Pooled Analysis of 2 Randomized Clinical Trials. *JAMA Neurol.* **77**, 1132–1140 (2020).

47. Calabrese, M. *et al.* Determinants and Biomarkers of Progression Independent of Relapses in Multiple Sclerosis. *Ann. Neurol.* **96**, 1–20 (2024).

48. Müller, J. *et al.* Harmonizing Definitions for Progression Independent of Relapse Activity in Multiple Sclerosis: A Systematic Review. *JAMA Neurol.* **80**, 1232–1245 (2023).

49. Alonso, R. *et al.* Progression independent of relapse activity (PIRA) in the Era of high-efficacy treatments. *Mult. Scler. Relat. Disord.* **104**, (2025).

50. Kapica-Topczewska, K. *et al.* Assessment of Disability Progression Independent of Relapse and Brain MRI Activity in Patients with Multiple Sclerosis in Poland. *J. Clin. Med.* **10**, (2021).

51. Graf, J. *et al.* Relapse-independent multiple sclerosis progression under natalizumab. *Brain Commun.* **3**, fcab229 (2021).

52. Prosperini, L. *et al.* Prognostic Accuracy of NEDA-3 in Long-term Outcomes of Multiple Sclerosis. *Neurology Neuroimmunology; Neuroinflammation* **8**, e1059 (2026).

53. Wegner, C. Recent insights into the pathology of multiple sclerosis and neuromyelitis optica. *Clin. Neurol. Neurosurg.* **115**, S38–S41 (2013).

54. Calvi, A. *et al.* In vivo imaging of chronic active lesions in multiple sclerosis. *Multiple Sclerosis Journal* **28**, 683–690 (2020).

55. Bagnato, F. *et al.* Imaging chronic active lesions in multiple sclerosis: a consensus statement. *Brain* **147**, 2913–2933 (2024).

56. Kuhlmann, T. *et al.* An updated histological classification system for multiple sclerosis lesions. *Acta Neuropathol.* **133**, 13–24 (2017).

57. Dal-Bianco, A., Oh, J., Sati, P. & Absinta, M. Chronic active lesions in multiple sclerosis: classification, terminology, and clinical significance. *Ther. Adv. Neurol. Disord.* **17**, 17562864241306684 (2024).

58. Hemond, C. C., Reich, D. S. & Dundamadappa, S. K. Paramagnetic Rim Lesions in Multiple Sclerosis: Comparison of Visualization at 1.5-T and 3-T MRI. *American Journal of Roentgenology* **219**, 120–131 (2021).

59. Unterrainer, M. *et al.* TSPO PET with [18F]GE-180 sensitively detects focal neuroinflammation in patients with relapsing–remitting multiple sclerosis. *Eur. J. Nucl. Med. Mol. Imaging* **45**, 1423–1431 (2018).

60. Mey, G. M., Mahajan, K. R. & DeSilva, T. M. Neurodegeneration in multiple sclerosis. *WIREs Mechanisms of Disease* **15**, e1583 (2023).

61. Grigoriadis, N. & van Pesch, V. A basic overview of multiple sclerosis immunopathology. *Eur. J. Neurol.* **22**, 3–13 (2015).

62. Lopez, J. A., Denkova, M., Ramanathan, S., Dale, R. C. & Brilot, F. Pathogenesis of autoimmune demyelination: from multiple sclerosis to neuromyelitis optica spectrum disorders and myelin oligodendrocyte glycoprotein antibody-associated disease. *Clin. Transl. Immunology* **10**, e1316 (2021).

63. Michaličková, D., Šíma, M. & Slanař, O. New insights in the mechanisms of impaired redox signaling and its interplay with inflammation and immunity in multiple sclerosis. *Physiol. Res.* **69**, 1–19 (2020).

64. Lassmann, H. Multiple Sclerosis Pathology. *Cold Spring Harb Perspect Med. 2018;8(3):a028936. Published 2018 Mar 1. doi:10.1101/cshperspect.a028936* (2018).

65. Chaudhuri, A. Multiple sclerosis is primarily a neurodegenerative disease. *J. Neural Transm.* **120**, 1463–1466 (2013).

66. Kompaníková, P. & Bryja, V. Regulation of choroid plexus development and its functions. *Cellular and Molecular Life Sciences* **79**, 304 (2022).

67. Courtney, el, Hochstetler, A. & Lehtinen, M. K. Choroid Plexus Pathophysiology. 20 (2025) doi:10.1146/annurev-pathmechdis.

68. Damkier, H. H., Brown, P. D. & Praetorius, J. Cerebrospinal Fluid Secretion by the Choroid Plexus. *Physiol. Rev.* **93**, 1847–1892 (2013).

69. MacAulay, N. & Toft-Bertelsen, T. L. Dual function of the choroid plexus: Cerebrospinal fluid production and control of brain ion homeostasis. *Cell Calcium* **116**, 102797 (2023).

70. Rodriguez-Mogeda, C. *et al.* Breaching Brain Barriers: B Cell Migration in Multiple Sclerosis. *Biomolecules* **12**, (2022).

71. Kratzer, I., Ek, J. & Stolp, H. The molecular anatomy and functions of the choroid plexus in healthy and diseased brain. *Biochimica et Biophysica Acta (BBA) - Biomembranes* **1862**, 183430 (2020).

72. Damkier, H. H. & Praetorius, J. Cerebrospinal fluid pH regulation. *Pflugers Arch.* **476**, 467–478 (2024).

73. Redzic, Z. B. & Segal, M. B. The structure of the choroid plexus and the physiology of the choroid plexus epithelium. *Adv. Drug Deliv. Rev.* **56**, 1695–1716 (2004).

74. Rodríguez-Lorenzo, S. *et al.* Altered secretory and neuroprotective function of the choroid plexus in progressive multiple sclerosis. *Acta Neuropathol. Commun.* **8**, 35 (2020).

75. Magliozzi, R. *et al.* Neuropathological and cerebrospinal fluid correlates of choroid plexus inflammation in progressive multiple sclerosis. *Brain Pathology* **35**, e13322 (2025).

76. Rodríguez-Lorenzo, S. *et al.* Inflammation of the choroid plexus in progressive multiple sclerosis: accumulation of granulocytes and T cells. *Acta Neuropathol. Commun.* **8**, 9 (2020).

77. Kooij, G. *et al.* Disturbed function of the blood–cerebrospinal fluid barrier aggravates neuro-inflammation. *Acta Neuropathol.* **128**, 267–277 (2014).

78. Židó, M. *et al.* Metabolomics of Cerebrospinal Fluid in Multiple Sclerosis Compared With Healthy Controls: A Pilot Study. *Front. Neurol.* **13**, (2022).

79. Giovannoni, G. Cerebrospinal fluid analysis. in *Handbook of Clinical Neurology* vol. 122 681–702 (2014).

80. Matsushita, T. *et al.* Characteristic Cerebrospinal Fluid Cytokine/Chemokine Profiles in Neuromyelitis Optica, Relapsing Remitting or Primary Progressive Multiple Sclerosis. *PLoS One* **8**, (2013).

81. Xie, Y. *et al.* Enlarged choroid plexus in relapsing-remitting multiple sclerosis may lead to brain structural changes through the glymphatic impairment. *Mult. Scler. Relat. Disord.* **85**, 105550 (2024).

82. Tonietto, M. *et al.* Periventricular remyelination failure in multiple sclerosis: a substrate for neurodegeneration. *Brain* **146**, 182–194 (2023).

83. Bergsland, N. *et al.* Choroid plexus enlargement is associated with future periventricular neurodegeneration in multiple sclerosis. *Mult. Scler. Relat. Disord.* **87**, 105668 (2024).

84. Giuseppe, P. *et al.* Determinants of deep gray matter atrophy in multiple sclerosis: A multimodal MRI study. *American Journal of Neuroradiology* **40**, 99–106 (2019).

85. Haider, L. *et al.* Multiple sclerosis deep grey matter: The relation between demyelination, neurodegeneration, inflammation and iron. *J. Neurol. Neurosurg. Psychiatry* **85**, 1386–1395 (2014).

86. Vercellino, M. *et al.* Demyelination, inflammation, and neurodegeneration in multiple sclerosis deep gray matter. *J. Neuropathol. Exp. Neurol.* **68**, 489–502 (2009).

87. Cao, Y. *et al.* Gray Matter Atrophy in the Cortico-Striatal-Thalamic Network and Sensorimotor Network in Relapsing–Remitting and Primary Progressive Multiple Sclerosis. *Neuropsychol. Rev.* **31**, 703–720 (2021).

88. Müller, J. *et al.* Choroid Plexus Volume in Multiple Sclerosis vs Neuromyelitis Optica Spectrum Disorder. *Neurology Neuroimmunology; Neuroinflammation* **9**, e1147 (2022).

89. Elliott, C. *et al.* Patterning Chronic Active Demyelination in Slowly Expanding/Evolving White Matter MS Lesions. *American Journal of Neuroradiology* **41**, 1584 (2020).

90. Poirion, E. *et al.* Structural and Clinical Correlates of a Periventricular Gradient of Neuroinflammation in Multiple Sclerosis. *Neurology* **96**, e1865–e1875 (2021).

91. Klistorner, Samuel, Barnett, Michael H, Graham, Stuart L, Wang, Chenyu & Klistorner, Alexander. The expansion and severity of chronic MS lesions follows a periventricular gradient. *Multiple Sclerosis Journal* **28**, 1504–1514 (2022).

92. Dal-Bianco, A. *et al.* Slow expansion of multiple sclerosis iron rim lesions: pathology and 7 T magnetic resonance imaging. *Acta Neuropathol.* **133**, 25–42 (2017).

93. Jäckle, K. *et al.* Molecular signature of slowly expanding lesions in progressive multiple sclerosis. *Brain* **143**, 2073–2088 (2020).

94. Absinta, M. *et al.* A lymphocyte–microglia–astrocyte axis in chronic active multiple sclerosis. *Nature* **597**, 709–714 (2021).

95. Klistorner, A. *et al.* Evidence of progressive tissue loss in the core of chronic MS lesions: A longitudinal DTI study. *Neuroimage Clin.* **17**, 1028–1035 (2018).

96. Elliott, C. *et al.* Chronic white matter lesion activity predicts clinical progression in primary progressive multiple sclerosis. *Brain* **142**, 2787–2799 (2019).

97. Wang, C. *et al.* Lesion activity and chronic demyelination are the major determinants of brain atrophy in MS. *Neurology Neuroimmunology; Neuroinflammation* **6**, e593 (2026).

98. Rubin, M. *et al*. Dynamics of choroid plexus volume is associated with the presence and development of fatigue in multiple sclerosis. *Journal of Neurology, Neurosurgery; Psychiatry* **96**, 443 (2025).

99. Penner, I.-K. Evaluation of cognition and fatigue in multiple sclerosis: daily practice and future directions. *Acta Neurol. Scand.* **134**, 19–23 (2016).