REVIEW ARTICLE

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Choroid plexus imaging in multiple sclerosis management — a systematic review

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ABSTRACT

Introduction. Multiple sclerosis (MS) is a central nervous system (CNS) disease associated with inflammation, demyelination, and neurodegeneration. It affects more than 2 million people globally, and usually occurs in young adults, three-quarters of whom are women. Importantly, accurate diagnosis and treatment are essential, as this disease can lead to the rapid development of disability. The choroid plexus (CP) is a structure widely known as the main cerebrospinal fluid source. However, it is also involved in immune cell trafficking to the cerebrospinal fluid, which is increased in different neurological disorders, particularly those associated with neuroinflammation.

As MS is generally thought to be caused by an autoimmune process, it has been suggested that the choroid plexus may play a significant role in its pathogenesis, manifesting via changes in imaging characteristics.

Material and methods. Although research regarding this topic has been very limited, the results of the available studies appear promising. To further investigate this subject, we performed a systematic literature review according to the PRISMA 2020 guidelines. The PubMed and Embase databases were searched for relevant articles, and after thorough analysis, 16 studies were included in our review.

Results. CP volume was significantly increased in MS patients compared to healthy individuals. Furthermore, some studies found that CP enlargement occurs even before a definite diagnosis. Moreover, a few articles reported correlations between CP volume and brain atrophy, or even disease severity.

Conclusions. Our findings show that CP imaging has the potential to become a novel and valuable tool in multiple sclerosis management.

Key words: choroid plexus, magnetic resonance imaging, multiple sclerosis, neuroinflammation, plica choroidea

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Introduction

Background information about multiple sclerosis

According to the European Committee of Treatment and Research in Multiple Sclerosis and the European Academy of Neurology (ECTRIMS/EAN) Guidelines [1], multiple sclerosis (MS) is a central nervous system (CNS) disease with a complex pathogenesis, associated with inflammation, demyelination, and neurodegeneration. Globally, more than 2 million people are affected by MS, three-quarters of whom are female [2]. Although disease onset usually occurs in young adults [3, 4], c.5% of patients develop their first symptoms before the age of 18 [5]. MS presentation differs widely between patients, with typical initial manifestations being acute unilateral optic neuritis, partial myelitis, brainstem syndrome, or sensory impairment [6].

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Evidence of dissemination in both time (DIT) and space (DIS) is required for an MS diagnosis, which can be based on clinical, laboratory, and/or radiological findings [7]. Differential diagnosis remains a significant challenge, and should include diseases with a similar clinical presentation, such as aquaporin-4 antibody–positive neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) [8, 9]. Because MS is generally thought to be caused by an autoimmune process [10], the main treatment approach is concentrated on suppressing this pathological immune reaction [11]. Accurate and personalised therapy is essential to alleviate the symptoms and to reduce the risk of rapid disability development, as well as avoid the potentially dangerous side effects of treatment [12].

Morphology and functions of choroid plexus

The choroid plexus (CP) consists of a highly vascularised stroma covered with a layer of secretory epithelial cells [13]. It is widely known as the main source of cerebrospinal fluid (CSF), a liquid substance filling the ventricular system, the central canal of the spinal cord, and the subarachnoid space [14].

Interestingly, it has been found that apart from CSF production, the CP also plays an important role in other physiological processes, such as neurogenesis and circadian rhythm regulation [15]. Moreover, the CP can function as a route of entry to the CSF for immune cells, which can also be found in its stroma [16]. The CP epithelium is particularly engaged in immune cell trafficking, as numerous adhesion molecules are expressed by its cells, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), P-selectin, and E-cadherin [17]. This immune cell passage can be particularly increased in different neurological disorders, especially those associated with neuroinflammation such as MS or infection of the CNS [18].

It is important to note that inflammatory changes, as well as altered morphology of the CP, can be found in patients with Alzheimer's Disease [19]. Altered macroscopic characteristics of the CP have also been discovered in patients with psychosis, whose choroid plexuses were found to be significantly enlarged in magnetic resonance imaging (MRI) [20].

Suggested value of CP in MS

It has long been known that the CP is involved in the inflammatory process during experimental autoimmune encephalomyelitis (EAE), a commonly used animal model of MS [21]. Furthermore, neuropathological studies have provided evidence for CP inflammation in MS, as well as its involvement in lymphocyte trafficking to the CSF [22].

Pathological processes occurring in the choroid plexuses of MS patients manifest themselves not only in molecular, but also in macroscopic, changes, such as CP enlargement [23]. Recently, brain volumetric measurement has become the subject of interest as potential MRI markers used in the context of MS for disease progression monitoring purposes [24]. Moreover, brain volume loss is considered to be a promising predictor of disability worsening, as it mirrors the progression of neurodegeneration [25]. According to the 2021 Magnetic Resonance Imaging in Multiple Sclerosis, Consortium of Multiple Sclerosis Centres, and North American Imaging in Multiple Sclerosis Cooperative (MAGNIMS–CMSC–NAIMS) consensus [26], volumetric measurements of the brain are not yet recommended as part of the routine MRI protocol during the MS diagnostic process. However, they can provide supplementary information in specific cases.

To enable the implementation of such techniques in everyday clinical practice, more evidence and the resolution of remaining technical issues are required, and thus further research on this subject is needed.

In this systematic review, we aim to summarise the present state of knowledge regarding the use of CP imaging in MS management.

Material and methods

We performed a systematic review (Fig. 1) according to the guidelines of Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA 2020) [27]. Concurrently, the PubMed database and the Embase database were searched for the following terms: choroid plexus OR plica choroidea AND multiple sclerosis. All records up to 30 October 2023 were identified.

Inclusion and exclusion criteria

Our review was designed to include only the most relevant research, providing us with valuable data. We included studies in which both choroid plexus imaging was performed and MS patients were included in the study group. We were seeking only primary research, and thus clinical and cohort studies were allowed. Included studies investigated the imaging characteristics of choroid plexuses, particularly their calculated volume. Commentaries, letters to editors, conference abstracts, reviews, and systematic reviews were all excluded. We also rejected case reports as we were seeking datasets consisting of information obtained from larger patient groups. Studies focusing on imaging structures other than choroid plexuses were also excluded.

Selection process

After the initial search using the abovementioned words, 369 articles from the Embase database and 166 from the Pubmed database were identified. Duplicate records were removed, and 387 studies remained for further analysis. Subsequent evaluation resulted in the exclusion of 345 articles due to inadequate article type or title. The 42 remaining studies were assessed by abstract, and 24/42 did not meet our inclusion criteria. Full-text assessment led to the exclusion of another

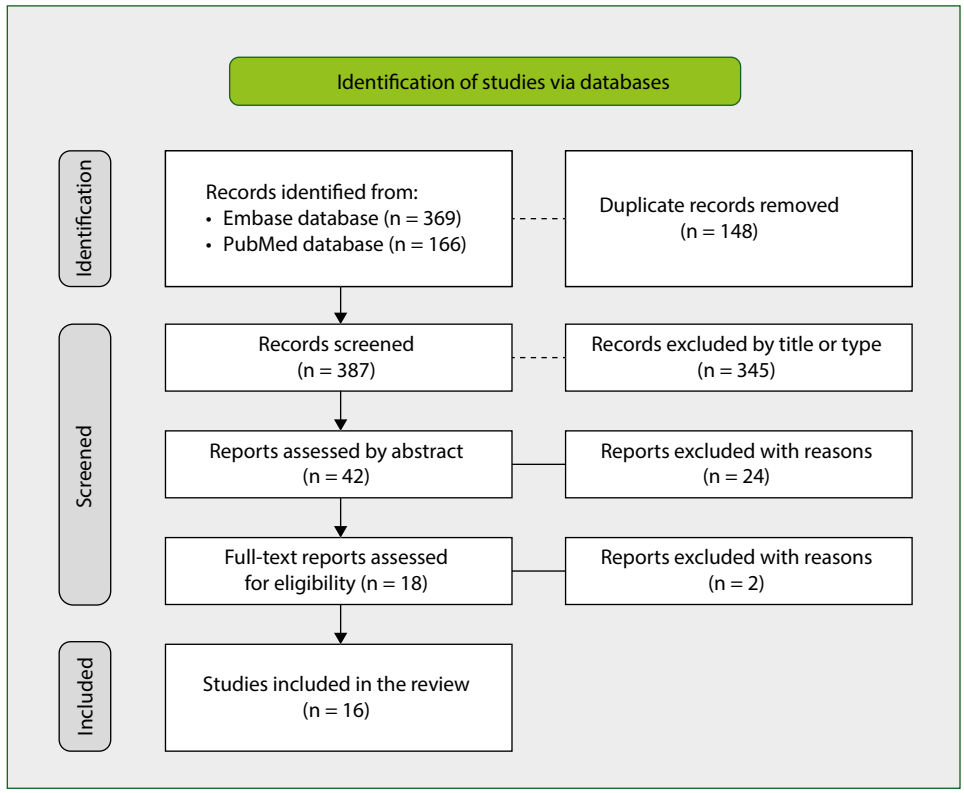

Figure 1. Flow diagram of selection process according to guidelines of Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA 2020); n — number of studies

two articles, as they were not eligible for this review based on the previously described criteria. Eventually therefore, the selection process provided us with 16 studies.

Choroid plexus imaging in MS

Over the years, neuroimaging has become a pivotal aspect of MS management. Recently, increasing attention has been paid to volumetric assessment of the brain and its numerous potential applications in clinical practice. Accordingly, choroid plexus volume (CPV) has been assessed in 15 out of the 16 studies included in this review.

We feel it is a particularly interesting observation that in all the studies to have compared the CPV of MS patients to that of healthy controls, there has been a significant enlargement of CP in the MS patient groups. Importantly, this difference in CPV remained significant despite a variety of CP segmentation and CPV calculation protocols. Furthermore, in some studies, CP enlargement was also reported in the early stages of MS development, thereby suggesting the potential for CPV to become in the future a factor in the risk assessment of definite MS diagnosis. Nonetheless, we must emphasise that the available research in this field is limited, and that therefore large multicentre studies are needed to validate these observations.

Although the use of CP imaging in MS diagnosis appears to be the primary research focus, the 16 included studies concurrently explored associations between CPV and other parameters important in the context of MS management. All of these studies and their crucial findings are thoroughly analysed below. However, it is important to emphasise that a considerable number of studies found white matter lesion load to be positively correlated with CPV in MS patients. This observation aligns with the abovementioned role of CP in neuroinflammation, thus suggesting its association with disease activity.

The use of CP imaging as a diagnostic or disease monitoring tool in MS is promising, but however it is a concept that has been insufficiently investigated. In order to conduct a thorough analysis of this subject, the research we included was divided into the following parts: (i) general use of choroid plexus in MS diagnosis; (ii) whether choroid plexus might be useful in MS severity assessment; (iii) choroid plexus imaging and disability status of MS patients; and (iv) choroid plexus in differentiation of MS and NMOSD.

General use of choroid plexus in MS diagnosis

Several studies regarding the analysed topic have focused on the use of choroid plexus in MS diagnosis in general, rather than other investigations or comparisons. Klistorner et al. [28] investigated patients with relapsing-remitting MS (RRMS) to find associations between MRI characteristics of CP and disease progression.

CPV, expressed as the ratio of TIV (total intracranial volume), was increased in MS patients compared to healthy controls at baseline. Importantly, the CPV/TIV ratio in MS patients did not change significantly during a 4-year follow-up period. For further analysis, the MRI protocol included separating periventricular brain tissue into bands, followed by assessing chronic lesion expansion within bands at baseline and follow-up. Lesion expansion rate was positively correlated with baseline CPV/TIV ratio in RRMS patients. Mean diffusivity (MD) inside chronic lesions, a tissue damage parameter, was also assessed. Increased baseline CPV/TIV ratio correlated with higher lesional core MD in RRMS patients at baseline and at follow-up. It was also associated with greater change in lesional core MD in the same group during the follow-up. It is worth underlining that increased CPV/TIV ratio at baseline predicted greater brain atrophy measured by larger ventricular expansion at follow-up in RRMS patients. Similarly, Jankowska et al. [29] also studied patients with RRMS. However, they compared MS patients receiving experimental cellular therapy (MS Treg) to treatment-naïve MS patients (MS tn) and to healthy controls. At baseline, the CPV/TIV ratio was significantly higher for MS patients (MS Treg and MS tn combined) compared to healthy controls. Furthermore, the authors observed a constant growth in the CPV/TIV ratio in both MS patient groups during a 1-year follow-up. Interestingly, plexuses of MS Treg patients with at least one relapse were larger than those of MS Treg patients without relapses. Moreover, the plexuses of MS Treg patients with contrast-enhancing lesions were larger compared to those of MS Treg patients without active lesions.

A study by Margoni et al. [30] is the only one in this review that focused on CP imaging in paediatric patients with MS. Further studies are required in this field. The authors investigated the utility of CPV as a possible diagnostic marker in paediatric MS patients. As expected, CPV was enlarged in the MS group compared to healthy controls. This association was also true when comparing sex-matched MS patients to healthy individuals. Interestingly, CP enlargement was significantly more substantial among girls, which suggests the need for further investigation to verify this observation. Moreover, a positive correlation was found between CPV and the volume of brain lesions, as well as the volume of lateral ventricles. On the other hand, larger CPV predicted lower brain and thalamic volumes. It should be noted that no significant associations between CPV and white matter volume, Expanded Disability Status Scale (EDSS) score, duration of disease, or cortical volume, were found.

Another interesting study was conducted by Storelli et al. [31], who proposed a new method i.e. FLAIR (fluid-attenuated inversion recovery) + T1 GMM (Gaussian Mixture Model), for fast and accurate CP segmentation. CPV values obtained using the FLAIR + T1 GMM method did not differ significantly compared to manual segmentation, unlike FreeSurfer (FS) and FS-GMM methods. All four methods showed that the choroid plexuses of MS patients are larger than those of healthy controls. Except for the FS method, larger CPV correlated with higher EDSS scores in MS patients. There was a positive correlation between T2 white matter lesion volume and CPV in MS patients for the FS and FS-GMM methods, but not for the FLAIR + T1 GMM or manual methods. A study by Yazdan-Panah et al. [32], although not directly related to this review, proposed another automatic CP segmentation method (2-step 3D U-Net). This was validated on healthy subjects, and on presymptomatic as well as clinically definite MS patients, and was found to be more accurate than the FS and FastSurfer-based methods.

These studies show that further research into CP segmentation methods is needed for more accurate and reliable results. All studies mentioned in this section plus some additional information are summarised in Table 1.

Choroid plexus imaging may be useful in MS type and severity assessment

Apart from general MS diagnosis, choroid plexus imaging may be helpful in MS type and severity evaluation. Klistorner et al. [33] carried out a study in which patients with optic neuritis as a clinically isolated syndrome (ON CIS patients) were compared to patients with RRMS and healthy controls. They showed that optic neuritis usually, but not always, precedes clinically definite MS. Choroid plexuses of ON CIS and RRMS patients had similar volumes, while they were significantly larger than choroid plexuses of healthy individuals. During 10 years of follow-up, 23/44 ON CIS patients developed clinically definite MS, and those were further studied. No correlations were found between CPV and optic nerve inflammation, retinal nerve fibre layer (RNFL), brain lesion load, or lesional tissue damage, in this group. However, a significant increase in CPV was observed within a subgroup of patients with new lesion activity. Patients without clinically definite MS were also included in a study by Ricigliano et al. [34], who investigated whether CP imaging may be useful before the onset of MS symptoms. In their study, patients with presymptomatic MS had 32% greater CPV compared to healthy controls. No significant difference between the CPV of presymptomatic MS patients and clinically definite MS patients was found. Moreover, the CP of one female patient with presymptomatic MS had 33% greater ^{18}F-DPA-714 uptake, which is a positron emission tomography (PET) tracer recognising translocator protein (TSPO) and indicating greater CP inflammation, compared to healthy controls. Importantly, this patient developed MS after eight months of follow-up.

Ricigliano et al. were also a source of other interesting observations in another article [35]. In MS patients, increased CPV was correlated with lower brain, normal-appearing white matter and thalamic volumes, as well as higher T2 white matter lesion volume. CPV was 35% greater in MS patients compared to healthy controls. Choroid plexuses of patients with RRMS remained significantly larger than those of healthy controls,

Table 1. Summary of research regarding general use of choroid plexus in multiple sclerosis

Ref.	Year	Population	Comparison	Methodology	MS type	Results
Klistorner et al. [28]	2022	49 MS pts	40 HC	CP by 3T MRI, CPV, normalised by TIV CP seg obtained by JIM 9 software and corrected manually	49 RRMS pts	↑ CPV/TIV in RRMS pts than in HC NSD between CPV/TIV at baseline and at 4y follow-up in RRMS pts (+) correlation between baseline CPV/TIV and lesion expansion rate at 4y follow-up in RRMS pts (+) correlation between baseline CPV/TIV and both baseline and 4y follow-up MD (lesional core) in RRMS pts (+) correlation between baseline CPV/TIV and change in MD (lesional core) during follow-up in RRMS pts ↑ CPV/TIV at baseline predicted ↑ ventricular expansion in RRMS pts
Jankowska et al. [29]	2023	14 MS Treg pts 18 MS tn pts	16 HC	CP by 1,5T MRI, CPV/TIV ratio CP seg obtained by BM software	32 RRMS pts	↑ CPV/TIV in MS pts than in HC ↑ CPV/TIV in both MS groups during a 1y follow-up ↑ CPV/TIV in MS Treg pts with ≥1 relapse than in MS Treg pts without relapses ↑ CPV/TIV in MS Treg pts with ≥1 contrast-enhancing lesion than in MS Treg pts without those lesions
Margoni et al. [30]	2022	69 paediatric MS pts	23 paediatric HC	CP by 3T MRI, CPV, volumes normalised for head size (multiplied by V scaling from SIENA×2 software) CP seg performed manually	69 RRMS pts	↑ CPV in MS pts (both male and female) than in HC Correlation significantly ↑ for females ↑ CPV correlated with ↑ brain lesional and lateral ventricle volumes as well as ↓ normalised brain and thalamic volumes No significant correlations between CPV and disease duration, EDSS score, normalised cortical and WM volumes
Storelli et al. [31]	2023	55 MS pts	Proposed automatic seg method (FLAIR + T1 GMM) to manual, FS and FS-GMM methods 60 HC	CP by 3T MRI CP seg by FLAIR + T1 GMM and other methods for comparison All CP volumes normalised for head size (multiplied by V scaling from FSL-SIENAX toolbox)	33 RRMS pts 22 PMS pts	FLAIR + T1 GMM had ↑ seg accuracy than FS and FS-GMM methods compared to manual seg ↑ CPV in MS pts than in HC (for all 4 methods) (+) correlation between CPV and EDSS score in MS pts (for all methods except for FS) Significant correlation between CPV and T2 WM lesion volume in MS pts for FS-GMM and FS but not for manual and FLAIR + T1 GMM method

(+) — positive; ↑ — increased; ↓ — decreased; BM — BrainMagix; CP — choroid plexus; CPV — choroid plexus volume; EDSS — Expanded Disability Status Scale; FLAIR — fluid-attenuated inversion recovery; FS — FreeSurfer; GMM — Gaussian Mixture Model; HC — healthy controls; MD — mean diffusivity; MRI — magnetic resonance imaging; MS — multiple sclerosis; NSD — no significant difference; PMS — progressive multiple sclerosis; pre-MS — presymptomatic multiple sclerosis; pts — patients; Ref. — reference; RRMS — relapsing-remitting multiple sclerosis; seg — segmentation; SPMS — secondary progressive multiple sclerosis; TIV — total intracranial volume; tn — treatment-naïve; Treg — receiving cellular therapy; WM — white matter; y — years

after adjusting for ventricular and brain volumes. However, this observation was not true for patients with progressive MS (PMS). Moreover, no significant difference was found between the CPV of RRMS and PMS patients. For RRMS patients, there was also a positive correlation between CPV and T2 white matter lesion volume as well as annualised relapse rate. Additionally, CP ^{18}F-DPA-714 uptake was 18.5% higher in MS patients compared to healthy controls, while enlarged CP was associated with higher ^{18}F-DPA-714 uptake in RRMS patients. CP enlargement also correlated with greater ^{18}F-DPA-714 binding in the thalami and normal-appearing white matter in MS patients.

CP imaging characteristics of patients with RRMS and PMS were also assessed by Morozumi et al. [36]. They used MRI to investigate several volumetric measures, including CPV. MS patients had significantly larger choroid plexuses compared to healthy controls. Consistently with the previous research, the difference between the CPV of patients with

Table 2. Summary of studies focusing on role of choroid plexus in assessment of multiple sclerosis type and severity

Ref.	Year	Population	Comparison	Methodology	MS type	Results
Klistorner et al. [33]	2023	44 ON CIS pts 50 MS pts	50 HC	CP by 3T MRI, CPV volumes corrected for head size by SIENAX software CP seg obtained by JIM 9 software and corrected manually	50 RRMS pts	↑ CPV in ON CIS and RRMS pts than in HC NSD in CPV between ON CIS and RRMS pts ↑ CPV in ON CIS pts regardless of CDMS development during a 10y follow-up, as compared to HC Transient CPV ↑ in pts with new lesion activity (ON CIS pts who developed CDMS) No correlation between CPV and optic nerve inflammation severity, optic nerve axonal loss, or brain lesion load in ON CIS pts who developed CDMS
Ricigliano et al. [34]	2022	27 pre-MS pts (26 RIS, 1 pt first as HC) 97 CDMS	53 HC	CP by 3T MRI, CPV, normalised by TIV (all groups) CP seg performed manually CP inflammation with TSPO ^{18}F-DPA-714 PET (1 pre-MS pt compared to 22 MS pts and 19 HC)	61 RRMS 36 PMS	32% ↑CPV in pre-MS pts than in HC NSD in CPV between pre-MS and MS pts 1 pre-MS pt who developed CDMS during follow-up had 33% ↑^{18}F-DPA-714 uptake by CP, as compared to HC
Ricigliano et al. [35]	2021	97 MS pts	44 HC	CP by 3T MRI, CPV, normalised by TIV (all groups) CP seg performed manually Crosscheck by FS software Neuroinflammation with TSPO ^{18}F-DPA-714 PET (37 MS pts and 19 HC)	61 RRMS 36 PMS	35% ↑ CPV in MS pts than in HC ↑ CPV in RRMS pts and NSD in PMS pts as compared to HC after adjusting for ventricular and brain volume NSD in CPV between RRMS and PMS pts ↑ CPV predicted ↓ normalised brain, NAWM, and thalamic volumes in MS pts ↑ CPV correlated with ↑T2 WM lesion volume in RRMS pts, but not PMS pts ↑ CPV correlated with a ↑ 4-year annualised relapse rate in RRMS pts but not PMS pts ↑ CPV correlated with ↑ ^{18}F-DPA-714 in thalami and NAWM in MS pts 18.5% ↑ ^{18}F-DPA-714 uptake by CP in MS pts than in HC ↑ CPV correlated with ↑ ^{18}F-DPA-714 uptake in RRMS pts
Morozumi et al. [36]	2023	81 MS pts	45 HC	CP by 3T MRI, CPV CP seg performed manually Volumes normalised by SIENAX software	27 RRMS pts 54 PMS pts	↑ CPV in MS pts than in HC NSD in CPV between RRMS and PMS pts ↑ CPV predicted ↓ normalised brain and thalamic volumes in all MS pts and normalised GM volume in RRMS pts
Tonietto et al. [37]	2023	19 MS pts (1st cohort)	8 HC	CP by 3T MRI, normalised CPV (both cohorts) and [^{11}C]PiB PET scans (only 1st cohort) CP seg performed manually	19 RRMS pts	↑ CPV correlated with ↑ periventricular demyelination at baseline and ↓ periventricular remyelination at follow-up in MS pts No correlation between CPV and subcortical remyelination in MS pts
		40 MS pts (2nd cohort)	39 HC		12 RRMS pts 28 PMS pts	↑ CPV correlated with ↑ periventricular demyelination at baseline and ↓ periventricular remyelination at follow-up in all MS pts, but only in RRMS pts after considering type ↑ CPV correlated with ↓ subcortical remyelination in MS pts

↑ — increased; ↓ — decreased; CIS — clinically isolated syndrome; CDMS — clinically definite multiple sclerosis; CP — choroid plexus; CPV — choroid plexus volume; FS — FreeSurfer; GM — grey matter; HC — healthy controls; MRI — magnetic resonance imaging; MS — multiple sclerosis; NAWM — normal-appearing white matter; NSD — no significant difference; ON — optic neuritis; PET — positron emission tomography; PiB — Pittsburgh compound B; PMS — progressive multiple sclerosis; pre-MS — presymptomatic multiple sclerosis; pt — patient; pts — patients; Ref. — reference; RIS — radiologically isolated syndrome; RRMS — relapsing-remitting multiple sclerosis; seg — segmentation; TIV — total intracranial volume; TSPO — translocator protein; WM — white matter; y — years

RRMS and those with PMS was insignificant. Furthermore, results revealed a negative correlation between CPV and both brain and thalamic volumes in all MS patients. However, grey matter volume was negatively correlated with CPV only in RRMS patients.

Tonietto et al. [37] also included patients with both RRMS and PMS in their research. They studied two independent cohorts to investigate associations between the distribution of myelin repair and neurodegeneration in MS patients. Among multiple significant correlations, those between myelin repair and CPV were found. In both cohorts, larger CPV correlated with increased periventricular demyelination at baseline and decreased periventricular remyelination at follow-up in MS patients. In the second cohort, this observation was also significant for RRMS patients but not PMS patients. Although no association between CPV and subcortical remyelination was found in MS patients from the first cohort, there was a negative correlation between CPV and subcortical remyelination in MS patients from the second cohort. These results suggest the role of the brain-blood barrier negatively impacting upon myelin repair, and require further investigation. All studies mentioned in this section plus some additional information are summarised in Table 2.

Choroid plexus imaging and disability status of MS patients

In a study conducted by Bergsland et al. [38], MRI scans of MS patients and healthy controls were performed at baseline and after an average follow-up of 5.5 years. CPV was significantly increased at baseline in MS patients, as well as choroid plexus pseudo-T2 (CP pT2), a proposed CP inflammation marker. Baseline CP pT2 was also positively correlated with clinical disability progression at follow-up, assessed by the EDSS. However, it should be noted that the CPV difference between MS patients and healthy controls at baseline was no longer significant after additional correction for brain and/or ventricular volumes.

Wang et al. [39] studied patients with RRMS and found that their CPV was 32% larger compared to healthy controls. Moreover, patients with iron rim lesions, a sign of persistent chronic inflammation, had 20% larger choroid plexuses than patients without these lesions. CP enlargement in MS patients correlated with higher white matter lesion volume but also lower whole brain, deep grey matter, and most regional deep grey matter, and nuclei volumes. Furthermore, the researchers observed associations between CPV and disability status as well as cognitive impairment in MS patients. However, these correlations regarding clinical characteristics were no longer significant after additional correction for brain lesion load or structure volume.

Fleischer et al. [40] carried out an interesting study on mice and humans to investigate the utility of choroid plexus imaging in neuroinflammation. The main cohort consisted of 267 MS patients and 63 CIS patients, while the replication cohort included 148 MS patients and 87 CIS patients. In the main cohort, increased CPV correlated with higher EDSS score (at baseline and after four years) as well as with lower cerebral cortex thickness and Symbol Digit Modalities Test (SDMT) score. The replication cohort later confirmed results regarding EDSS score and cerebral cortex thickness. Furthermore, CPV was larger in patients with evidence of disease activity than in those without. Additionally, a larger CP predicted a higher T2 lesion load in patients. A correlation was also found between CSF (but not serum) albumin levels and CPV. All studies mentioned in this section plus some additional information are summarised in Table 3.

Choroid plexus in differentiation of MS and NMOSD

Several studies have found the choroid plexus to be promising in making a differential diagnosis between MS and NMOSD, a distinction which poses challenges in daily practice. Müller et al. [41] measured CPV in patients with MS, NMOSD, migraine, and healthy individuals. They trained a deep learning algorithm (Multi-Dimensional Gated Recurrent Units) and used it to segment choroid plexuses on MRI scans. CPV expressed as a CPV/TIV ratio was 20.5%, 21.4%, and 23% higher in MS patients compared to NMOSD patients, to patients with migraine, and to healthy controls, respectively. Furthermore, NMOSD patients, patients with migraine, and healthy individuals did not differ significantly when it came to CPV. Interestingly, CPV was positively correlated with the number of T2-weighted lesions in MS patients, something which was not true for patients with NMOSD.

Kim et al. [42] also focused on CP characteristics in MS and NMOSD patients. Although previously described studies investigated mainly CPV, Kim et al. focused on CP thickness and enhancement. Differences in CP thickness between MS patients, NMOSD patients, and healthy controls were insignificant. CP enhancement was increased in MS, as well as in NMOSD, patients compared to healthy controls.

Chen et al. [43] conducted another study on MS and NMOSD patients and compared them to healthy individuals. Choroid plexuses of MS, but not NMOSD patients, were larger than those of healthy controls. However, there were no significant differences between CPV in NMOSD patients compared to MS patients or the control group. Moreover, CPV was not increased significantly at follow-up in either group. In both MS and NMOSD groups, greater CPV correlated with reduced cerebral cortex thickness. There was also a positive correlation between CPV and lateral ventricle, 3rd ventricle, 4th ventricle, and CSF volumes in patients with MS. The same observation was true for NMOSD patients (except for 4th ventricle volume). On the other hand, total brain tissue and deep grey matter volumes were not associated with CPV in either group. However, we note that CPV in this study was not normalised for TIV. All studies mentioned in this section plus some additional information are summarised in Table 4.

Table 3. Summary of research about correlations between choroid plexus imaging and disability status in multiple sclerosis patients

Ref.	Year	Population	Comparison	Methodology	MS type	Results
Bergsland et al. [38]	2023	174 MS pts	56 HC	CP by 3T MRI, CP pT2 mapping, and CPV CP seg obtained by FS software, refined by a GMM method, corrected manually Normalised volumes calculated by SIENAX software	118 RRMS pts 56 PMS pts	↑ CPV and ↑ CP pT2 in MS pts at baseline than in HC (NSD for CPV after control for brain or ventricular volumes) (+) correlation between ↑ CP pT2 at baseline and clinical disability progression at follow-up
Wang et al. [39]	2023	99 MS pts	60 HC	CP by 3T MRI, CPV, normalised by TIV CP seg performed manually	99 RRMS pts	30% ↑CPV in RRMS pts than in HC 20% ↑ CPV in RRMS pts with IRLs compared to RRMS pts without IRLs (+) correlation between CPV and WM lesion volume in RRMS pts ↑ CPV correlated with ↓ normalised brain, deep GM and most regional deep GM nuclei (except amygdala) volumes in MS pts ↑ CPV correlated with presence of cognitive impairment (by MoCA scores), ↓ SDMT scores and ↑EDSS scores in RRMS pts (Correlations between CPV and scale scores were no longer significant after controlling for brain lesion load/structure volume)
Fleischer et al. [40]	2021	63 CIS pts, 267 MS pts (main cohort)	57 HC	CP by 3T MRI, CPV Results adjusted for TIV where noted CP seg by using FS 6.0 software	267 RRMS pts	↑ CPV in pts than in HC (+) correlation between CPV and EDSS score in pts at baseline and 4y follow-up (adjusted for TIV) ↑ CPV correlated with ↓ cerebral cortex thickness in pts ↑ CPV correlated with ↓ SDMT score in pts (adjusted for TIV) ↑ CPV in EDA pts than in NEDA pts ↑ CPV in pts with higher T2 lesion load (+) correlation between CPV and CSF albumin but not serum albumin (assessed in 71 pts)
		87 CIS pts, 148 MS pts (second cohort)			148 RRMS pts	(+) correlation between CPV and EDSS score in pts at baseline and 4y follow-up (adjusted for TIV) ↑ CPV correlated with ↓ cerebral cortex thickness in pts (adjusted for TIV)

(+) — positive; ↑ — increased; ↓ — decreased; CIS — clinically isolated syndrome; CP — choroid plexus; CPV — choroid plexus volume; EDA — evidence of disease activity; EDSS — Expanded Disability Status Scale; FS — FreeSurfer; GM — grey matter; GMM — Gaussian Mixture Model; HC — healthy controls; IRLs — iron rim lesions; MoCA — Montreal Cognitive Assessment; MRI — magnetic resonance imaging; MS — multiple sclerosis; NEDA — no evidence of disease activity; NSD — no significant difference; PMS — progressive multiple sclerosis; pT2 — pseudo-T2; pts — patients; Ref. — reference; RRMS — relapsing-remitting multiple sclerosis; SDMT — Symbol Digit Modalities Test; seg — segmentation; TIV — total intracranial volume; WM — white matter; y — years

Conclusions and future perspectives

For many years, the choroid plexus has been known mainly as a structure involved in CSF production. Only recently has attention turned to its role in numerous processes in healthy and diseased brains. The CP has been found to participate in various immune reactions occurring in the CNS, including those associated with infectious pathogens as well as those of autoimmune origin. The latter underlies the pathogenesis of many diseases, with one of the most common being MS. As MS usually affects young adults, the effects of this condition particularly worsen their quality of life. Severe disability at this age makes it challenging to perform parental as well as professional duties, meaning that early diagnosis and the most appropriate selection of treatment are exceptionally important. These two aspects have been the focus of many scientists who have been looking for novel diagnostic tools and therapeutic agents useful in MS management.

The CP, due to its probable involvement in the autoimmune process in MS, seems to be an applicable research target. However, studies regarding the putative use of CP imaging in the context of MS remain scarce. Despite the relatively small amount of research on this subject, those that are available

Table 4. Summary of studies showing role of choroid plexus in differentiation of multiple sclerosis and neuromyelitis optica spectrum disorder

Ref.	Year	Population	Comparison	Methodology	MS type	Results
Müller et al. [41]	2022	180 MS pts 98 NMOSD pts	94 HC 47 migraine pts	CP by 3T MRI, CPV CP seg by a deep learning algorithm trained manually CPV/TIV was calculated	135 RRMS pts 45 SPMS pts	20.5%, 21.4%, and 23% ↑ CPV/TIV in MS pts compared to NMOSD pts, HC and migraine pts, respectively NSD in CPV between NMOSD pts, migraine pts and HC (+) correlation between CPV and number of T2-weighted lesions in MS pts but not NMOSD pts
Kim et al. [42]	2020	51 MS pts 32 NMOSD pts	28 HC	CP thickness (thickest part of CP body) and CP enhancement (brightest part of CP/adjacent WM ratio) by 1.5T MRI/3T MRI, based on gadolinium-enhanced T1-weighted images	–	↑ CP enhancement ratio in MS pts and NMOSD pts compared to HC No significant correlations for CP thickness
Chen et al. [43]	2023	51 MS pts 42 NMOSD pts	56 HC	CP by 3T MRI, CPV, volumes were not normalised CP seg was obtained by FS 6.0 software	–	↑ CPV in MS pts than in HC NSD in CPV in NMOSD pts than in MS pts and HC ↑ CPV correlated with ↓ cerebral cortex thickness in both MS and NMOSD pts (+) correlation between CPV, ventricular volumes, and CSF volume in MS and NMOSD pts (except for 4th ventricle in NMOSD pts) No significant correlations between CPV, total brain tissue, and deep GM volume in MS and NMOSD pts NSD between baseline and follow-up CPV in MS and NMOSD pts

(+) — positive; ↑ — increased; ↓ — decreased; CP — choroid plexus; CPV — choroid plexus volume; FreeSurfer; GM — grey matter; HC — healthy controls; MRI — magnetic resonance imaging; MS — multiple sclerosis; NMOSD — neuromyelitis optica spectrum disorder; NSD — no significant difference; ON — optic neuritis; pts — patients; Ref. — reference; RRMS — relapsing-remitting multiple sclerosis; seg — segmentation; SPMS — secondary progressive multiple sclerosis; TIV — total intracranial volume; WM — white matter

have provided promising results and allow us to make valuable conclusions, summarised below (Fig. 2).

CPV has been found to be significantly greater in MS patients than in healthy controls in all the studies that have compared CPV between these groups. Moreover, some studies have indicated that this enlargement occurs even before the definite diagnosis of MS, at the stage of clinically or radiologically isolated syndrome.

This is a particularly interesting observation, as greater CPV could indicate an increased likelihood of MS development. Furthermore, a significant number of the assessed studies have shown a positive correlation between the CPV and white matter lesion load in MS patients, which further supports the notion of CPV as a promising marker of disease activity. It is important to note that results reported by independent studies are not consistent as to whether CPV changes significantly during the course of the disease, and therefore further research is needed on this subject.

Two separate studies found that CPV does not differ significantly between patients with RRMS and PMS. However, in one of these studies, only RRMS but not PMS patients had larger choroid plexuses than healthy individuals. Interestingly, the same research showed a connection between relapses and increased CPV in patients with RRMS. Although based on limited data, these observations further encourage a thorough investigation into CPV as a putative marker indicative of future MS course. The search for such markers is crucial, as early prediction of the disease course remains daunting still today. Furthermore, the MS diagnostic process involves differentiation from other disorders, including NMOSD. Three studies have evaluated patients with MS and NMOSD, two of which compared the CPV of each group to the CPV of healthy controls. Both these studies found that MS patients, but not NMOSD patients, had greater CPV compared to healthy individuals. Although the third study obtained results showing similar CP features in these two diseases, imaging markers other than CPV were used in this study, such as the CP enhancement ratio.

Neurodegeneration is an inherent element of MS pathogenesis, and so a few studies have analysed associations between CPV and other volumetric measurements of the brain in MS patients. Interestingly, increased CPV correlated with decreased brain and thalamic volumes in most of these studies, with the results regarding other volumetric markers being more inconsistent.

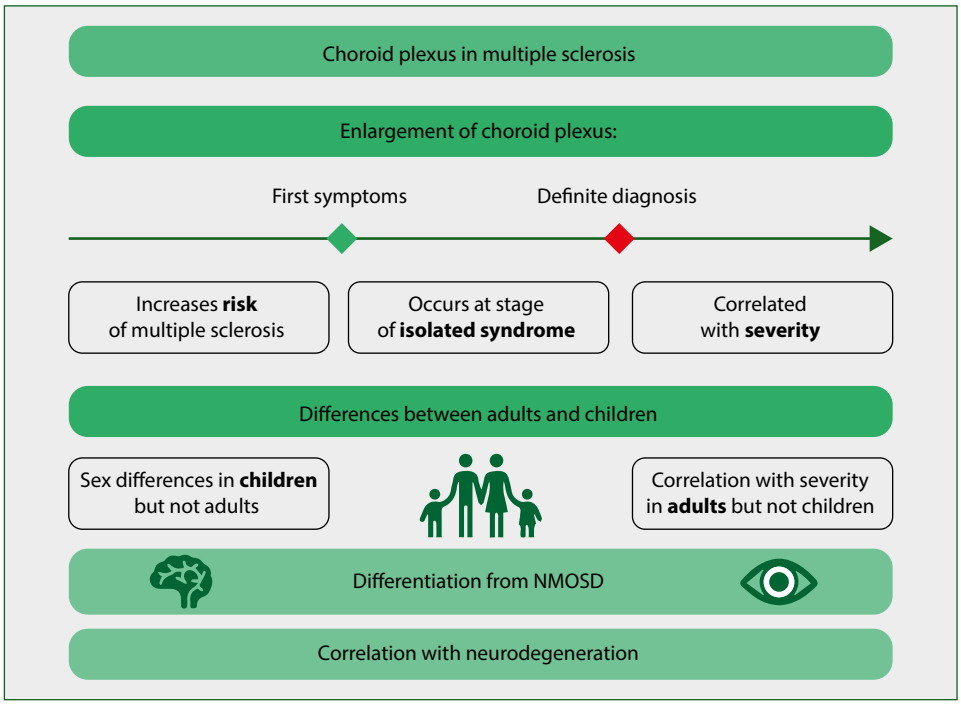

Figure 2. Graphical presentation of main characteristics of choroid plexus in multiple sclerosis; NMOSD — neuromyelitis optica spectrum disorder

However, three separate studies have reported that greater CPV predicts increased ventricular volumes, thereby supporting a correlation between CPV and brain atrophy in MS.

It is important to note that there was only one study on paediatric patients with MS analysed in our review. Interestingly, this provided results suggesting a significant influence of sex on CPV, which other research groups have not reported. Further studies are required to assess whether this observation is repeatable, particularly regarding adult patients. When it comes to associations between CP imaging and clinical presentation, it is difficult to obtain reliable results from a study with a limited number of patients. However, a few studies have found a correlation between disability status and CPV in MS patients. On the other hand, the paediatric MS study showed no such correlation. This discrepancy could be caused by differences between MS of paediatric as opposed to adult onset, but nevertheless, this subject needs further investigation.

We conclude that according to the available literature, choroid plexus imaging may play an important role in MS diagnosis, and also could become a novel marker of expected disease course. Further research in this field is highly warranted, as it could provide innovative developments beneficial for the better management of MS.

Limitations

The results of the abovementioned studies are exceptionally promising and encourage further research. Nevertheless, the number of available studies was very limited, as was the size of the patient groups. Furthermore, only one research group investigated CP characteristics in paediatric patients with MS. Importantly, one study that showed a difference between the CPV of MS patients and healthy controls found that this was no longer significant after additional correction for brain and/or ventricular volumes. These observations underline the need for unification of the CPV calculation methods and for research to be conducted on larger groups of patients, in order to obtain results that reliably evaluate the use of CP imaging in MS management. We encountered various CP segmentation and CPV calculation protocols, and therefore some of the discrepancies between analysed studies may be attributable to the differences between selected methods. Finally, the reviewed studies had volumetric measurements normalised according to different algorithms, or even lacked this step in their protocols, which could therein have additionally influenced the obtained results.

We found the use of CP imaging to be a promising technique with the potential to improve MS management. To enable its routine use in this field, thorough and extensive research is required. However, CP imaging undoubtedly presents an interesting and novel opportunity for better MS understanding, diagnosis, and treatment.

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