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Leptomeningeal enhancement in multiple sclerosis: a focus on patients treated with hematopoietic stem cell transplantation

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Background: Leptomeningeal enhancement (LME) is considered an MRI marker of leptomeningeal inflammation in inflammatory neurological disorders, including multiple sclerosis (MS). To our knowledge, no disease-modifying therapies (DMTs) have been demonstrated to affect LME number or morphology so far.

Methods: Monocentric study investigating the frequency and number of LME in a cohort of people with (pw)MS who performed a 3T brain MRI with a standardized protocol (including a post-contrast FLAIR sequence), and exploring the impact of autologous hematopoietic stem cell transplantation (AH SCT) on this marker. In a longitudinal pilot study, consecutive MRIs were also analyzed in a subgroup of pwMS, including patients evaluated both pre- and post-AH SCT.

Results: Fifty-five pwMS were included: 24/55 (44%) had received AH SCT (AH SCT group) and 31 other treatments (CTRL group). At least one LME was identified in 19/55 (35%) cases (42 and 29% in the AH SCT and CTRL groups, respectively; $p = 0.405$). In the AH SCT group, LME number correlated with age at AH SCT ($R = 0.50$; $p = 0.014$), but not with age at post-treatment MRI. In the longitudinal pilot study ($n = 8$), one LME disappeared following AH SCT in 1/4 patients, whereas LME number was unchanged in the remaining four pwMS from the CTRL group.

Discussion: These results suggest that AH SCT may affect development and persistence of LME, strengthening the indication for early use of effective therapies bioavailable within the central nervous system (CNS), and therefore potentially targeting compartmentalized inflammation.

KEYWORDS

multiple sclerosis, leptomeningeal enhancement, magnetic resonance imaging, autologous hematopoietic stem cell transplantation, transplant, chronic inflammation, biomarker

1 Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the Central Nervous System (CNS), characterized by demyelinating lesions and axonal damage (1). The presence of inflammatory cell infiltrates in the leptomeninges of MS patients has been described for several years in histopathological studies (2–5). Leptomeningeal inflammation ranges from sparse infiltrates of inflammatory cells to well-organized structures that resemble lymphatic tissue, the latter defined as Ectopic Lymphoid Follicle-like structures (ELFs) (6). It has been hypothesized that ELFs correspond to chronic inflammation compartmentalized within the CNS and contribute to disease progression through the release of soluble factors (i.e., cytokines and chemokines) that promote cortical damage (7, 8).

ELFs can be visualized with Magnetic Resonance Imaging (MRI) in T2/fluid-attenuated inversion recovery (FLAIR) sequences performed after the injection of gadolinium-based contrast agent, possibly due to increased permeability of the blood–brain barrier (BBB) within ELFs. These radiological findings are defined as Leptomeningeal Enhancement (LME) (9). However, LME is not a finding specific to MS, as it was observed with similar frequency in MS patients and patients with other inflammatory and non-inflammatory diseases of the CNS (10).

In MS patients, LME is reported with a variable frequency across different studies, being the proportion higher when adopting high-magnetic field (7-Tesla–7T) MRI compared to a 3T magnet. Typically, the frequency of LME is higher in the progressive than in the relapsing–remitting (RR) form of the disease (9, 11). A direct association between LME and age, disease duration, and Expanded Disability Status Scale (EDSS) score was reported in the literature, but with some inconsistencies across studies. Patients with LME had a lower total brain and cortical volume (9, 12, 13), but the spatial association between LME and cortical lesions detected by MRI remains controversial (14, 15). LME tends to remain stable over time. Rare cases of disappearance of LME following high-dose steroids were reported (16), but no disease-modifying therapies (DMTs) have been demonstrated to affect LME number or morphology so far (17–19).

To our knowledge, there are no data on the prevalence of LME in patients with MS treated with autologous hematopoietic stem cell transplantation (AH SCT), a hematological procedure endorsed as a standard of care for the treatment of aggressive RR-MS refractory to conventional DMTs (20).

2 Materials and methods

2.1 Aim of the study

The main aim of the study was to describe the prevalence and characteristics of LME in MS patients treated with AH SCT compared to MS patients treated with DMTs/untreated, exploring differential correlations between LME number and clinical-demographic characteristics in the two groups.

The impact of AH SCT on LME number was then explored in a pilot series of patients evaluated both before and after AH SCT at pre-defined timepoints, and in control patients not receiving AH SCT who had longitudinal MRI follow-up.

2.2 Patient population

Consecutive patients affected by MS in clinical follow-up at the Neurology 2 Department of the Careggi University Hospital in Florence, Italy, who had performed at least one 3T brain MRI with a standardized protocol (including post-contrast volumetric FLAIR) at the Neuroradiology Unit of the same hospital over an 18-month period.

The MS cohort included RR- and secondary progressive (SP-) MS patients diagnosed according to the Poser and McDonald criteria (21, 22). Patients were further stratified according to the previous treatment with AH SCT into the AH SCT group and control (CTRL) group, the latter including those cases who had not undergone AH SCT. MS patients not treated with AH SCT who are in clinical follow-up at our center and who performed a brain MRI at our facility over the pre-defined period were consecutively included in the CTRL group.

AH SCT patients received the transplant in an open-label monocentric study in collaboration with the Cell Therapy and Transfusion Medicine Unit of the Careggi University Hospital, according to the inclusion/exclusion criteria of the center, as previously reported (23). Briefly, RR- or SP-MS patients were eligible for transplant if they showed highly active disease or disability progression with signs of inflammation despite receiving treatment with high efficacy DMTs approved for MS; PP-MS and patients with medical conditions contraindicating the procedure were excluded. Patients were mobilized with cyclophosphamide 4 g/m² body surface area and granulocyte-colony stimulating factor (G-CSF; 10 µg/kg per day); the conditioning protocol used was the intermediate intensity regimen BEAM+ATG (20), encompassing BCNU (Carmustine) 300 mg/m² at on day –6, ARA-C (Cytosine-Arabinoside) 200 mg/m²/day and VP-16 (Etoposide) 200 mg/m²/day from day –5 to day –2, and Melphalan 140 mg/m² at on day –1; rabbit anti-thymocyte globulin (ATG, Thymoglobulin™, Sanofi) was added at a dose of 3.75 mg/kg/die day on day +1 and +2 (total dose 7.5 mg/Kg).

2.3 MRI analysis

All the patients underwent a brain MRI with the same scanner and standardized protocol. Two MRI examinations taken at least 6 months apart were available for a subset of patients, including a pre-transplant MRI scan and at least one MRI performed after AH SCT for those in the AH SCT group.

Patients treated with AH SCT underwent brain MRIs at pre-defined timepoints, i.e., before AH SCT, at month 6 and 12 after AH SCT and then yearly; no unscheduled MRIs were analyzed in this study. The time interval between AH SCT and post-AH SCT MRI was dependent on the time interval between AH SCT and 3T machine purchase.

The scans were obtained with a 3T MRI scanner (Ingenia, Philips Healthcare, The Netherlands). The standardized protocol included a 3D-volumetric T2-FLAIR sequence acquired 3–4 min after the injection of gadolinium-based (0.1 mL/kg) contrast, and 3D T1 post-contrast sequence. A T2-FLAIR sequence acquired before gadolinium administration was not available as it was not included in the protocol of the Center.

LME was defined according to the literature as “high signal intensity within the subarachnoid space that is substantially greater than that of brain parenchyma” (9). The presence of LME foci was investigated by analyzing all the slices of T2-FLAIR scans for each patient; the analyses were performed by two raters trained in neuroimaging, who were blind to the demographical and clinical information of the patients. Cohen’s kappa (κ) for inter-rater agreement was 0.8. Longitudinal changes in LME number were confirmed by a third trained rater.

Contrast enhancement in the context of the pachymeninges (Dura Mater Enhancement, DME) and around the meningeal blood vessels (meningeal Vessel Wall Enhancement, VWE) was also evaluated (24).

2.4 Statistical methods

Baseline characteristics of the study population are reported as median (range) or number (frequency) for continuous and dichotomous variables, respectively. The Mann–Whitney U test or Chi-square were used to compare the baseline characteristics between the groups, as appropriate according to data distribution. Bivariate Spearman correlation was used to explore correlations between the number of LME and baseline characteristics of the patients, corrected for age at MRI. The statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS, IBM, Armonk, NY, United States, version 25.0).

3 Results

3.1 Characteristics of the patient population

Fifty-five MS patients (40 RR-MS; 15 SP-MS) were included (Table 1). Twenty-four/55 (44%) patients had received AH SCT a median of 44 (5–229) months before the MRI scan. All the patients in the AH SCT group were free from DMTs at the time of MRI; 61% of

the cases in the MS CTRL group were receiving active treatment (Figure 1A). DMTs received prior to MRI are detailed in Figure 1B. No differences in proportion of patients treated with each DMT were observed between AH SCT and CTRL patients, except for fingolimod, which was received by 33 and 10% of cases from the AH SCT and CTRL groups, respectively ($p=0.043$). Most of the patients were affected by RR-MS (Table 1). No differences were observed between the two groups in clinical-demographic characteristics, except for the duration of treatment with DMTs and the number of previous DMTs, that were both higher in the AH SCT group than in the CTRL group ($p=0.024$ and <0.001 , respectively; Table 1).

3.2 Leptomeningeal enhancement

At least one LME focus was identified in 19/55 (35%) MS patients, including 15/40 (38%) RR-MS and 4/15 (27%) SP-MS ($p=0.537$; Figure 2).

Ten/24 (42%) cases from the AH SCT group and 9/31 (29%) from the CTRL group showed at least one LME. Fifty percent of the RR-MS patients from the AH SCT group were LME-positive versus 29% of those in the CTRL group (Figure 2).

LME-positive patients showed a median of 1 (range 1–3) LME foci, ranging between 1 and 2 and 1 and 3 in the CTRL and AH SCT groups, respectively (Figure 3).

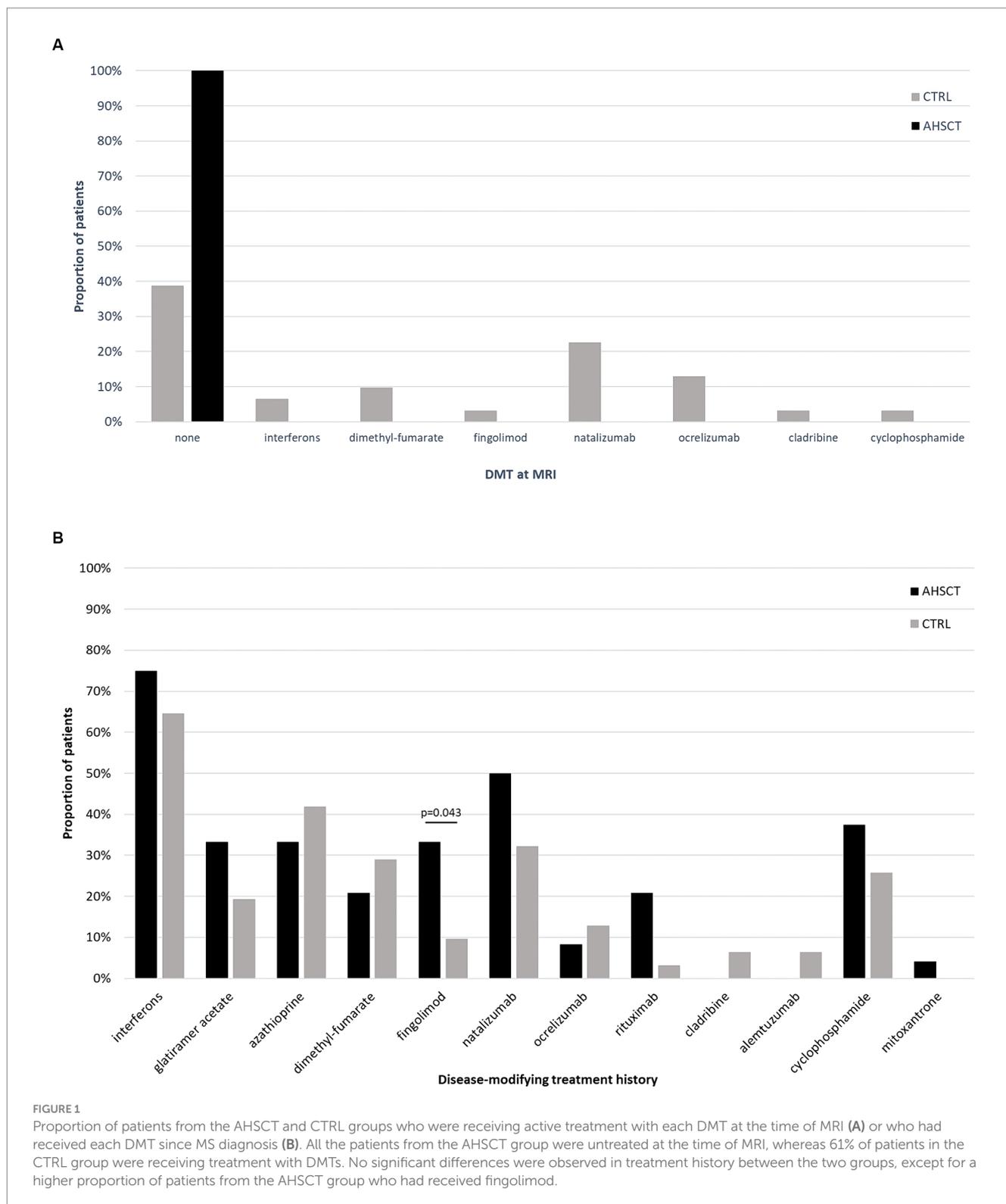
3.3 Factors associated with leptomeningeal enhancement

In the AH SCT group, the number of LME was directly correlated with age at AH SCT ($R=0.50$; $p=0.014$), but not with age at the time of MRI, and it was inversely correlated with the time between AH SCT and MRI ($R=-0.49$; $p=0.018$) (Table 2). MS duration showed a mild negative correlation with LME number in the whole cohort. No other significant correlations between LME number and clinical-demographic characteristics were observed in the overall cohort or CTRL group.

TABLE 1 Clinical-demographic characteristics of the overall cohort and the AH SCT and CTRL groups at the time of the MRI scan.

	Overall ($n = 55$)		AH SCT group ($n = 24$)		CTRL group ($n = 31$)		p Value
	Median	(Range)	Median	(Range)	Median	(Range)	
Age, years	46	(22–74)	46	(29–57)	43	(22–74)	0.753
Disease duration, years	16	(0–52)	17	(6–31)	13	(0–52)	0.391
Progressive phase duration, years	6	(1–24)	6	(1–24)	6	(1–8)	0.620
Treatment duration, years	11	(0–26)	13	(5–26)	10	(0–25)	0.024
EDSS	4.0	(0.0–7.0)	3.5	(1–7)	4.0	(0.0–7.0)	0.385
Number of previous DMTs	3	(0–7)	4	(2–7)	2	(0–5)	<0.001
	n	(%)	n	(%)	n	(%)	p value
Gender, female	39	(71%)	20	(83%)	19	(61%)	0.133
MS phenotype: RR-MS	40	(73%)	16	(67%)	24	(77%)	0.375
Patients receiving treatment with DMTs at MRI	19	(35%)	0	(0%)	19	(61%)	<0.001

AH SCT, Autologous hematopoietic stem cell transplantation; CTRL, Controls, i.e., patients who did not receive AH SCT; DMTs, Disease-modifying treatments; EDSS, Expanded disability status scale; MRI, Magnetic resonance imaging; MS, Multiple sclerosis; RR-, Relapsing–remitting.



3.4 Dural and vessel wall enhancement

Contrast enhancement was also observed in the context of the dura mater (DME) and meningeal vessels (VWE). The median DE and VWE number were 0 (0–1) and 0 (0–4), respectively. Median VWE number was 0 (0–4) and 1 (0–4) in the AHST and CTRL groups, respectively.

3.5 Longitudinal pilot study

Seriate MRI scans were available for four MS CTRL (four RR-MS) and four MS AHST (two RR-MS; two SP-MS). In the former group, two MRI were analyzed for each patient, taken a median of 11 (6–13) months apart. In the AHST group, one MRI was taken before undergoing AHST (baseline scan) and at least one after transplant

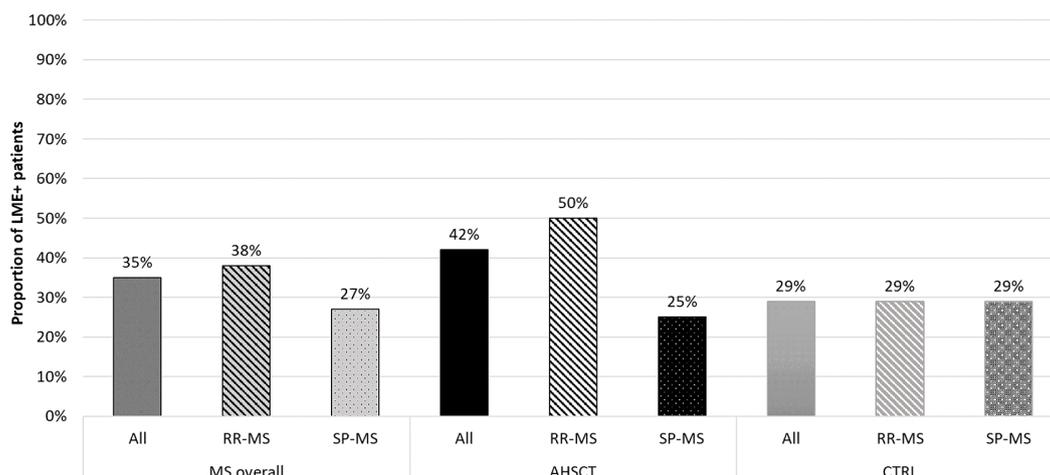


FIGURE 2 Proportion of LME-positive patients in the overall MS cohort and in the AHSCT and CTRL groups, and in patients from each group stratified according to the MS form (relapsing–remitting, RR, or secondary–progressive, SP). RR-MS patients from the AHSCT group tended to higher proportion of LME positivity compared to those in the CTRL group.

TABLE 2 Correlations between LME number and clinical-demographic characteristics of MS patients at the time of the MRI scan, corrected for age at the MRI.

	MS overall (n = 55)		AHSCT (n = 24)		CTRLS (n = 31)	
	R	(p value)	R	(p value)	R	(p value)
Age, years	0.07	(0.590)	0.13	(0.540)	0.07	(0.727)
Disease duration, years	−0.27	(0.044)	−0.40	(0.060)	−0.17	(0.379)
Treatment duration, years	−0.10	(0.92)	−0.41*	(0.049)	0.10	(0.615)
Progressive phase duration, years	−0.29	(0.341)	−0.57	(0.234)	0.11	(0.837)
N prior DMTs	0.08	(0.542)	−0.08	(0.705)	0.13	(0.477)
EDSS	−0.12	(0.929)	−0.06	(0.787)	0.02	(0.900)
Age at AHSCT, years	N.A.	N.A.	0.50*	(0.014)	N.A.	N.A.
Time AHSCT-MRI, years	N.A.	N.A.	−0.49*	(0.018)	N.A.	N.A.

Significant correlations are marked with *. AHSCT, Autologous hematopoietic stem cell transplantation; CTRL, Control group; DMTs: Disease-modifying treatments; EDSS, Expanded disability status scale; LME, Leptomeningeal enhancement; MRI, Magnetic resonance imaging; MS, Multiple sclerosis; N.A., Not applicable.

according to a pre-defined schedule, with a median interval of 16 (7–27) months between the pre-AHSCT scan and the latest follow-up available.

In AHSCT patients, the disappearance of one LME detected in the baseline scan was observed in one/four cases at month 6 after AHSCT (Figure 4), and the number of LMEs remained stable at a subsequent exam taken 6 months later. The number and morphology of LME were unchanged at follow-up MRIs (6 and 12 months after AHSCT) in the remaining three patients.

No changes in the number of LME (median 1, range 1–2) were observed in the four patients from the MS CTRL group in the follow-up MRI scan.

4 Discussion

In the present study, the presence of LME was explored in people with MS, as it has been proposed as a potential MRI biomarker of

compartmentalization of the immune response in the CNS. We observed a prevalence of LME similar between RR-MS and SP-MS patients, a finding conflicting with most of the published studies (9, 24) that show a significantly higher frequency of LME in progressive MS compared to RR-MS. Such difference could be attributed, at least in part, to a selection bias toward patients affected by highly active or aggressive MS recruited in the AHSCT program, who could bear signs of compartmentalized inflammation early on during disease course. A trend for a higher frequency of LME-positive cases was indeed observed in RR-MS patients treated with AHSCT compared to RR-MS patients from the CTRL group.

It has been hypothesized that some of the currently available DMTs may act on leptomeningeal follicles, however longitudinal studies with rituximab, dimethyl-fumarate, and teriflunomide (17–19) did not show any reduction in LME number over time; on the contrary, an increase in the number of LME positive patients and LME foci was observed in dimethyl-fumarate and teriflunomide treated MS patients over a 24-month follow-up (17). To our knowledge, only

CTRL group. As such correlation is reported in wide cohorts (12, 24), but not consistently described in small patient populations like that included in this study (13), the detection of a potential weak correlation between LME number and age at MRI could be undermined by the small sample size of the CTRL group.

In the longitudinal pilot study, a reduction in LME number was observed following AHST in one out of four cases analyzed, a finding that needs to be confirmed in larger patient populations. In the remaining three patients, the number and morphology of LMEs were not affected by AHST, although the observation was performed over a short-term follow-up. No changes in LME number were observed in the four CTRL patients evaluated longitudinally. However, in our opinion, it cannot be excluded that irreversible structural modification had already occurred in the BBB and structures within ELF and that other elements may be responsible for their persistent enhancement. In this latter hypothesis, if inflammatory infiltrates within ELF were effectively removed by a DMT, LME could persist indefinitely over time without actually corresponding to ELF. If this was true, a possible dissociation between this marker and clinical outcomes may be observed over long-term. However, the small sample size and the lack of a long-term prospective follow-up after AHST did not allow us to further explore this intriguing hypothesis.

Our study has several limitations. First of all, the sample size in the longitudinal pilot study was small and the post-AHST follow-up relatively short, therefore these findings should be considered as exploratory. Comparisons between the AHST and CTRL groups should be taken with caution for a possible selection bias in the CTRL group, as no matching for clinical-demographic characteristics was performed. Serum biomarkers could not be analyzed as biological samples were not available due to the retrospective design of the study. Although the frequency and number of DE and VWE were recorded, a formal analysis of possible correlations with clinical-demographic variables was not performed as their role in MS is debated, and their detection and interpretation were challenging due to potential artifacts.

5 Conclusion

In the present study, a similar prevalence of LME was observed between MS patients who had received AHST and those who had not. However, the observation of a direct correlation between the number of LMEs and patients' age at AHST, but not at MRI, and the disappearance of one LME focus after AHST in one case suggest that AHST may halt the formation of new LMEs. If this hypothesis was true, early treatment with high-efficacy therapies reaching the CNS compartment could reduce leptomeningeal inflammatory infiltrates organized in ELF and possibly prevent (or revert) the compartmentalization of inflammation. Longitudinal prospective studies with long-term follow-up are needed to clarify if LME can represent a marker of response to treatments bioavailable within the CNS.

Data availability statement

The datasets presented in this article are not readily available according to privacy regulations. Aggregated data will be shared upon motivated request to the corresponding author. Requests to access the datasets should be directed to alice.mariottini@unifi.it.

Ethics statement

The studies involving humans were approved by Comitato Etico Area Vasta Centro—Regione Toscana. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LeM: Writing – original draft, Investigation. AM: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. VV: Writing – original draft, Resources, Investigation, Data curation. ABI: Writing – review & editing, Resources. CN: Writing – review & editing, Resources. AR: Writing – review & editing, Resources. RB: Writing – review & editing, Resources. AG: Writing – review & editing, Resources. VD: Writing – review & editing, Resources. ABa: Writing – review & editing, Resources. SC: Writing – review & editing, Resources. RS: Writing – review & editing, Resources. EF: Writing – review & editing, Investigation. LuM: Writing – review & editing.

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Conflict of interest

AM reports personal fees from Sanofi, Janssen, Biogen, and Novartis; non-financial support from Biogen, Novartis, and Sanofi, outside the submitted work. RS reports consulting fees from Sanofi and Therakos. LuM reports non-financial support from Biogen, Novartis, Merck Serono, Genzyme, and Teva, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

- Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. *Lancet*. (2018) 391:1622–36. doi: 10.1016/S0140-6736(18)30481-1
- Magliozzi R, Howell O, Vora A, Serafini B, Nicholas R, Puopolo M, et al. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. *Brain Pathol.* (2004) 14:1089–104. doi: 10.1093/brain/awm038
- Serafini B, Rosicarelli B, Magliozzi R, Stigliano E, Aloisi F. Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. *Brain Pathol.* (2004) 14:164–74. doi: 10.1111/j.1750-3639.2004.tb00049.x
- Choi SR, Howell OW, Carassiti D, Magliozzi R, Gveric D, Muraro PA, et al. Meningeal inflammation plays a role in the pathology of primary progressive multiple sclerosis. *Brain*. (2012) 135:2925–37. doi: 10.1093/brain/awb189
- Lucchinetti CF, Popescu BF, Bunyan RF, Moll NM, Roemer SF, Lassmann H, et al. Inflammatory cortical demyelination in early multiple sclerosis. *N Engl J Med.* (2011) 365:2188–97. doi: 10.1056/NEJMoa1100648
- Wicken C, Nguyen J, Karna R, Bhargava P. Leptomeningeal inflammation in multiple sclerosis: insights from animal and human studies. *Mult Scler Relat Disord.* (2018) 26:173–82. doi: 10.1016/j.msard.2018.09.025
- Lisak RP, Benjamins JA, Nedelkoska L, Barger JL, Ragheb S, Fan B, et al. Secretory products of multiple sclerosis B cells are cytotoxic to oligodendroglia in vitro. *J Neuroimmunol.* (2012) 246:85–95. doi: 10.1016/j.jneuroim.2012.02.015
- Magliozzi R, Howell OW, Reeves C, Roncaroli F, Nicholas R, Serafini B, et al. A gradient of neuronal loss and meningeal inflammation in multiple sclerosis. *Ann Neurol.* (2010) 68:477–93. doi: 10.1002/ana.22230
- Absinta M, Vuolo L, Rao A, Nair G, Sati P, Cortese IC, et al. Gadolinium-based MRI characterization of leptomeningeal inflammation in multiple sclerosis. *Neurology.* (2015) 85:18–28. doi: 10.1212/WNL.0000000000001587
- Absinta M, Cortese IC, Vuolo L, Nair G, De Alwis MP, Ohayon J, et al. Leptomeningeal gadolinium enhancement across the spectrum of chronic neuroinflammatory diseases. *Neurology.* (2017) 88:1439–44. doi: 10.1212/WNL.0000000000003820
- Ineichen BV, Tsagkas C, Absinta M, Reich DS. Leptomeningeal enhancement in multiple sclerosis and other neurological diseases: a systematic review and meta-analysis. *NeuroImage Clin.* (2022) 33:102939. doi: 10.1016/j.nicl.2022.102939
- Zivadinov R, Ramasamy D, Hagemeyer J, Kolb C, Bergsland N, Schweser F, et al. Evaluation of leptomeningeal contrast enhancement using pre-and postcontrast subtraction 3D-FLAIR imaging in multiple sclerosis. *Am J Neuroradiol.* (2018) 39:642–7. doi: 10.3174/ajnr.A5541
- Zivadinov R, Ramasamy DP, Vaneckova M, Gandhi S, Chandra A, Hagemeyer J, et al. Leptomeningeal contrast enhancement is associated with progression of cortical atrophy in MS: a retrospective, pilot, observational longitudinal study. *Mult Scler.* (2017) 23:1336–45. doi: 10.1177/1352458516678083
- Ighani M, Jonas S, Izbudak I, Choi S, Lema-Dopico A, Hua J, et al. No association between cortical lesions and leptomeningeal enhancement on 7-tesla MRI in multiple sclerosis. *Mult Scler J.* (2020) 26:165–76. doi: 10.1177/1352458519876037
- Zurawski J, Tauhid S, Chu R, Khalid F, Healy BC, Weiner HL, et al. 7T MRI cerebral leptomeningeal enhancement is common in relapsing-remitting multiple sclerosis and is associated with cortical and thalamic lesions. *Mult Scler J.* (2019) 26:177–87. doi: 10.1177/1352458519885106
- Titelbaum DS, Engisch R, Schwartz ED, Napoli SQ, Sloane JA, Samaan S, et al. Leptomeningeal enhancement on 3D-FLAIR MRI in multiple sclerosis: systematic observations in clinical practice. *J Neuroimaging.* (2020) 30:917–29. doi: 10.1111/jon.12774
- Zivadinov R, Bergsland N, Carl E, Ramasamy DP, Hagemeyer J, Dwyer MG, et al. Effect of teriflunomide and dimethyl fumarate on cortical atrophy and leptomeningeal inflammation in multiple sclerosis: a retrospective, observational, case-control pilot study. *J Clin Med.* (2019) 8:344. doi: 10.3390/jcm8030344
- Bhargava P, Wicken C, Smith MD, Strowd RE, Cortese I, Reich DS, et al. Trial of intrathecal rituximab in progressive multiple sclerosis patients with evidence of leptomeningeal contrast enhancement. *Mult Scler Relat Disord.* (2019) 30:136–40. doi: 10.1016/j.msard.2019.02.013
- Bonnan M, Ferrari S, Courtade H, Money P, Desblache P, Barroso B, et al. No early effect of intrathecal rituximab in progressive multiple sclerosis (EFFRITE clinical trial). *Mult Scler Int.* (2021) 2021:1–7. doi: 10.1155/2021/8813498
- Sharrack B, Saccardi R, Alexander T, Badoglio M, Burman J, Farge D, et al. Autologous haematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: updated guidelines and recommendations from the EBMT autoimmune diseases working party (ADWP) and the joint accreditation committee of EBMT and ISCT (JACIE). *Bone Marrow Transplant.* (2019) 55:283–306. doi: 10.1038/s41409-019-0684-0
- Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol.* (2011) 69:292–302. doi: 10.1002/ana.22366
- Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetsee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* (2018) 17:162–73. doi: 10.1016/S1474-4422(17)30470-2
- Mariottini A, Marchi L, Innocenti C, Di Cristinzi M, Pasca M, Filippini S, et al. Intermediate-intensity autologous hematopoietic stem cell transplantation reduces serum neurofilament light chains and brain atrophy in aggressive multiple sclerosis. *Front Neurol.* (2022) 13:820256. doi: 10.3389/fneur.2022.820256
- Hildesheim FE, Ramasamy DP, Bergsland N, Jakimovski D, Dwyer MG, Hojnacki D, et al. Leptomeningeal, dura mater and meningeal vessel wall enhancements in multiple sclerosis. *Mult Scler Relat Disord.* (2021) 47:102653. doi: 10.1016/j.msard.2020.102653
- Mariottini A, De Matteis E, Muraro PA. Haematopoietic stem cell transplantation for multiple sclerosis: current status. *BioDrugs.* (2020) 34:307–25. doi: 10.1007/s40259-020-00414-1