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Keywords:	radiologically isolated syndrome, choroid plexus, MRI, NfL, GFAP, Kappa index
Abstract:	<p>Background: Choroid plexus (ChP) enlargement is an emerging radiological biomarker in multiple sclerosis (MS).</p> <p>Objectives: This study aims to assess ChP volume in a large cohort of patients with radiologically isolated syndrome (RIS) versus healthy controls (HC) and explore its relationship with other brain volumes, with disease activity, and with biological markers.</p> <p>Methods: RIS individuals were included retrospectively and compared with HC. ChPs were automatically segmented using an in-house automated algorithm and manually corrected.</p> <p>Results: 124 patients fulfilled the 2023 RIS criteria, and 55 HCs were included. We confirmed that ChPs are enlarged in RIS versus HC (mean (\pmSD) normalized ChP volume: 17.24 (\pm4.95) and 11.61 (\pm3.58), respectively, $p < 0.001$). Larger ChPs were associated with more periventricular lesions volume and more periventricular lesion number ($\rho = 0.26$; $r^2 = 0.27$; $p = 0.005$, and $\rho = 0.2$; $r^2 = 0.21$; $p = 0.002$, respectively). Conversely, ChP volume did not correlate with biological markers. No significant difference in ChP volume was observed between subjects who presented or did not have a clinical event or between those with or without imaging disease activity.</p> <p>Conclusions: This study provides evidence that ChP volume is higher in RIS and is associated with measures reflecting periventricular pathology, but does not correlate with biological, radiological, or clinical markers of disease activity.</p>

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3 **Choroid plexus enlargement correlates with periventricular pathology but not with**
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7 **disease activity in radiologically isolated syndrome.**
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Abstract

Background: Choroid plexus (ChP) enlargement is an emerging radiological biomarker in multiple sclerosis (MS).

Objectives: This study aims to assess ChP volume in a large cohort of patients with radiologically isolated syndrome (RIS) versus healthy controls (HC) and explore its relationship with other brain volumes, disease activity, and biological markers.

Methods: RIS individuals were included retrospectively and compared with HC. ChPs were automatically segmented using an in-house automated algorithm and manually corrected.

Results: One hundred twenty-four patients fulfilled the 2023 RIS criteria, and 55 HCs were included. We confirmed that ChPs are enlarged in RIS versus HC (mean (\pm SD) normalized ChP volume: 17.24 (\pm 4.95) and 11.61 (\pm 3.58), respectively, $p < 0.001$).

Larger ChPs were associated with more periventricular lesions ($p = 0.26$; $r^2 = 0.27$; $p = 0.005$ for the correlation with lesion volume, and $p = 0.2$; $r^2 = 0.21$; $p = 0.002$ for the correlation with lesion number) and lower thalamic volume ($p = -0.38$; $r^2 = 0.44$; $p < 0.001$), but not with lesions in other brain regions. Conversely, ChP volume did not correlate with biological markers. No significant difference in ChP volume was observed between

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2 subjects who presented or did not have a clinical event or between those with or without
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5 imaging disease activity.
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10 Conclusions: This study provides evidence that ChP volume is higher in RIS and is
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13 associated with measures reflecting periventricular pathology but does not correlate with
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15
16 biological, radiological, or clinical markers of disease activity.
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21 Keywords: radiologically isolated syndrome, choroid plexus, MRI, NfL, GFAP, Kappa
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24 index.
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33 **Introduction**

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37 The radiologically isolated syndrome (RIS) represents the earliest detectable
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39
40 asymptomatic multiple sclerosis (MS) phase. The 2009 RIS criteria were defined to
41
42
43 characterize individuals with incidental abnormal MRI studies (1) and were updated in
44
45
46 2023 to harmonize dissemination in space characteristics with the current MS criteria
47
48
49 (2). Analysis of a worldwide RIS cohort demonstrated that younger age, male sex, and
50
51
52 the presence of spinal cord, infratentorial, gadolinium-enhancing lesions, and
53
54
55 cerebrospinal fluid (CSF) restricted oligoclonal bands (OCBs) are associated with a risk
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1
2 of conversion to a first clinical demyelinating event (3,4). International efforts are
3
4
5
6 underway to increase the specificity of incidental MRI findings during the asymptomatic
7
8
9 phase and identify biomarkers that could determine mimics or predict which individuals
10
11
12 will evolve into clinical MS, such as the central vein sign (5) and paramagnetic RIM sign
13
14
15
16 (6). The potential of choroid plexus (ChP) volume to differentiate MS from its mimics
17
18
19 with relatively high specificity utilizing clinically routine sequences and widely available
20
21
22 segmentation techniques (7) is a promising development.
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25

26
27 The ChP is a complex stromal-vascular network that produces cerebrospinal fluid (CSF)
28
29
30 (8). The structure is pivotal in immunosurveillance, controlling part of immune cell
31
32
33 trafficking into the central nervous system (CNS) (9). A cross-sectional magnetic
34
35
36 resonance imaging (MRI) study demonstrated that ChP volume in healthy subjects
37
38
39 increases with age (10), while data about sex differences in ChP volume remains limited
40
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44 (11).
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49 In recent years, the ChP has emerged as a critical brain structure of interest in the
50
51
52 pathophysiology of neurodegenerative disorders, particularly those with an inflammatory
53
54
55 component like multiple sclerosis (MS). ChPs in MS could potentially act as a gateway
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58 for immune cell infiltration into the CNS (12–16). *In vivo* imaging studies have shown an
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1
2 enlargement of ChPs through MRI and a higher translocator protein (TSPO) expression
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4
5 on positron emission tomography (PET), indicating inflammation in ChPs of people with
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7
8
9 MS compared with healthy controls (HC) (14–16). This ChP size increase is associated
10
11
12 with focal and diffuse tissue damage, reflected by lesion load and atrophy, respectively,
13
14
15
16 and brain parenchymal inflammation, revealed by PET imaging (14). Longitudinal data
17
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19 on ChP volume in MS patients show progressive ChP enlargement and demonstrate
20
21
22 that ChP volume is linked to chronic lesion expansion and neurodegeneration of
23
24
25
26 periventricular white and grey matter (17).

27
28
29
30 Some preliminary data in a limited number of RIS cases comparing patients and HC
31
32
33 suggest that the volumetric and inflammatory alterations described in clinically defined
34
35
36 MS (CDMS), reflected by a higher CP uptake on ^{18}F -DPA-714 uptake on TSPO PET,
37
38
39 are already detected at the presymptomatic stage of the disease (18). Due to the small
40
41
42 sample and the limited number of conversion events, a definitive conclusion on the role
43
44
45 of ChP enlargement as a predictor of future CDMS could not be drawn from the
46
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48 published study. Moreover, to date, no data exists on correlations between biological
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51 markers of the disease and ChP volume in MS. Recently, a positive correlation between
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1
2 ChP volume and serum neurofilament light chain (sNfL) was described for patients with
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6 frontotemporal lobar degeneration spectrum (19), but was never explored in MS.
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10 In the present study, we examined choroid plexus volume in a large cohort of RIS
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12
13 subjects versus HC to better understand the clinical relevance of volumetric ChP
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16 modifications before MS symptom onset. We evaluated the association with metrics
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19 reflecting either whole brain or regional pathology. Finally, we investigated the
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21
22 relationship of ChP volume with conversion to CDMS, future radiological activity during
23
24
25 the asymptomatic phase, and biological markers of disease such as kappa-free light
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28 chains (KFLC), sNfL, and glial fibrillary acidic protein (GFAP).
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39 **Methods**

40 41 42 43 *Study population*

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46 According to French laws, individuals with RIS received appropriate research
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49 information, and non-opposition participation documentation was available. The study
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51
52 received approval from the institutional review board of the Nice University Hospital, and
53
54
55 the protocol was registered under the reference 2024-EI-609. All the subjects fulfilling
56
57
58
59
60 the 2023 RIS criteria were retrospectively selected from their first brain MRI, including

1
2 the following sequences on the baseline and the follow-up scans: pre-gadolinium 3D-
3
4
5
6 T1, post-gadolinium T1-SE, and 3D T2-FLAIR. RIS individuals were selected from the
7
8
9 International RIS database (NCT05388331). HCs having a non-enhanced 3D-T1 MRI
10
11
12 scan were retrospectively collected from 4 studies performed at the Paris Brain Institute
13
14
15
16 between 2009 and 2023 (EUDRACT-2008-004174-40; NCT02305264; NCT01651520;
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18
19 NCT03691077), for which written informed content had been obtained. As per study
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21
22
23 protocols, cross-sectional scans of HC were performed on a 3T MRI Siemens Trio
24
25
26 (n=32) or Prisma (n=23) system with a 32-channel head coil.
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31 *Postprocessing*

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36 T2 lesions were semi-automatically segmented and manually edited from 3D T2-FLAIR
37
38
39 images of baseline scans using ITK-SNAP. They were classified according to the
40
41
42 location: periventricular, cortical/juxtacortical, infratentorial, or deep white matter (20)
43
44
45
46 and their number and volume for each of these four regions were extracted. The number
47
48
49
50 of gadolinium-enhancing lesions at baseline and follow-up was assessed on post-
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52
53 gadolinium T1-SE images. In contrast, the number of new and/or enlarging T2 lesions
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56
57 on longitudinal imaging was obtained by registering the 3D T2-FLAIR images of follow-
58
59
60 up scans compared to the previous scan (CJA, LM).

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2 ChPs of lateral ventricles were automatically segmented on non-enhanced 3D T1-
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5
6 weighted gradient-echo scans having the exact millimetric resolution in RIS and HC
7
8
9 scans using the in-house automated algorithm previously described (21,22). They were
10
11
12 then manually corrected using ITK-SNAP by trained analysts jointly revising the images
13
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15
16 to reach an adjudicated consensus on segmentation (CLC, VAGR), and their volume
17
18
19 was calculated. The analysts were blinded to subject status (HC or RIS) and clinical
20
21
22
23 data (**Figure 1**).

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27
28 The following additional brain volumes were extracted on index scans using *Volbrain*
29
30
31 (**Figure 1**): lateral ventricle volume, cortex volume, subcortical grey matter volume, and
32
33
34 thalamic volume. To reduce inter-subject variability, measured volumes were divided by
35
36
37 total intracranial volume (TIV) to obtain the corresponding normalized value.
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42 ***Biological markers***

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47 Biological markers were acquired at the same time as the MRI acquisition. Blood, CSF
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50 IgG, albumin, and KFLC were measured by turbidimetry with the analyzer Optilite (The
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52
53 Binding Site, Birmingham, UK) using the serum-free light chain immunoassay Freelight
54
55
56
57
58 (The Binding Site, Birmingham, UK), following the manufacturer's instructions.
59
60

1
2 Isoelectric focusing on agarose gel using subsequent immunoblotting with IgG-specific
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4
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6 antibody staining was used for unique OCB detection (Hydrasys platform; Sebia, Lisses,
7
8
9 France). OCB patterns were classified as positive (patterns II and III) or negative (other
10
11
12 patterns). The determination of intrathecal synthesis of KFLC was evaluated by
13
14
15 calculating the K-index using the formula: $K\text{-index} = (\text{CSF KFLC}/\text{serum KFLC})/(\text{CSF}$
16
17
18 $\text{albumin}/\text{serum albumin})$ (23). A cut-off of ≥ 2 CSF restricted bands or K-index of ≥ 8.92
19
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21 defined CSF positivity (24).
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28 Quanterix's Simoa® platform assay measured sNfL and sGFAP levels according to the
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31 manufacturer's instructions.
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36 ***Statistical Analysis***

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40 Statistical analyses were performed using the online application EasyMedStat (version
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43 3.22). Continuous variables were described by mean, standard deviation (SD), and
44
45
46 categorical variables by count and percentage. The normality and heteroscedasticity of
47
48
49 the data were assessed using the Shapiro-Wilk and Levene's tests. According to data
50
51
52 distribution, continuous variables were compared across groups using the ANOVA,
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54
55 Welch ANOVA, or Kruskal-Wallis tests. The comparison of binary variables across
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1
2 groups was assessed using the Chi-square test. Pearson's or Spearman's correlation
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4
5 was used for univariate analysis to measure statistical dependence between numerical
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7
8 variables. Then, multivariable logistic regressions for binary outcomes, considering i.
9
10 RIS individuals who developed clinical symptoms versus those who remained
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12 asymptomatic, and ii. RIS individuals who developed radiological progression or not,
13
14 and multivariable linear regressions for continuous outcomes were fitted to assess the
15
16 association between ChP enlargement, set as an independent variable, and conversion
17
18 status or radiological progression, lesion volume or number, other brain volumes, or
19
20 biological markers, all set as dependent variables. Since the distribution of T2 lesion
21
22 volume was not normal, a logarithmic transformation was applied to the lesion load to
23
24 manage outliers. Models were adjusted for age, sex, and the ratio of ChPs to ventricular
25
26 volume. The absence of multicollinearity and the independence of explanatory variables
27
28 were verified using the variance inflation factor (VIF) test. Outputs were expressed in
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30 terms of rho and r squared to indicate the proportion of variation of the dependent
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32 variable predicted by the independent variable and the p-value for significance.
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Multivariate Cox regression was used to test the relationship between ChP volume and

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2 time to clinical symptoms among RIS individuals who developed clinical symptoms. In
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6 all tests, a p-value < 0.05 was considered statistically significant.
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15 Results

16 17 18 19 *Clinical Characteristics*

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23 One hundred twenty-four RIS individuals and 55 HC were included. The mean (\pm SD)
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25
26 age at the index scan was 38.62 years (\pm 12.54) and 40.58 years (\pm 13.19), respectively
27
28
29
30 (p=0.423); 92 RIS (74.2%) and 29 HC (52.7%) were females (p=0.008). The mean
31
32
33 (\pm SD) time since the RIS index scan was 1.98 years (\pm 2.31), and the mean clinical
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35
36
37 follow-up duration after the index scan was 4.18 (\pm 3.36) years (**Table 1**). The mean
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39
40
41 (\pm SD) number of follow-up MRI scans available per individual was 3.56 (\pm 2.56).
42
43

44 CSF analysis was performed in 102 of 124 (82.3%) RIS subjects. It was consistent with
45
46
47 intrathecal inflammation in 73/102 (71.6%), 71/102 (69.6%) with more than 2 OCBs, and
48
49
50
51 21/28 (75%) with an increased KFLC index.
52
53

54 At the time of analysis, on February 1, 2024, 46 (37.1%) subjects had experienced their
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56
57
58 first clinical event. The mean (\pm SD) follow-up duration was 4.2 ± 3.29 years in subjects
59
60

1
2 who evolved to clinical MS and 4.17 ± 2.91 years in asymptomatic individuals ($p=0.774$)
3
4
5
6 (Table 1). Clinical symptoms were progressive from onset for two people (4.55%) and
7
8
9 acute for 44 (95.45%), consisting of myelitis in 18/44 (40.9%), optic neuritis in 6 (13.6%),
10
11
12 long sensory or motor tracts other than myelitis in 12 (27.3%), brainstem syndrome in 3
13
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16 (6.8%), and unspecified in 5 (11.4%).
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23 *Imaging Characteristics*

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26 Baseline spinal cord imaging was performed at the treating physician's discretion at
27
28
29 each study site, and 115 RIS (92.7%) had an available spinal cord MRI at the index
30
31
32 brain MRI scan date. Regarding the different brain regions, 120 RIS (96.8%) had
33
34
35 periventricular lesions, 117 (94.4%) had cortical/ juxtacortical lesions, 118 (95.2%) had
36
37
38 deep white matter lesions, and only 53 (42.7%) had infratentorial lesions. Data on the
39
40
41 presence or absence of gadolinium-enhancing lesions was available for all subjects. At
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43
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45
46
47 least one gadolinium-enhancing lesion on the enhanced-3DT1 was observed in 29 RIS
48
49
50
51 (23.4%) with a mean of 1.05 ± 3 gadolinium-enhancing lesion per patient.
52
53

54 Data on the presence or absence of new and/or enlarging T2 lesions or gadolinium-
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56
57
58 enhancing lesions on follow-up scans was available for 118 subjects (95.2%). MRI
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60

1
2 advancement was present in 81/118 subjects (68.6%) and was identified on the brain
3
4
5 MRI for 53/81 subjects (65.4%), on the spinal cord for five subjects (6.2%), and on both
6
7
8 for 23 subjects (28.4%) (**Table 1**). Sixty-one subjects (79.2%) presented one or more
9
10
11 new T2 lesions, 14 (18.2%) presented new and enlarging T2 lesions, and 2 (2.6%)
12
13
14
15 presented only enlarging T2 lesions.
16
17

18
19 No difference was observed in regional brain volumes or lesion load between patients
20
21
22 who converted to MS and patients who remained asymptomatic (**Table 2**).
23
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25

26 27 *Choroid Plexus Volume in Radiologically Isolated Syndrome Individuals and Healthy*

28 29 30 31 *Controls*

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35 Mean normalized ChP volume was significantly higher in RIS individuals than in HC,
36
37
38 with values of $17.2 \pm 0.495 \times 10^{-4}$ and $11.6 \pm 0.358 \times 10^{-4}$, respectively ($p < 0.001$) (**Figure**
39
40
41
42
43 2). As previously described, ChP volume was correlated with lateral ventricle volume
44
45
46 both in RIS (Pearson's $r = 0.37$; $p < 0.001$) and HC (Pearson's $r = 0.46$; $p = 0.001$)
47
48
49

50 51 *Choroid plexus volume and its relation to periventricular lesions and thalamic atrophy.*

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53
54
55 In the RIS cohort, a higher normalized ChP volume was associated with higher
56
57
58 normalized periventricular lesion load ($p = 0.26$; $r^2 = 0.27$; $p = 0.005$), higher number of
59
60

1
2 periventricular lesions ($p=0.2$; $r^2=0.21$; $p=0.002$), lower subcortical gray matter volume
3
4
5
6 ($p=-0.25$; $r^2=0.28$; $p=0.01$), and lower thalamic volume ($p=-0.38$; $r^2=0.44$; $p<0.001$).
7

8
9 ChP volume was also associated with whole brain lesion load ($p=0.26$; $r^2=0.28$;
10
11
12 $p=0.007$) but not with total lesion number ($p=0.18$).
13
14
15

16
17 On the contrary, normalized ChP volume was not correlated with the lesion volume and
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21 with the number of lesions in the other three brain locations: cortical/juxtacortical
22
23
24 ($p=0.611$ and $p=0.472$), deep white matter ($p=0.705$ and $p=0.348$), and infratentorial
25
26
27 ($p=0.735$ and $p=0.411$). It was also not correlated with the number of active lesions (Gd-
28
29
30
31 enhancing lesions) at baseline ($p=0.3$) or with cortical gray matter volume ($p=0.11$).
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35

36 *Relationship between choroid plexus volume and first clinical event*

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38
39

40 No significant difference was observed between the two groups when assessing ChP
41
42
43
44 volume as a risk factor for clinical evolution. The mean baseline normalized ChP volume
45
46
47 was $17.3 \pm 5.29 \times 10^{-4}$ (CI=[16.1; 18.5]) in the RIS group that remained asymptomatic
48
49
50
51 and $17.1 \pm 4.36 \times 10^{-4}$ (CI= [15.8; 18.4]); $p=0.812$ in the RIS group experiencing a first
52
53
54
55 clinical event (**Table 2**).
56
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1
2 We then explored the relationship between baseline ChP enlargement and the time to
3
4
5 clinical symptoms (hazard ratio (HR) =1.04 (95% CI: [0.535; 2.02], p=0.903)) with no
6
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8
9 significant associations found.
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13 *Choroid plexus volume is not associated with MRI indices of disease activity over time*
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17 *nor with biological markers.*
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22 Normalized ChP volume at baseline did not differ between the subjects who experienced
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25 future MRI advancement on follow-up scans and individuals with no dissemination in
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28 time (mean (\pm SD) normalized ChP volume: $17.71 (\pm 4.96) \times 10^{-4}$; CI= [16.62; 18. 80]) in
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31 the group who had radiological activity, and $16.62 (\pm 4.59) \times 10^{-4}$; CI= [15.07; 18.17]) in
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33
34 the group who did not, p=0.23, **Figure 3**). This result was confirmed by the absence of
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36
37 an association between baseline ChP volume and evidence of radiological activity over
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43 time, expressed by the number of new and/or enlarging T2 lesions or new gadolinium-
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45
46 enhancing lesions (**Table 3**).
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51 Regarding biological markers, ChP volumetric increase was not correlated with serum
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54 GFAP, serum NFL, and KFLC index value, respectively (p=0.329, p=0.366, and
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58 p=0.697) (**Figure 4**).
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Discussion

The transition from RIS to clinical MS is a complex phenomenon involving immune-mediated inflammation and neurodegenerative processes. This study explored ChP volumetric changes in a large cohort of RIS subjects compared with HC and their relationship with regional brain pathology, clinical and radiological measures of disease activity over time, and biological markers.

In agreement with a preliminary study performed on a smaller RIS cohort (18), our results demonstrate ChP enlargement in RIS subjects versus healthy controls and a positive correlation with lateral ventricle volume, findings previously described in presymptomatic and established MS groups (14,18). Furthermore, we showed that: *i*) larger ChPs are associated with higher periventricular lesion load, a higher number of periventricular lesions, and lower thalamic volume; *ii*) baseline ChP volumes are similar between RIS who evolve clinically over time and those who remain asymptomatic, mirroring previous findings (18), and *iii*) ChP enlargement is not associated with radiological activity over time nor with biological markers of disease.

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2 These results suggest a relationship between ChP characteristics and periventricular
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6 lesion formation and thalamic integrity, potentially reflecting neuro-axonal loss in the
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9 regions surrounding ventricular CSF, that can be identified early at the presymptomatic
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12 stage. Whether this association is related to the modulation of inflammatory cell
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15 trafficking into the CNS through the ChP gateway, as seen in animal models of MS (12),
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18 needs more translational investigation. Previous clinical studies have suggested a
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21 relationship between ChP enlargement and focal acute or chronic inflammation in MS,
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24 reflected by white matter lesion volume (13–16,25), expansion of chronic lesions (26),
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27 iron rim lesions (25), or lesions with a persisting innate immune component detected by
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30 TSPO PET (27). A more specific link between ChP modifications and lesional fate in the
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33 periventricular area has been highlighted. Indeed, ChP enlargement correlated with the
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36 frequency of chronic active lesions detected by PET (27) and remyelination failure in the
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39 periventricular regions (28). Our study aligns with this association at the presymptomatic
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42 stage of the disease. In regional lesion analysis, we found a correlation between ChP
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45 volume and T2 lesion load or number in the periventricular area but not in
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48 cortical/juxtacortical, deep white matter, or infratentorial locations. Based on these
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51 findings, we may speculate that in the presymptomatic stage of the disease, the
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2 pathophysiological effect of ChP is more pronounced in parenchymal regions close to
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5 these structures, with an early impact on the development and fate of periventricular
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9 lesions (29).

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13 The negative association between ChP volume and deep parenchymal volumes in RIS
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16 also aligns with previous studies linking ChP size increase and brain atrophy in MS
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19 patients (17,25,26,29). This effect was detected in periventricular tissue, such as the
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23 thalamus and subcortical gray matter, but not in the cortex. Altogether, these findings
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27 support the hypothesis that ChP dysfunction predominantly affects periventricular fate,
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31 for example, through the persistence of inflammation and the failure of repair (27,28)
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35 rather than distant gray matter regions.

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39 We observed that the ChP volumes were similar in subjects with RIS, who evolved to a
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43 first clinical event, compared to those who remained stable, suggesting that ChP
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46 volumetry may not be a reliable predictive metric of conversion. The finding of a
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50 detectable enlargement of ChPs at the RIS stage compared to controls suggests that
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54 the pathogenic inflammatory processes linked to ChP dysfunction are already engaged
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58 independently of conversion and remain under symptom threshold at this early stage.
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62 In RIS, the lack of association with the clinical outcome may resemble the

1
2 clinicopathological paradox observed in MS, with inconsistencies between ChP volume
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6 and the observed clinical course of the disease (31). This result might appear in contrast
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8
9 with the previous findings by Ricigliano et al., (14) where ChP enlargement was
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12 associated with a 4-year annualized relapse rate (ARR) in MS patients. However, in that
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16 paper, the ARR was measured two years before and two years after the baseline scan
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19 to assess ChP volume. Therefore, the described association indicated that ChP
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22 enlargement captured the ongoing, more inflammatory disease status rather than
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26 predicting future relapses.
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30 Similarly, we did not identify a predictive function of ChP volume on future clinical events
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33 in RIS. Conversely, correlations with pathological disease markers are present in pre-
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36 symptomatic and clinically defined conditions. These results suggest that ChP
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39 alterations may influence tissue pathology in areas bordering the CSF (17,26,32) in both
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45 RIS and MS. However, this pathophysiological role does not lead to detectable
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48 correlations with clinical activity.
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53 Regarding the biological markers of disease, a recent study has shown an association
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56 of ChP volume with serum biomarkers in a large cohort of patients with frontotemporal
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60 lobar degeneration compared with healthy controls (19). Our study did not find a similar

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2 correlation between ChP volume and sNFL levels. This negative result could be due to
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6 the small size (87/124) of the sample for which this information was available, and more
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9 serum data would be required to confirm this result.
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13 The findings reported here should be evaluated in the context of study limitations. First,
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16 this is an observational, retrospective study with longitudinal RIS data but only cross-
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19 sectional HC imaging data, and no longitudinal analysis of ChP enlargement over time
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22 was performed in the RIS cohort. We lack normative values on the physiological ChP
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25 volumetric increase over time in HC. We, therefore, chose not to analyze ChP volumetry
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28 longitudinally in RIS, as we would not be able to conclude regarding the proportion of
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31 change due to pathology rather than normal aging. Secondly, the multicentric cohort of
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34 subjects with RIS and the control group were acquired on different machines, and no
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37 correction for scan/center was performed. Therefore, a residual effect of this possible
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40 methodological bias on the observed ChP size difference between RIS and HC cannot
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43 be formally excluded. However, this is a minor concern since several published studies
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46 have shown that scanner heterogeneity does not impact ChP volumetric differences in
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49 patients versus controls (14,16). Instead, segmentation is comparable across different
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52 machines, even in the real world (18), if the resolution of the MRI sequences used for
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2 volume assessment is consistent across the cohorts (16). Third, the evaluation of
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6 expanding lesions was limited to the count of hyperintensities who showed a volumetric
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9 change in follow-up scans. Still, no quantitative analysis of lesion expansion rate over
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12 time associated with ChP volume in MS (26) was performed. This choice was due to the
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15 heterogeneity of MRI acquisitions within and across patients in a multicentric study
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19 setting. This raised methodological issues for the quantitative analysis of longitudinal
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issues.

In conclusion, this study represents the most extensive effort to explore the clinical and
pathophysiological relationship between ChP enlargement and disease advancement in
a longitudinal cohort of subjects with RIS and HC. Our results demonstrate that structural
changes of the ChP already exist in those with RIS, impacting periventricular pathology
but not influencing risk for future clinical evolution to MS. These results suggest possible
pathological changes in ChPs well before symptomatic manifestations of the disease.

Given the higher accessibility of MRI and the development of artificial intelligence-based
methods for automatic ChP segmentation, ChP volumetric analysis represents an easy

1
2 and promising *in vivo* biomarker of MS neuroinflammation. However, future studies are
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6 needed to evaluate this measure's added value. The clinical consequences of
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9 periventricular pathology influenced by the ChP may arise later in the disease course.
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12 Future studies aimed at determining not only the structural but also the functional
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15 alterations of ChPs, e.g., modifications of blood-CSF barrier permeability, cells and
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18 solutes trafficking at the presymptomatic stage of the disease, would be of great value
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23 to disentangle the contribution of these structures to the early spread of autoimmune
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27 pathology into the RIS brain and their link with clinical conversion.
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3 **Declaration of Conflicting Interests' statement**
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5

6
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46
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54
55

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16
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19
20
21 intellectual property licensed by The Board of Regents of The University of Texas
22
23
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25

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28 B.S. has received personal speaker fees from Janssen, Biogen, Novartis, Merck, and
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34

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39

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52 C.L.-C. and C.L.-F. had full access to all the data in the study and took responsibility for
53
54
55 the integrity of the data and the accuracy of the data analysis. Authors will share
56
57
58
59 deidentified individual participant data and others with academic investigators following
60

1
2
3 publication and approval of a data access agreement by the Nice University Hospital.
4
5

6
7 All requests should be submitted to C.L.-C (landes.c@chu-nice.fr).
8
9

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Table 1. Subjects' demographic characteristics

Demographic variables					
	RIS patients (N=124)		<i>p</i> -value	Healthy controls (N=55)	<i>p</i> -value
	RIS Symptomatic MS (N=46)	to RIS (N=78)			
Gender, Female, N (%)	34 (73.91%)	58 (74.36%)	>0.999	29 (52.7)	0.008*
Age at enrolment, years, mean (\pm SD)	36.77 (\pm 10.90)	39.71(\pm 13.36)	0.235	40.58 (\pm 13.19)	0.423*
Disease duration at enrolment, years, mean (\pm SD)	2.23 (\pm 2.66)	1.83 (\pm 2.08)	0.662		
Duration of the follow-up, years, mean (\pm SD)	4.2 (\pm 3.29)	4.17 (\pm 2.91)	0.774		
Documented reason for first MRI, N (%)			0.262		
Headache	12 (26.09%)	25 (32.47%)			
Follow-up of other neurological disorders	11 (23.91%)	17 (22.08%)			
Ear-nose-throat	12 (26.09%)	11 (14.29%)			
Mood disorders	3 (6.52%)	7 (9.09%)			
Ophthalmological	1 (2.17%)	7 (9.09%)			
Endocrinopathy	5 (10.87%)	2 (2.6%)			
Dummy scan	1 (2.17%)	3 (3.9%)			
Trauma	1 (2.17%)	2 (2.6%)			
Familial history of MS	0	3 (3.9%)			
Positive CSF, N (%)	22/36 (61.11%)	49/66 (74.24%)	0.249		
Patients with brain lesions in the 4 different locations, N (%):					
Periventricular	46 (100%)	75 (96.2%)			

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Cortical/juxtacortical	45 (97.8%)	72 (92.3%)		
Deep white matter	45 (97.8%)	73 (93.6%)		
Infratentorial	24 (52.2%)	29 (37.2%)		
Patients with spinal cord lesions, N (%)	20 (43.48%)	29 (37.18%)		
Cervical	11 (55.0%)	16 (55.17%)		
Thoracic	2 (10.0%)	1 (3.45%)		
Both	7 (35.0%)	12 (41.38%)		
Patients with MRI activity, N (%)	35 (76.09%)	46 (58.97%)		
New/enlarging T2 lesion(s)	13 (28.26%)	24 (30.77%)		
Enhancing lesion(s)	1 (2.17%)	3 (3.85%)		
Both	21 (45.65%)	19 (24.36%)		

**Healthy control group (N=55) was compared to RIS patients (N=124).*

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging, MS, multiple sclerosis; SD, standard deviation.

Table 2. Comparison of brain volumetric data between RIS presenting a clinical event and those not.

Volumes (cm ³)	RIS to Symptomatic MS (N=46)	RIS (N=78)	<i>p</i>
Total intracranial volume (TIV)	1368.49 (±114.93)	1349.52 (±137.95)	0.434
Total brain volume	1153 (±98.19)	1147.55 (±129.16)	0.775
White matter volume	486.32 (±50.93)	487.51 (±87.07)	0.513
Subcortical grey matter volume	39.07 (±5.87)	39.29 (±4.42)	0.778
Cortical grey matter volume	522.64 (±52.78)	516.36 (±62.85)	0.582
Internal cerebrospinal fluid volume	196.15 (±57.48)	182.88 (±45.28)	0.283
External cerebrospinal fluid volume	164.18 (±39.46)	156.32 (±38.27)	0.277
Cerebrum total volume	1016.6 (±87.70)	1011.54 (±118.40)	0.643
Cerebellum total volume	127.87 (±14.50)	127.10 (±15.17)	0.779
Brainstem volume	18.98 (±3.04)	19.10 (±2.18)	0.887
Thalamus total volume	10.9 (±1.70)	10.78 (±1.53)	0.684
Lateral ventricle total volume	28.07 (±24.11)	22.76 (±15.02)	0.760
3rd ventricle volume	1.32 (±0.75)	1.33 (±0.69)	0.778
4th ventricle volume	1.96 (±0.74)	1.83 (±0.58)	0.290
ChP volume	2354.50 (±689.28) x10 ⁻³	2336.51 (±756.90) x10 ⁻³	0.704
ChP volume/TIV	1.71 (±0.44) x10 ⁻³	1.73 (±0.53) x10 ⁻³	0.812
Total T2 lesion volume/TIV	10.3 (± 12.78) x10 ⁻³	7.94 (± 8.05) x10 ⁻³	0.508
PV lesion volume/TIV	90.64 (± 124.5) x10 ⁻⁴	67.03 (± 75.3) x10 ⁻⁴	0.481
JC/C lesion volume/TIV	6.57 (± 6.87) x10 ⁻⁴	7.35 (± 11.01) x10 ⁻⁴	0.801
IF lesion volume/TIV	1.01 (± 2.47) x10 ⁻⁴	0.548 (± 1.01) x10 ⁻⁴	0.161
Deep brain lesion volume/TIV	3.95 (± 2.81) x10 ⁻⁴	3.79 (± 3.81) x10 ⁻⁴	0.361

ChP, choroid plexus; IF, infratentorial; JC/C, juxtacortical/cortical; MS, multiple sclerosis; PV, periventricular; RIS, radiologically isolated syndrome; TIV, total intracranial volume.

Table 3. Multivariable analysis comparing RIS who will present a clinical and those who will not and RIS who will present a radiological progression and those who will not, depending on explanatory variables.

Variables	RIS to Symptomatic MS (N=46) compared to RIS (N=78) OR; [CI], p-value	RIS DIT+ (N=81) compared to RIS DIT- (N=37) OR; [CI], p-value
Age at enrolment, years	0.98 [0.94; 1.01], 0.188	1.00 [0.96; 1.04], 0.887
Gender (reference: woman)	1.16 [0.47; 2.86], 0.754	0.32 [0.12; 0.90], 0.031
Number of PV lesions	1.05 [0.96; 1.15], 0.293	1.09 [0.97; 1.21], 0.146
Normalized subcortical grey matter volume	0.48 [0.04; 5.55], 0.554	6.55 [0.27; 157.94], 0.247
Normalized thalamus volume	175.51 [0.16; 193470.31], 0.148	1.5e-3 [4.37e-7; 5.16], 0.118
Normalized T2 lesion volume	1.04 [0.93; 1.17], 0.478	0.97 [0.91; 1.03], 0.260
Normalized ChP volume/TIV	1.03 [0.94; 1.13], 0.479	1.39 [0.50; 3.81], 0.528

ChP, choroid plexus; CI, confidence interval; DIT, dissemination in time; MS, multiple sclerosis; OR, odds ratio; RIS, radiologically isolated syndrome; PV, periventricular; TIV, total intracranial volume.

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4 *ChP, choroid plexus; HC, healthy controls; RIS, radiologically isolated syndrome; TIV,*
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6 *total intracranial volume.*
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3 *ChP, choroid plexus; DIT-, No dissemination in time; DIT+, Evidence of dissemination*
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6 *in time; MS, multiple sclerosis; RIS, radiologically isolated syndrome; TIV, total*
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8 *intracranial volume.*
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3 *ChP, choroid plexus; MS, multiple sclerosis; RIS, radiologically isolated syndrome; sGFAP,*
4 *serum glial fibrillary acidic protein; sNFL, serum neurofilament light chain. P= Spearman's*
5 *rho; r= Pearson's correlation coefficient.*
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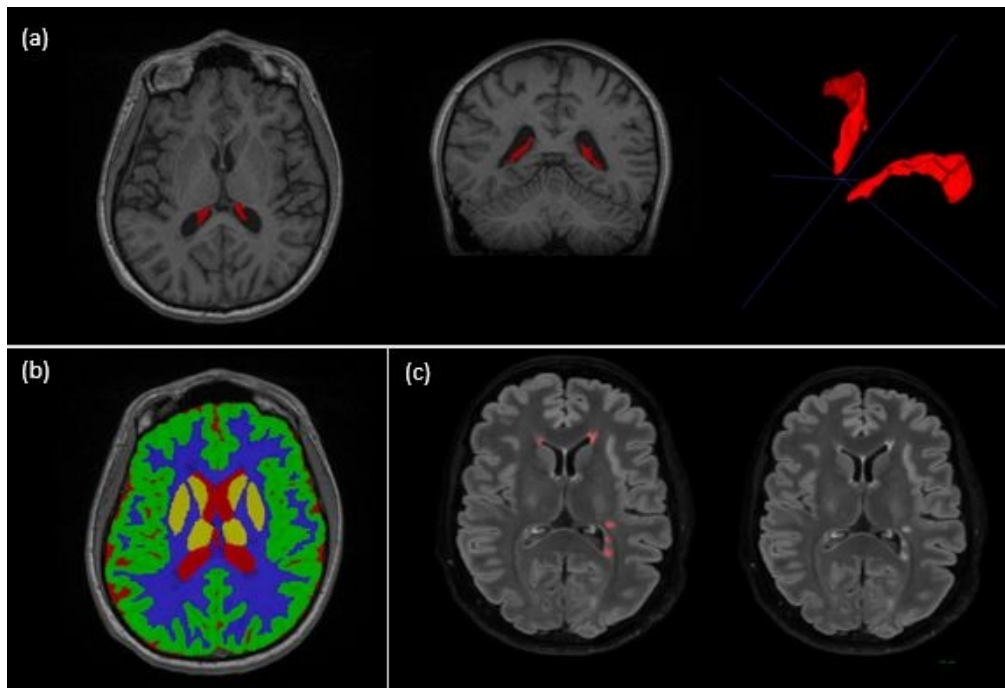


Figure 1. (a) Choroid plexus segmentation, (b) brain tissue segmentation using Volbrain, and (c) manual lesional segmentation using ITK-SNAP.

151x102mm (96 x 96 DPI)

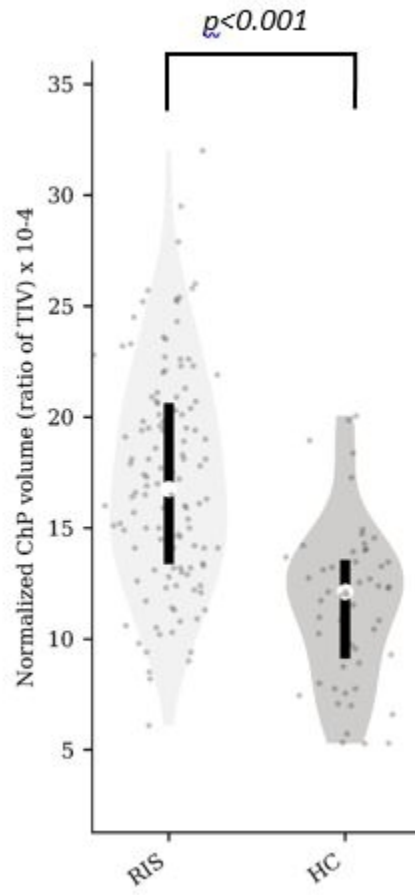


Figure 2. Comparison of normalized ChP volume between RIS and HC.

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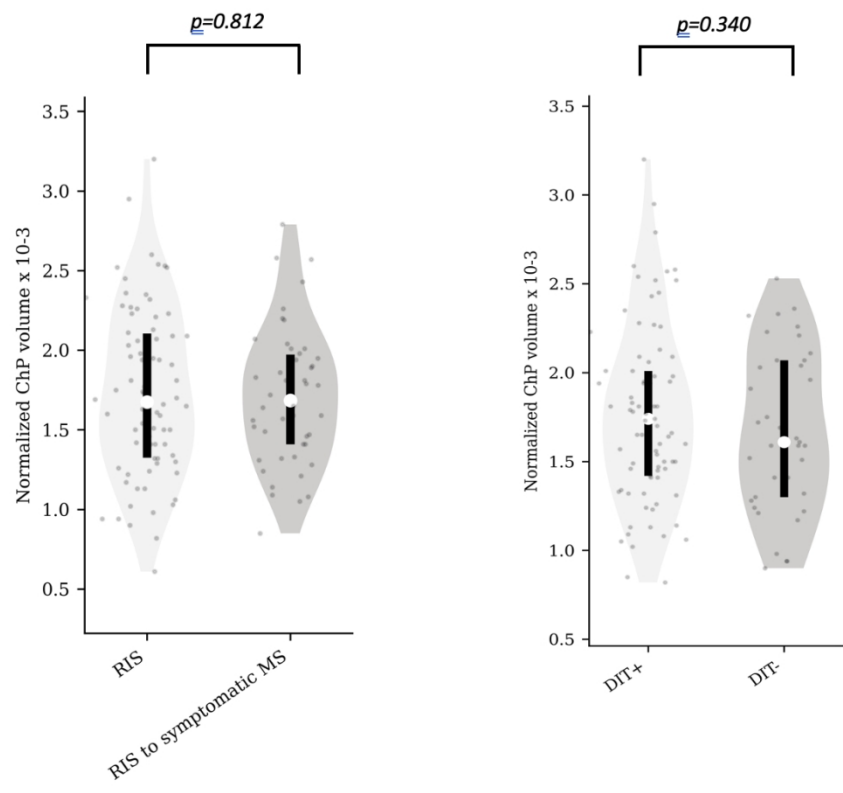


Figure 3. Comparison of normalized ChP volume between RIS who present a clinical event or an MRI dissemination in time and those who do not.

230x190mm (144 x 144 DPI)

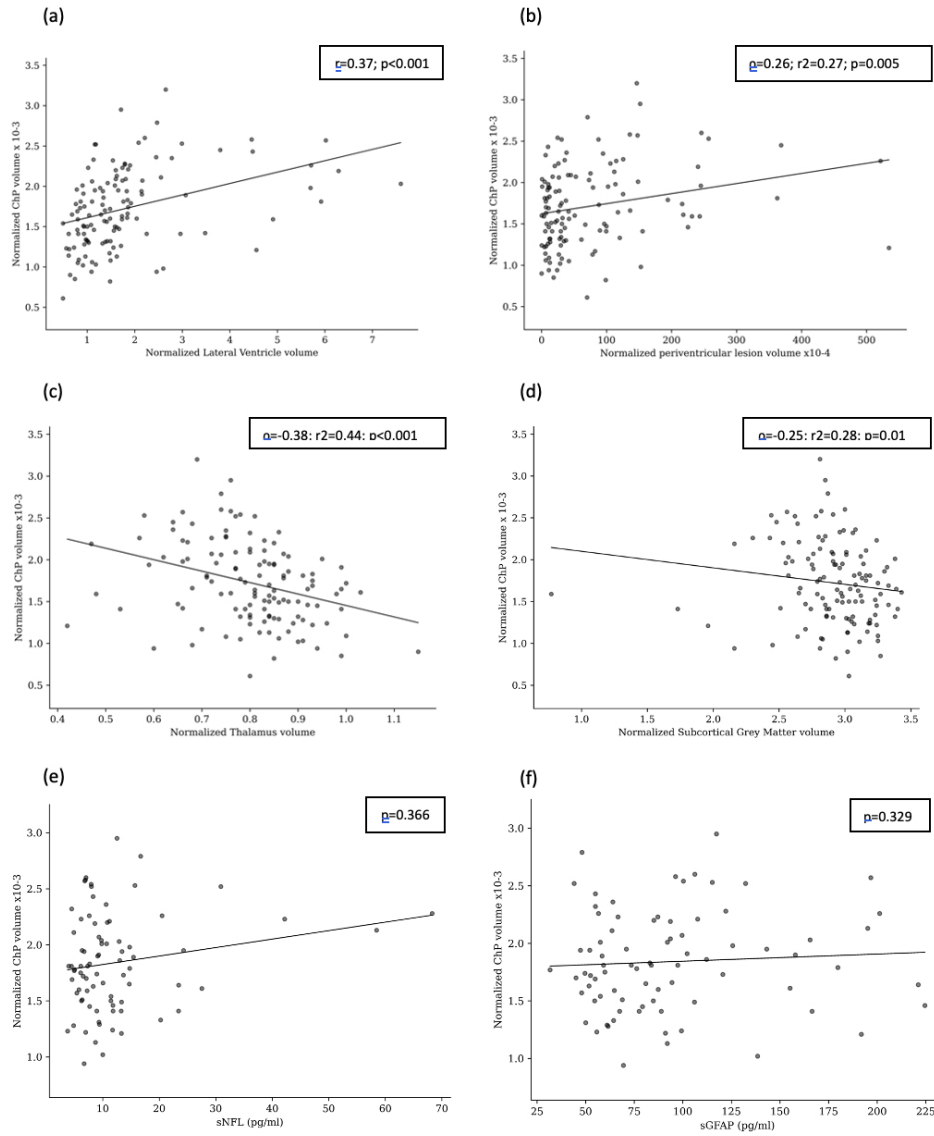


Figure 4. Correlations between normalized ChP volume in RIS and (a) lateral ventricle volume; (b) periventricular lesion volume; (c) thalamus volume; (d) subcortical gray matter volume; (e) sNFL; (f) sGFAP.

190x219mm (144 x 144 DPI)