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Hippocampal volume in cases of relapsing remitting multiple sclerosis and its correlation with cognitive impairment

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ABSTRACT

Background. Multiple sclerosis (MS) is a chronic inflammatory immune-mediated disease, distinguished by demyelination and oligodendropathy in the central nervous system. Cognitive impairment (CI) can impact patients at any stage of MS, including those with clinically isolated syndrome (CIS).

Patients and methods. This is a prospective cross-sectional study which enrolled 60 patients with RRMS. They were subjected to cognitive scale assessment, routine brain MRI study and volumetric assessment of hippocampus.

Results. This study found a significant positive correlation between duration of disease and Subjective memory complaints questionnaire (r=0.525, p=0.001). A significant negative correlation existed between disease duration and MMSE score (r=-0.404, p=0.001) and between disease duration and MoCA score (r=-0.310, p=0.016). No significant difference between both groups regarding the relative hippocampal volume. Mean relative right hippocampal volume is 0.0026 for cases versus 0.0027 among control group and mean relative left hippocampal volume is 0.0025 for cases versus 0.0026 among control group.

Conclusion. Multiple sclerosis disease duration had an impact on cognitive state. However, hippocampal volume assessment did not predict the cognitive affection in patient with RRMS.

Keywords: RRMS, volumetry, cognitive, hippocampus

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory immune-mediated disease, distinguished by demyelination and oligodendropathy in the central nervous system. Immune-mediated myelin damage is associated with chronic progressive neurodegeneration within the CNS, leading to brain atrophy and cognitive impairment affecting 75% of the patients [1].

Cognitive impairment (CI) can impact patients at any stage of MS, including those with clinically isolated syndrome (CIS) [2]. Moreover, an uncommon occurring variant of MS, with an exclusive CI, has been described (Amato and Portaccio, 2012). Also, Cognitive deficit tends to deteriorates with increasing disability and disease duration [1].

Focal inflammatory demyelinating grey matter and/or white matter lesions might cause disruption of interconnected cognitive pathways in early disease stages leading to subtle changes in cognitive function commonly presented with inattention and psychomotor slowing, while diffuse cortical and white matter pathology in later disease stages gives rise to cognitive dysfunction same as dementia [3,4].

According to current memory models, the hippocampus has an important role in new episodic memories [5]. Neuroimaging procedures have proven to be significant for studying neuroanatomical alterations in MS, and attempts were made to associate them with specific cognitive impairments. Indeed, some studies evaluated the association between anatomic hippocampal damage and memory deficit among MS subjects. In our study, we want to assess any possible correlation between the CI in MS patients and the hippocampal volume.

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AIM OF THE WORK

Our aim was to assess the CI in patients with relapsing remittent multiple sclerosis (RRMS) and to measure the volume of hippocampi to find any possible correlation between the cognitive impairment and the hippocampal volume among patients with RRMS.

PATIENTS AND METHODS

This is a prospective cross-sectional study which was performed at the Neurology department, Mansoura university hospital. This study enrolled 60 patients with RRMS who were admitted to neurology department in Mansoura University Main Hospital and outpatient clinic. Also, age and sex-matched control subjects were included. Studied patients were selected randomly in the period between September 2021 and September 2022. Patients with RRMS meeting revised 2017 Mcdonald's criteria for MS diagnosis [6], age between 20-40 years were included in our study

The exclusion criteria were: Any preexisting chronic illness that can affect cognition as chronic kidney, liver diseases, thyroid disorders or psychiatric diseases. Any patient with a contraindication for MRI like cardiac pacemaker and metallic foreign body in the body. Bad general condition and a need for life support.

All patients were subjected to the following: detailed medical and neurological examination, routine laboratory investigations, expanded Disability Status Scale (EDSS) and Cognitive assessment tests.

Cognitive assessment tests were done using: First; Subjective Memory Complaints Questionnaire (SMCQ); which evaluates memory problems in general and daily living. It is formed of fourteen items that reflects aspects of SMCs, representing metacognition of general and specific memories [7].

Second; Mini-Mental state examination (MMSE): It is a 30-point test. It contains orientation (10 points), registration (3 points), attention and calculation (5 points), recall (3 points), language and praxis (9 points) [8]. MMSE is scored from 0 to 30 [9].

Third; Montreal cognitive assessment (MoCA), which is a rapid screening instrument used to detect Mild Cognitive Impairment (MCI) and mild Alzheimer's disease (AD) [10]. The MoCA-Arabic version has shown 92.3% sensitivity and 85.7% specificity for detecting MCI in older adults in Egypt [11].

MR Imaging Examinations:

Brain MRI was done on a 1.5T Siemens Aera, Germany, and closed-configuration whole body scan utilizing a standard quadrature head coil. The MS cases in our study were subjected to MRI scanning: Routine MRI examination of the brain. 3D T1 WI mprage (TR 2200 msec, TE 2.88 msec, slice thickness 1mm, FOV 250 x 250 mm). T2 space dark fluid (TR 5000 msec, TE 336 msec, slice thickness 1mm, FOV 256, TI 1800).

Image analysis was carried out by one neurologist (observer 1) and one neuro-radiologist (observer 2) who were blinded to patients' identities. MRI data collected by observer 2 was utilized in correlational analysis.

All the acquired images ware processed through: Automated Segmentation of the Hippocampus (figure below) will be performed utilizing a subset pipeline of software called "FSL-FIRST". FSL-FIRST uses model-based registration/segmentation methods based on manually segmented images provided by the Center for Morphometric Analysis, MGH, Boston. Measuring the volumes of each structure bilaterally was carried out utilizing (FSL-STATS) pipeline of the software package, then these volumes were compared with healthy controls to observe any volumetric alterations.

Statistical Analysis

Data analysis was done using SPSS program, v 18 (SPSS Inc., PASW statistics for windows, Chicago). Qualitative data were expressed as frequencies and percentages. Quantitative data were expressed as medians (minimum and maximum) (interquartile ranges) for non-normally distributed data and means ± Standard deviations for normally distributed data following testing normality by Kolmogrov-Smirnov test/Shapiro Wilk test. Significance of a result was set at (0.05) level.

Chi-Square was utilized to compare qualitative data among the study groups. Student-t test was utilized for comparison between two independent groups for normally distributed data. One Way ANOVA test was utilized for comparison >2 independent groups with Post Hoc Tukey test to detect pair-wise comparison. The Spearman's rank-order correlation was utilized to determine the strength and direction of a linear correlation between 2 non-normally distributed continuous variables and/or ordinal variables. Receiver operating characteristics curve (ROC curve) was utilized to calculate sensitivity and specificity of continuous variables with calculation of best cut off point.

RESULTS

This study was conducted upon 60 patients with RRMS meeting the revised 2017 McDonald's criteria for MS diagnosis who were recruited over 1 year at neurology department in Mansoura University Main Hospital and its outpatient clinics. Sixty age and sex-matched control subjects were also recruited, to

measure the volume of the hippocampi, evaluation of the cognitive impairment and correlation between the cognitive impairment and hippocampal volume.

This study found a non-significant difference between both groups as regards age, sex and education. Age of our cases ranged between 20-40 years with mean age of cases is 31.27 years versus 29.02 among controls. Among both cases and controls; 66.7% are females and 33.3 are males. Among cases; 43.3 % had high school education, 43.3% graduated from college and 13.3% had only 8th grade education. Among control group; 48.3% had high school education, 35% graduated from college and 16.7% had only 8th grade education. Median disease duration among cases was 2 years ranging from 3 days to 13 years.

This study among studied cases shows; 53.3% did not yet use DMDS, 46.7% used DMDs. They vary between 13.3% used Rebif, 13.3 used Avonex, 10% used Gelenya, 6.7% used Avonex then Gelenya and 3.3% used Tysabri. This study shows that median EDSS among studied cases is 3 ranging from 0 to 8.

This study illustrates that median Subjective Memory Complaints Questionnaire is four among cases ranging from 0 to 12 with 26 (43.3%) of cases have significant complaints. This study demonstrates that MMSE score ranges between 17-30 with mean 27.6 among cases with six (10%) of cases have MCI and 2 (3.3%) of cases have severe CI. This study shows that MoCA score ranges between 15-30 with mean score is 23.43 among cases with 24 (40%) have mild CI and 8 (13.3%) have moderate CI. (Table 1).

This study revealed a non-significant difference between both groups regarding the relative hippocampal volume. Mean relative right hippocampal volume is 0.0026 for cases versus 0.0027 among control group and mean relative left hippocampal volume is 0.0025 for cases versus 0.0026 among control group (Figure 1).

TABLE 1. Results of cognitive assessment scales among studied patients:

	Cases N=60	%
SMCQ median (minimum-maximum) 4 (0-12)		
Normal	34	56.7
Significant	26	43.3
MMSE Mean ± SD 27.60 ± 3.42		
Normal	52	86.7
Mild CI	6	10.0
Severe CI	2	3.3
MOCA Mean ± SD 23.43±4.84		
Normal	28	46.7
Mild CI	24	40.0
Moderate CI	8	13.3

N: number, SMCQ: subjective memory complaint questionnaire, MMSE: mini-mental state examination, CI: cognitive impairment MoCA: Montreal cognitive assessment

This study revealed a non-significant difference relationship (p>0.05) between Subjective memory complaints questionnaire and relative hippocampal volume (Table 2).

This study found a significant positive correlation between duration of disease and Subjective memory complaints questionnaire (r=0.525, p=0.001). A significant negative correlation existed between disease duration and MMSE score (r=-0.404, p=0.001) and between disease duration and MoCA score (r=-0.310, p=0.016) (Table 3).

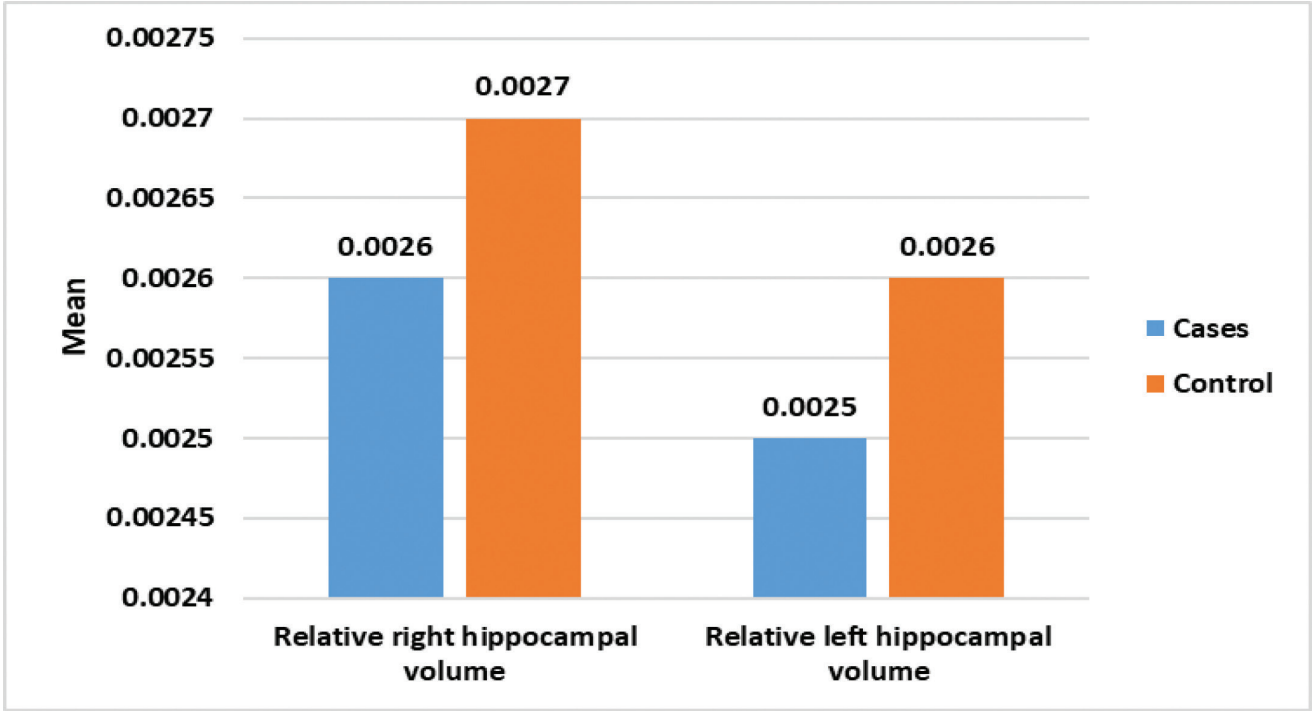


FIGURE 1. Relative hippocampal volume between studied groups

TABLE 2. Relation between subjective memory complaints questionnaire and relative hippocampal volume among studied cases:

	Subjective memory complaints questionnaire		test of significance
	Normal	Significant	
Relative right hippocampal volume	0.0026±0.00048	0.0026±0.0003	t=0613 p=0.542
Relative left hippocampal volume	0.0025±0.0004	0.0025±0.0003	t=0.029 p=0.977

TABLE 3. Relation between disease duration and both cognitive function and hippocampal volume:

		Duration disease /years
SMCQ	R	**0.525**
	P	**0.001***
MMSE	R	**-0.404**
	P	**0.001***
MOCA	R	**-0.310**
	p	**0.016***
Relative right hippocampal volume	r	0.045
	p	0.731
Relative left hippocampal volume	r	0.078
	p	0.552

*r: Spearman correlation coefficient, p: probability, *: statistically significant*

TABLE 4. Relation between Subjective memory complaints questionnaire MMSE score, MOCA score and relative hippocampal volume among studied cases:

		Subjective memory complaints questionnaire	MMSE	MOCA
Relative right hippocampal volume	r	-.108	-.216	.032
	p	.410	.097	.810
Relative left hippocampal volume	r	-.069	-.147	.156
	p	.599	.263	.234

r: Spearman correlation coefficient

TABLE 5. Relation between EDSS, SMCQ, MMSE, MoCA and hippocampal volume:

	EDSS	
	r	P value
SMCQ	0.099	**0.601**
MMSE	-0.186	**0.325**
MoCA	-0.181	**0.338**
Right relative hippocampal volume	0.137	**0.469**
Left relative hippocampal volume	**0.168**	**0.374**

r: Spearman correlation coefficient

There was no significant association (p>0.05) between Subjective memory complaints questionnaire, MMSE score, MoCA score and hippocampal volume (Table 4).

This study illustrates non statistically significant association between EDSS and SMCQ (r=0.099, p=0.601), between EDSS and MMSE (r=-0.186 m, p=0.325), between EDSSS & MOCA (r=-0.181, p=0.338), between right, left relative hippocampal volume and EDSS (r=0.137, p=0.469 & r=0.168, p=0.374) (Table 5).

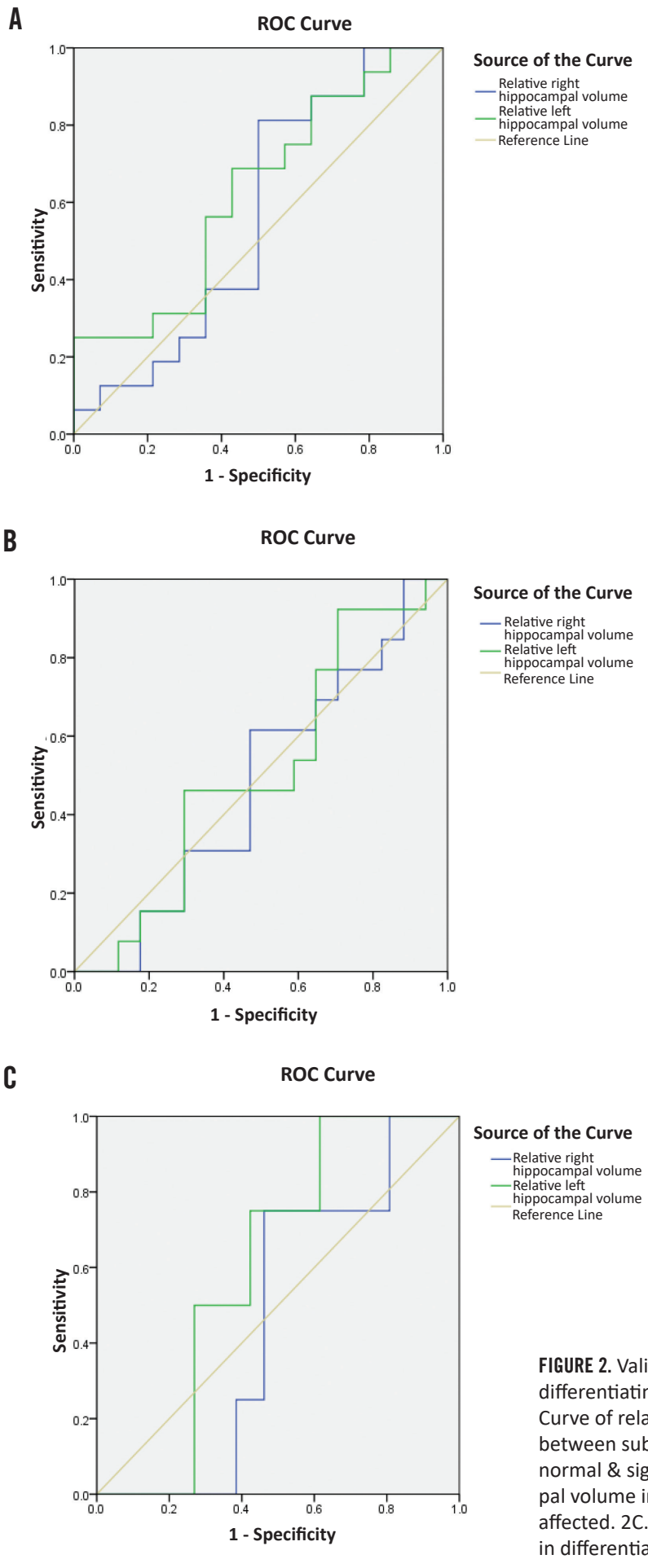
This study shows that area under curve for hippocampal volume is not statistically significant with accuracy of differentiating between normal & significant subjective memory complaints questionnaire (52.9% & 35.3%, respectively for right & left), in differentiating MMSE (53.8% & 57.7%, respectively for right & left) or in differentiating MOCA (50% & 35.7%, respectively for right & left) (Figure 2).

DISCUSSION

Cognitive impairment affects 75% of MS patients during their disease course [1]. Cognitive impairments have been demonstrated at all types of MS, although it is more frequent and severe in progressive forms [12]. The interest in MS related cognitive dysfunction is growing up especially in the last decade. Many cohort studies have shown that there were many structural MRI changes, as global and regional damage of white matter and grey matter in terms of focal lesions and functional network connectivity abnormalities [13,14].

Our study showed a significant positive correlation between duration of disease and Subjective memory complaints questionnaire, as well as a significant negative correlation between disease duration and MMSE score and between disease duration and MOCA score. In consistence with our study, Achiron et al., who found reduction in all cognitive domains after 5 years from diagnosis [15].

Cognitive affection could be varying between MS patients depending on many factors as patient age, disease duration, type of MS and EDSS. In our study, we found that routine MMSE could not detect cognitive deficit in most MS patients this come in agreement with many previous studies reported that cutoff of 24 on the



MMSE was not sensitive to detect cognitive deficits in MS patients [16,17].

In contrary to our study, Reuter et al., found that cognitive impairment may be present in patients diagnosed as clinically isolated syndrome and recently diagnosed (2–3 years) RRMS cases [18]. Also, other studies found that the onset of CI was not well-correlated with disease duration, can be present at initial diagnosis and may not follow the same severity pattern as physical disability [19-21]. The cause of such variability is not known, however might be partially clarified by cognitive reserve.

In our study, we found no correlation between EDSS and cognition or hippocampal volume. In concordance with our study, other studies found that cognition is not always correlated with the EDSS score and CI can be found in early MS [21,22]. Also, Sicotte NL et al, found that total hippocampal volume was not correlated with EDSS in neither RRMS nor SPMS cases [23]. On the other hand, Nelson et al., found in their study of total 39 MS patients, 71.8% of them were cognitively impaired and 28.2% were not impaired. The severity of CI showed significant negative correlation with EDSS [24].

In this study, no significant correlation was found between Subjective memory complaints questionnaire, MMSE score, MoCA score and hippocampal volume. In agreement with our results, one study evaluated hippocampus volume in MS cases and did not report a significant association between manually traced hippocampal volume and memory performance. The explanation for this non-significant association was that memory is formed of heterogeneity cognitive functions, partly instantiated outside the hippocampus. Such heterogeneity

FIGURE 2. Validity of relative hippocampal volume in differentiating memory and cognition affection. 2A. ROC Curve of relative hippocampal volume in differentiating between subjective memory complaints questionnaire; normal & significant. 2B. ROC Curve of relative hippocampal volume in differentiating between MMSE; normal & affected. 2C. ROC Curve of relative hippocampal volume in differentiating between MoCA; normal & affected.

might have limited the power of the correlation analysis [25].

In addition, Kiy and his colleagues on his study that was done on 64 cases with RRMS, diagnosed based on the McDonald criteria, and 8 cases with PPMS, he used temporal horn volume as an indirect method for hippocampus volume [26]. He found that the volumes of left and right temporal horns did not show significant difference for the whole group nor in separate analyses for patient and control groups. Tremblay A et al, used volumetric MRI measures of hippocampus to 41 MS cases [27]. This study did not support a direct association between hippocampal atrophy and verbal memory. A non-significant difference in the hippocampal volume was reported between both groups.

In contrast to our study, there are studies which support the role of hippocampus atrophy in CI. Sicotte et al. investigated the total volume of the right and left hippocampi and their segments in early RRMS, SPMS and in control subjects in terms of performance on memory tasks [23]. The RRMS and SPMS showed lower absolute hippocampal volume in comparison to control group, which was localized to the CA1 region in RRMS and more significantly involved in SPMS. An inverse association was reported between the number of trials required to learn new words and absolute hippocampal, CA1 and subiculum volume.

In another study, hippocampal volumes of 46 RRMS cases (diagnosed based on revised McDonald criteria) and 25 healthy controls were evaluated [28]. Authors found that the right and left relative hippocampal volumes were significantly lower in the whole MS patients compared to controls [29].

A prospective study examined 32 MS patients and age-matched control subjects who underwent a neuropsychological evaluation at baseline, at the first year and at the fifth year of follow up. In addition, patients underwent MRI at the 3 time points, whereas control subjects underwent MRI only at baseline and at the 5-year follow-up [30]. They found a significant reduction in hippocampal volume from baseline to the fifth year and from first year to the fifth year as compared to control group. They also reported a substantial reduction in hippocampal volume between baseline, first year and fifth year, signifying progressive tissue changes from the early stages of MS [31]. This is consistent with earlier in vivo MRI studies that found hippocampal volume loss among MS cases [32].

SUMMARY AND CONCLUSION

Multiple sclerosis disease duration had an impact on cognitive state. However, hippocampal volume assessment did not predict the cognitive affection in patient with RRMS.

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