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Radiodiagnosis

Evaluation of Leptomeningeal Enhancement in Patients with Multiple Sclerosis

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ABSTRACT

Background: Multiple Sclerosis (MS) is an inflammatory with overlapping demyelinating and neurodegenerative phases of the central nervous system (CNS) with large attribution to progressive neurological disability in MS by the latter phase. Grey matter atrophy has been found to have a role in neurodegenerative etiology and has a greater link to impairment than white matter abnormalities. Many investigations have shown a link between leptomeningeal inflammation in the form of ectopic lymphocytic aggregates and cortical disease.

Aim of the work: To evaluate the value of detection of Leptomeningeal enhancement in patients with various phenotypes of multiple sclerosis patients as prognostic marker for the clinical course regards prognosis.

Patients and Methods: This is prospective research that lasted 16 months and included 52 patients with multiple sclerosis of various phenotypes who attended the Neurology MS clinic at Al-Azhar University Hospitals. The following was done to all of the patients: - Comprehensive history taking, illness severity evaluation using the Expanded Disability Status Scale (EDSS), Symbol Digit Modalities Test at baseline and follow-up, normal laboratory tests Radiological assessment using a 3T MRI brain with contrast and post-contrast FLAIR sequences.

Result: The study's findings found a substantial link between presence of leptomeningeal enhancement and EDSS progression

Conclusion: 3Tesla MRI brain with post contrast FLAIR in patients with Multiple sclerosis could be used as an in vivo marker for detection of leptomeningeal inflammation which could be used as prognostic marker for progressive disability conversion to SPMS with early aggressive management and individualization of treatment

Keywords: *Multiple Sclerosis; Leptomenigeal Enhancement; MRI Brain with Post Contrast Flair; EDSS Progression.*

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INTRODUCTION

Multiple sclerosis (MS) is a devastating neurological illness that has no recognized cause. This illness has complicated and varied pathogenesis, although it is commonly characterized by multifocal demyelinated plaques, inflammation, and axonal damage.[1]

Neurodegeneration is increasingly becoming identified as another pathogenic process that contributes to MS's progressive neurological impairment. Previously, it was considered that axonal damage was limited to persistently demyelinated lesions induced by trophic factor deficiency or maladaptive responses in chronically demyelinated axons. However, axonal injury may occur in connection with inflammation in grey matter and more diffusely in normal-appearing white matter, irrespective of white matter demylination.[2]

A substantial neurodegenerative component begins early in the illness course, according to a number of recent investigations. Grey matter lesions and grey matter atrophy, which may be identified using the double inversion-recovery (DIR) sequence, have been demonstrated to play a role in the pathophysiology of neurodegeneration and have a greater link to impairment than white matter lesions and total brain atrophy. MS causes grey matter disease in both deep grey matter regions (thalamus, etc.) and the cortex. Advanced stages of secondary and primary progressive MS have been demonstrated to have substantial cortical damage.[2,4]

Many investigations have shown a link between leptomeningeal ectopic lymphocytic aggregates and cortical disease. Magliozzi et al. found a gradient of necroptosis and demyelination severity in the cortex

underneath these leptomeningeal aggregates, with the highest intensity in subpial regions. In another investigation, similar aggregates were seen in subarachnoid space, deep inside cortical sulci, all throughout the brain.[2]

Massive B cell infiltration has been shown to be a component of such aggregates in immunostaining studies. These B cell enriched aggregates are most likely associated with the development of IgG and/or IgM intrathecal oligoclonal bands (OCB) and Ig-free light chains (FLC).

Due to the tiny size of leptomeningeal infiltrates, which are generally less than 1 m, detecting leptomeningeal pathology in MS is challenging. The failure of the leptomeningeal blood-brain barrier is presumably the cause of this lymphatic follicles.[3]

Recently, post-contrast fluid-attenuated inversion recovery (FLAIR) MRI has sparked attention, since it may identify mild augmentation in the CSF space caused by leptomeningeal BBB malfunction when post-contrast T1W MRI fails to detect these abnormalities. This is not unique to MS, since it has been shown in a variety of illnesses linked to BBB failure, such as localized cerebral ischemia after intracerebral hemorrhage, posterior reversible encephalopathy syndrome, brain tumors, vasculitis, neurosarcoidosis, and CNS infections. In MS, post contrast FLAIR is not routinely performed. We hypothesized that BBB dysfunction might be detectable also in the leptomeningeal vascular segment of patients with MS, which points to leptomeningeal inflammation that could be used as prognostic marker for progressive disability and conversion to SPMS and could help us for more understanding the disease pathophysiology and developing efficient well controlling medical regimen.[4]

The purpose of this study to assess the value of Leptomeningeal enhancement detection in patients with various phenotypes of multiple sclerosis as a prognostic marker for the clinical course in terms of prognosis, as well as its utility in patients with clinically isolated syndrome (CIS) phenotype as a predictive marker for conversion to clinically definite multiple sclerosis.

PATIENTS AND METHODS

Study approval: The present research was authorized by the Al-Azhar University's Faculty of Medicine's ethics committee. After a thorough explanation of all research stages, all participants signed a written informed consent form.

Study design: A prospective study.

Subjects: Included 52 patients with multiple sclerosis: 35 patients with relapsing remitting multiple sclerosis, 11 patients with secondary progressive multiple sclerosis and 6 patients with CIS phenotype. They were recruited from Neurology MS clinics of Al-Azhar University– Hospitals and followed up for 16 month in the period from April 2020 to October 2021.

A clinically isolated syndrome (CIS) is described as the initial clinical event that is indicative of MS, with no prior bouts of demyelination in the patient's history or on imaging.[5]

Mcdonald criteria 2017 as used for diagnosis of Multiple sclerosis.[6]

In the absence of a relapse, secondary progressive multiple sclerosis was defined as a disability progression of 1 EDSS step in patients with an EDSS less than 5.5 or 0.5 EDSS steps in patients with an EDSS more than 6, a minimum EDSS score of 4 and pyramidal FS. With a score of 2 and a three-month track record of improvement, includes confirmation from the most powerful FS.[7]

Increases in EDSS score of $\geqslant$ 1.5 points from an EDSS score of 0.0, $\geqslant$ 1.0 point from an EDSS score of 1.0–5.5, or $\geqslant$ 0.5 point from an EDSS score of $\geqslant$ 6.0 were considered as EDSS worsening and progression events.[8]

Inclusion criteria: Patients diagnosed with different phenotypes of MS regarding McDonald criteria 2017 [6].All patients aged from18 to 50 years.

Exclusion criteria: 1 - Patients with MRI white matter abnormalities interfere with results such as: (vascular disorder - brain injury-metabolic and toxic disorders). 2- Hx of contrast contraindications (Renal impairment) and contrast hypersensitivity. 3_presence of relapse or steroid treating within 30 days of inclusion (as It may affect the enhancement pattern or mimic it).[9]

Study population and procedure: 52 subjects aged 31.83 (8.609), with females compromised 65.4% of the subjects. Most of them were Relapsing remitting multiple sclerosis phenotypes about 35 subjects (67.3%) besides 11 patients with SPMS (21.2%) and 6 (11.5%) subjects with CIS phenotypes. All of the subjects were educated, at least with above intermediated qualifications with 11.92 (1.453) years of educations. All except 8 (15.4%) subjects were on different treatment at the time of enrollment, two of them were shifted to Interferon and one was escalated to Rituximab for better control from Fingolimod. (Table 1)

The following was done to all of the patients: At baseline and at the conclusion of the trial, a detailed history was taken, a clinical examination was performed, and the illness severity was assessed using the Expanded Disability Status Scale (EDSS) and the Symbol Digit Modalities Test Arabic Version (SDMT).[10] Radiological analysis

The SDMT consists of nine symbols, each of which is associated with a single number in a key at the top of a standard sheet of paper. For 90 seconds, patients must write down the digit connected with each symbol as quickly as possible. There is just one result, which is the number of right answers throughout a 90-second period. The Symbol Digit Modalities Test (SDMT) is the most sensitive neurocognitive function metric in multiple sclerosis (MS), and it's always viewed as a measure of information processing speed (IPS).[11]

Radiological evaluation includes:

At baseline and at the conclusion of the trial, 3 Tesla routine MRI brain imaging was performed, including a post-contrast 3D FLAIR sequence and post-contrast T1 imaging. A 3.0T MRI equipment was used for all of the MRI experiments (MAGNETOM Skyra, Siemens, Erlangen, Germany, 20-channel head coil, 50-cm field of view)

Statistical analysis: The data was organized, tabulated, and statistically analyzed using SPSS, version 24 (SPSS Inc. USA), on an IBM compatible computer. The mean and standard deviation were used to depict quantitative data (SD). Relative frequency and percentage were used to depict qualitative data. For quantitative and qualitative data, the student samples (t) test or the Chi square test were used to compare groups. If $p < 0.05$, the result is regarded substantial; if $p < 0.001$, the result is considered extremely substantial.

RESULTS

		Frequency
Age	Mean (SD)	31.83 (8.609
years of education	Mean (SD)	14.92 (1.453
Duration of illness (months)	Mean (SD)	82.92 (75.867)
Age of onset of disease	Mean (SD)	26.08 (7.35)
Total number attacks	Mean (SD)	4.13 (2.997)
Frequency per year	Mean (SD)	0.97 (0.49)
Time bet onset of disease and diagnosis in months	Mean (SD)	17.85 (29.57)
Phenotypes	RRMS	35 (67.3%)
	SPMS	11 (21.2%)
	CIS	6 (11.5%)

Table 1: Demographics.

		Frequency
EDSS at baseline	Mean (SD)	4.15 (2.27)
EDSS at follow up	Mean (SD)	4.35 (2.47)
SDMT at baseline	Mean (SD)	29.63 (17.7)
SMDT at follow up	Mean (SD)	29.44 (18.06)
Motor affection	No weakness	14 (26.9%)
	Monoparesis	7 (13.5%)
	Hemiparesis	18 (34.6%)
	Paraparesis	5 (9.6%)
	Quadriparesis	8 (15.4%)
	Yes	25 (48.1%)
Bladder affection	No	23 (44.2%)
	Yes	29 (55.8%)

Table 2: Clinical data.

	Frequency
Juxta Cortical lesions	48 (88.5%)
Periventricular lesions	52 (100%)
Brainstem lesions	27 (51.9%)
Cerebellar lesions	21 (40.4%)
Lep enhancement baseline	14 (26.9%)
Lep enhancement at follow up	13 (25%)
T 1 lesion enhancement at baseline	15 (28.8%)
T 1 lesion enhancement at follow up	10 (19.2%)
Oligoclonal bands in CSF	47 (90.3%)

Table 3: Radiological and lab data.

		N	Mean	SD	P
Age	Patients without Lep enhancement	38	29.26	7.88	<0.001
	Patients with Lep enhancement	14	38.79	6.51	
years of education	Patients without Lep enhancement	38	14.11	1.42	0.138
	Patients with Lep enhancement	14	13.43	1.45	
Duration of illness (months	Patients without Lep enhancement	38	56.32	62.43	<0.001
	Patients with Lep enhancement	14	155.14	61.63	
Age of onset	Patients without Lep enhancement	38	25.29	7.65	0.206
	Patients with Lep enhancement	14	28.21	6.20	
Total number attacks	Patients without Lep enhancement	38	6.03	2.31	0.331
Time bet onset and diagnosis months	Patients without Lep enhancement	38	11.24	19.18	0.007
	Patients with Lep enhancement	14	35.79	43.68	
EDSS at baseline	Patients without Lep enhancement	38	3.34	2.04	<0.001
	Patients with Lep enhancement	14	6.35	1.08	
EDSS at follow up	Patients without Lep enhancement	38	3.39	2.05	<0.001
	Patients with Lep enhancement	14	6.92	1.49	
SDMT at baseline	Patients without Lep enhancement	38	35.95	16.76	<0.001
	Patients with Lep enhancement	14	12.50	2.59	
SDMT at follow up	Patients without Lep enhancement	38	36.13	16.66	<0.001
	Patients with Lep enhancement	14	11.29	1.77	
T2 lesions at baseline	Patients without Lep enhancement	38	7.42	3.25	0.080
	Patients with Lep enhancement	14	10.21	5.25	
T2 lesions at follow up	Patients without Lep enhancement	38	7.63	3.50	0.057
	Patients with Lep enhancement	14	10.79	5.38	

Table 4: Comparisons between leptomeningeal enhancement and age, EDSS progression, duration of illness.

			Lep enhancement baseline		P value
			No	Yes	
Phenotype	RRMS	Count	28	7	0.005
		%	80.0%	20.0%	
	SPMS	Count	4	7	
		%	36.4%	63.6%	
	CIS	Count	6	0	
		%	100.0%	0.0%	

Table 5: Comparison between leptomeningeal enhancement and phenotype.

		N	Mean	SD	P value
EDSS	EDSS at baseline	14	6.357	1.0818	0.001
	EDSS at follow up	14	6.929	1.4917	
SDMT	SDMT at baseline	14	12.50	2.594	0.006
	SMDT at follow up	14	11.29	1.773	
T2 lesions	T2 lesions at baseline	14	10.21	5.250	0.026
	T2 lesions at follow up	14	10.79	5.381	

Table 6: Comparison between patients with leptomeningeal enhancement and disease progression.

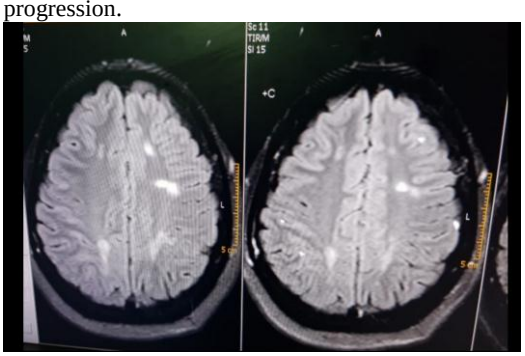

Fig. 1: showed multiple Foci of leptomeningeal enhancement (nodular pattern) in left Frontal and both Parietal lobes in MRI post contrast FLAIR (left picture compared to precontrast FLAIR right picture).

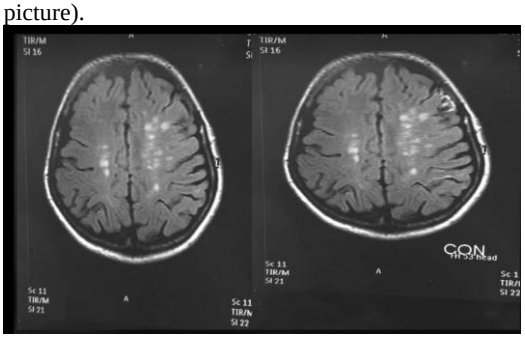

Fig. 2: showed Leptomenigeal enhancement in postcontrast FLAIR (subarachnoid spread pattern) in left Frontal and Parietal lobes (left picture in comparison to the right one).

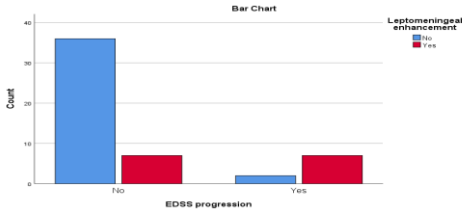

Fig. 3: Showed comparison between Leptomeningeal enhancement and EDSS progression.

The table 1 showed that our study has 52 subjects aged 31.83 (8.609), with females compromised 65 % of the subjects. Most of them were Relapsing remitting multiple sclerosis phenotypes about 35 subjects (67.3%) besides 11 patients with SPMS (21.2%) and 6(11.5%) subjects with CIS phenotypes. All of the subjects were educated, at least with above intermediated qualifications with 11.92 (1.453) years of educations. All except 8 (15.4%) subjects were on different treatment at the time of enrollment. (Table 1)

Table two showed EDSS at baseline of the study group was 4.15(2.27) and at follow up was 4.35 (2.47).The main motor affection was hemiparesis 18 (34.6%) then quadriparesis 8(15.4%) SDMT at baseline was 29.63(17.7 and was 29.44(18.06) at follow up. (Table 2)

The table 3 showed that most of the study group subjects have positive oligoclonal bands in csf profile and almost stable pattern of leptomeningeal enhancement as Leptomeningeal enhancement was 26.9% (14 patients) at baseline an was 25%(13 patients) at follow up . All patients has Subarachnoid spread pattern except one has nodular foci (figure 1 and 2)

(Table 3)

There was substantial correlation between the presence of leptomeningeal enhancement and age ,EDSS ,duration of illness, SDMT an duration between the onset of symptoms and diagnosis as patients with Leptomenigeal enhancement were older ,has higher EDD score,longer duration of disease an lower SDMT score and longer interval between the onset of symptoms and diagnosis (Table 4)

This table showed that patients with leptomeningeal enhancement has SPMS phenotype more than RRMS phenotype (63.6% vs 20% respectively).No reported cases of CIS has leptomeningeal enhancement (Table 5)

This table showed that there is substantial variation between baseline and follow up for patient with leptomeningeal enhancement regards EDSS, SDMT and without substantial variation between baseline and follow up regards T2 lesions.

(Table 6)

Figure 3 showed substantial correlation between Leptomenigeal enhancement and EDSS progression

DISCUSSION

Multiple sclerosis (MS) is an inflammatory, immune-mediated illness of the central nervous system (CNS) that was previously considered to affect only the white matter. Gray matter participation has lately been established as a result of continuous study into the meningeal function in the progression of cortical injury and accumulated disease.

This study is prospective study for in vivo imaging detection of leptomeningeal enhancement and its prognostic value in patients with multiple sclerosis

LME was showed in 14 patients in the whole group with more prevalent in patients with SPMS 63.6 % than in patients with RRMS 20 % .Actually, ME prevalence is greatly variable ranging from comparable results to us 24.7 % in study done by Absinta et al. [(9)] to greatly lower percentage 0.9 % in study done by Eisele et al.[(12)].This great discrepancy could be due to difference in sample group of patients (few numbers of patients with progressive course about 13.4 % in Eisele etal compared to 21.1% in our study and 42.8 % in Absinta etal)and difference in MRI protocol . Eisele etal use 2 dimensional postcontrast T2 FLAIR MRI at 3T with the acquisition relied on 5-mm-thick contiguous slices in contrast to 3 mm thickness at 3T in our study.

There was no apparent predilection for hemisphere or lobe given its diffuse pathological process. It's found that there is correlation between sex and presence of leptomeningeal enhancement as its more in males and it could be explained that male gender is associated with progressive course of the disease for which, leptomeningeal enhancement is one of its marker.

In this study it was shown that it could start while the patient still in the relapsing remitting phenotype but it is more commonly detected in progressive phenotype, with overall percentage 26.9% at baseline and 25 % at follow up . it was not detected in any patients with CIS phenotype so it couldn't be used as marker for conversion to clinically definite multiple sclerosis.

There was no substantial association between LME and routine CSF analysis (total protein, leukocyte count, and CSF-restricted oligoclonal bands), suggesting that LME can identify subtle and focal abnormalities of pathology affecting the blood–meningeal barrier. This in line with another studies who also did not detect any association like Absinta etal ,enforcing the principle that those are two different pathologies.[9]

There was significant decrease in SDMT at baseline and follow up in patients with leptomeningeal enhancement compared to patients without leptomeningeal enhancement and this is could be indirect surrogate to cortical demylination and degeneration.

Cortical grey matter tissue loss is confirmed directly in multiple studies either in cross sectional studies as Barkhof F and Reich DS[13] or longitudinal studies as that was done by Harrison DM et al.[14] that showed that At the 5-year follow-up, MS patients with LM CE demonstrated an accelerated development of cortical and total GM atrophy.

some studies showed correlation of presence of leptomeningeal enhancement with overall grey matter and cortical loss apart from the deep grey volume and other studies included the deep grey matter also there was no substantial variance regards white matter lesion load between patients with vs without leptomeningeal enhancement and this in line with many other studies confirming furthermore , the idea that white matter disease and cortical grey matter dysfunction are at least somewhat independent of one another.[15]

There was substantial difference in EDSS progression when comparing patients with (50%) vs without leptomeningeal enhancement (5.3%). This is could be due to different reasons in addition to leptomeningeal inflammation as confirmed in Zivadinov et al.[15] and this is may be due to older age of patients enrolled to our study compared to them and greater percentage of patients with progressive course.

There was no significant difference regards annualized relapse rate when comparing patients with (0.95 ± 0.32) vs without leptomeningeal enhancement (1.09 ± 0.50) and this is not surprised as this parameter is more correlated with breakdown of BBB and white matter lesion load rather than chronic inflammation and breakdown of meningeal blood barrier .

Mimics of LM CE, such as meningeal blood vessels, large subarachnoid veins, and high signal intensity areas adjacent to dural venous sinuses and basal meninges related to cerebrospinal fluid (CSF) improvement, can be confused with real LME, so routine imaging of LME to be translated into clinical practice in the near future will require the proper development and validation of consensus guidelines.

CONCLUSION

Its recommended to include imaging of leptomeningeal involvement in the routine protocol of follow up imaging Of patients with multiple sclerosis for early identification of leptomeningeal enhancement so early shift of medical treatment to the appropriate regimen.
More studies for evaluation of LME for proper development of clear distinction of LME from its mimics and validation of consensus guidelines in the near future.
Conflict of interest : none

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