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The association of Inflammatory markers and ICAM-1 with neurological disabilities in Relapsing Remitting Multiple Sclerosis (RRMS) patients

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ABSTRACT

Background: The Multiple Sclerosis (MS) disease is considered as chronic, demyelinating, immune –mediated disease of the central nervous system (CNS) . The immunity mediated by T-lymphocyte plays the most effective destructive process in the CNS in MS. High levels of circulating soluble form of Inter Cellular Adhesion Molecule-1 (sICAM-1) have been detected in the serum of MS patients . The inflammatory marker neutrophil-lymphocytic ratio (NLR) is an index , had been reported to be cheap, readily available, and easy to measure. The estimation of immunoglobulin M (IgM) molecules is predictive for a more severe disease course with a shorter time period to the next relapse, and higher grade of disability. Also, C-Reactive Protien CRP was elevated in response to inflammation as acute phase protein reactant , CRP can be used as useful marker for the detection of inflammation-mediated MS.

Aim of work: to estimate ICAM-1 levels in remitting-relapsing multiple sclerosis (RRMS) during remission and to evaluate its correlation with neurological disability , and then assess correlation of some inflammatory markers (CRP, NLR ,IgM) with neurological disability in MS patients.

Subjects and methods: This study consist of 85 subjects ,and classified in to three groups , 50 relapsing remitting MS patients who subdivided into 25 patients without neurological disability and 25 patients with disability(their age range from 19 to 42 year , subdivided to 33 females and 17 males , duration of MS disease is ranged from 1 to 14 years) and 35 healthy control (their age range from 20 to 40 year and subdivided to 24 females and 11 males) . All cases were examined neurologically, and then assessment of neurological disability according to Expanded Disability Status Scale (EDSS). Blood levels of ICAM-1, CRP , IgM and NLR were done to all subjects. **Results:** There was a significant decrease of ICAM-1 level in MS patients (with and without disability) when compared to healthy control group. There was an increasing of ICAM-1 levels among MS patients with disability compared to MS patients without disability. There is high significant positive correlation between EDSS and CRP, ICAM-1, IgM and NLR. There is an increase in ICAM-1 , NLR, CRP and IgM concentration with Cerebellar, brain stem compared to other lesions. **Conclusion:** The ICAM-1 levels were decreased in MS patients in RRMS during remission as compared to healthy controls, MS patients with neurological disability had high concentrations of ICAM-1 when compared to patients without disability, Increased levels of CRP, NLR and IgM in MS patients with disability with Cerebellar, brain stem dysfunction When compared to patients without disability

Keywords: Multiple Sclerosis, ICAM-1, inflammatory biomarkers.

INTRODUCTION

Multiple sclerosis is an inflammatory, demyelinating ,destructive and autoimmune disease of the central nervous system (CNS) ,It affects more than two million people worldwide . Approximately, 85% of MS patients have a biphasic disease course characterized by alternative episodes of neurological disability and then remission, which is known as relapsing remitting MS (RRMS) and characterized by the presence of demyelinated plaques with multi-focal inflammatory lesions caused by auto- reactive immune cells . **[1]**

The neurological disability in MS patients - resulting from accumulation of relapses during the progressive phase of the disease - is partly the result of attacks of adaptive and innate immune systems. **[2]**

Cellular mediated immunity by T- lymphocytes plays the most important process in the CNS destruction in MS. T-cell infiltration of CNS leads to formation of inflammatory plaques, brain inflammation, edema and destruction of blood brain barrier .The Pro-inflammatory cytokine pathways are significant for T-lymphocytes differentiation and functions. **[3]**

Recruitment of Leukocytes to inflammatory sites within CNS is generally caused by different cellular adhesion molecules, known as (ICAM-1, vascular Cellular Adhesion Molcule-1(VCAM-1)). It is still unknown if the inflammation initiates neuro-destruction or neuro-destruction occurs regardless of that inflammation**.** The inflammatory destruction is thought to be due to an interaction between multiple immune system cells as T cells, B cells, macrophages, dendritic cells, and endothelial cells. **[4]**

Inter Cellular Adhesion Molcule-1(ICAM-1; CD54), is a membrane -bound glycoprotein that is found on endothelial cells and leukocytes, its receptor on leukocytes, called lymphocyte function-associated antigen-1 (LFA-1; CD 1 ldCD 18).The Interaction between ICAM-1 and LFA-1 facilitates the migration of leukocytes into the CNS across Blood Brain Barrier (BBB). **[3]**

The soluble circulating ICAM-1 (sICAM-1) released mainly by CNS microvascular endothelial cells, and can be detected in the serum of healthy individuals but , higher concentrations may be associated with pathological conditions as MS. ICAM-1 is considered as useful indicator of inflammatory disease, integrity of the BBB and its damage as it affects the migration of leukocyte trans-endothelially within the inflamed BBB and so can be used it as MS activity peripheral marker . **[5]**

C- reactive protein (CRP) as an inflammatory marker was elevated in MS patients especially those with high disability score (EDSS) and can be used as marker for adverse outcomes in MS. **[6]**

The measurement of IgM- as a biomarker in progressive disease-was correlated with increased concentration of Nuclear Factor –Light Chain (NF-L) in CSF, a higher MS Severity Score, increased lesion number on MRI, and thinning of the retinal nerve fiber layer, suggesting a role for intrathecal IgMs in the ongoing axonal damage in MS. **[7]**

Neutrophil lmphocytic ratio (NLR) used as an index which represents the ratio between neutrophil and lymphocyte count in blood picture .It reflects increased neutrophil count as in acute inflammatory conditions and lymphopenia that develops following acute physiological stress .NLR is low-cost and simple inflammatory marker, which was investigated in multiple diseases with inflammatory features during the acute phase, such as MS. **[8]**

Aim and objectives: to estimate ICAM-1 levels in RRMS during remission and to evaluate its relation with neurological disability, and then assess correlation of some inflammatory markers (CRP, NLR ,IgM) with neurological disability in these patients.

SUBJECTS AND METHODS:

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine Zagazig University. The study was done according to The Code of Ehics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

A case control study conducted at the clinical pathology and Neurology departments, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University (Institutional Research Board IRB). The study included 85 subjects classified to three groups. The first group was healthy control group consists of 35 healthy control (their age range from 20 to 40 year and subdivided to 24 females and 11 males), The second group was RRMS in remission without neurological disability; their age was ranged from 19 to 42 year , subdivided into 18 females and 7 males, duration of disease was ranged from 1 to 12 year and EDSS was <5,The third group was RRMS in remission with neurological disability ; their age was ranged from 19 to 42 year , subdivided into 16 females and 9 males, duration of disease was ranged from 1 to 14 year and EDSS was >5.

Inclusion criteria:

The patients were diagnosed according to the revised McDonald diagnostic Criteria for MS 2017

[9] , age ranged from 19 to 42 years and of both sexes.

Exclusion criteria:

Patients received any interferon or corticosteroid treatment within two months before sampling ,With no infection and associated other autoimmune diseases

METHODS

All patients were subjected to complete history taking including sex, age, past history of other medical conditions, history of current illness including illness duration ,the time and number of relapses, history of drug intake, and last relapse before sampling,and then examined generally, neurologically, assessment of disability according to Expanded Disability Status Scale (EDSS) . **[10]**. Blood sampling for measurement of levels of ICAM-1, CRP and IgM, Complete blood picture for NLR was also done.

Laboratory investigations:

Blood ICAM-1concentrations were assayed by enzyme-linked immunoadsorbent assay (ELISA) according to the manufacturer's protocol using ELISA Kits supplied by Shanghai Sunredbio (SRB) technology co., Ltd. CRP and IgM were determined by immunoturbidometric assay on cobas c 311/501 Roche Diagnostics GmbH Mannheim-Germany analyzers, Complete blood picture for NLR was done on by Sysmex XS system(Siemens).

Statistical Analysis:

Data Analysis was done using Statistical Program for Social Science version 20 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described in the form of mean and standard deviation. Qualitative variables were described as number and percent. In order to compare parametric quantitative variables between two groups, Student t test was performed. Qualitative variables were compared using chi-square (X2) test or Fisher's exact test when frequencies were below five. Pearson correlation coefficients were used to assess the association between two normally distributed variables. When a variable was not normally distributed, Man Whitney test for comparing two non-Parametric variables. Kruskal wallis test for comparing more than two non-Parametric variables. Spearman's correlation P value < 0.05 is considered significant coefficients were used to assess the association between two variables which are not normally distributed. Data were collected and submitted to statistical analysis.

RESULTS:

There is no significant difference between the control group and MS as regard age , there is no a significant difference between them as regard sex while there is significant difference in sex of MS patients as most of MS patients are females by a percent of 66%.(table 1)

This table shows that the most frequent focal lesion is pyramidal lesion by a percent of 22% followed by sensory lesions by a percent of 18%.(table 2)

Table (3) shows the number of MS patients by score on each functional scale on EDSS

There was a significant decrease of ICAM-1 concentration between MS patients (with and without disability) compared to control healthy group (table 4). ICAM-1 levels were decreased among MS patients with disability compared to MS patients without disability. There was increasing of ICAM-1 levels among control compared to MS patients (table 5). The sensitivity of ICAM-1and specificity were 92% and 85.7% respectively for diagnosis of MS, (table 6). Diagnostic performance of ICAM-1 to detect disability among MS patients it has 80% sensitivity and 64% specificity, predictive value positive 75%, predictive value Negative 88.8% and accuracy 80%. (Table 7). Some inflammatory markers were decreased in MS patients with disability compared to MS patients without disability (table 8). There were significant positive correlation between Expanded Disability Status Scale (EDSS) and CRP, ICAM-1, IgM and NLR. While there is no significant correlation between it and age (table 9). There is ascending increase in ICAM-1 concentration with Cerebellar and brain stem compared to other lesions and a high significant relation between site of lesion and NLR, CRP and IgM as increased of their levels in brain stem, cerebellar and pyramidal lesions while their levels were decreased in other sites lesions. (table 10)

there is no significant difference between the control group and MS as regard age while there is a significant difference between them as regard sex as most of MS patients are females by a percent of 66%.

Table (1): Studying of demographic data in between the studied groups:

Variable	Control group (n=35)	Multiple sclerosis group (n=50)	t-test	P value
Age: (year)				
Mean ± SD Range	30.95± 5.51 20 – 40	34.54± 7.38 19 – 42	1.96	0.054 (NS)

	No.	%	No.	%	χ^2	P value
Sex:						
Female	24	68.5	33	66.0	5.6	0.018
Male	11	31.5	17	34.0		

Table (2): Frequency of site of sclerotic lesions of the studied MS cases:

Lesion (N=50)	Number of cases	%
Brain stem	7	14.0
Cerebellar	8	16.0
Mental	4	8.0
Pyramidal	11	22.0
Sensory	9	18.0
Sphincter	4	8.0
Visual	7	14.0

Table (3): Number of MS patients by score on each functional scale on EDSS:

Affected functional systems	0-1	1.5-2	2.5-3	3.5-4	4.5-5	5.5-6	6.5-7	7.5-8	8.5-9	9.5-10
Pyramidal	-	-	-	1	1	4	4	1	-	-
Cerebellar	-	-	-	-	2	5	1	-	-	-
Brain stem	-	-	-	-	2	4	1	-	-	-
Mental	1	2	1	-	-	-	-	-	-	-
Sensory	1	2	3	1	2	-	-	-	-	-
Sphincter	1	1	2	-	-	-	-	-	-	-
Visual	3	3	1	-	-	-	-	-	-	-

Table (4): Comparison between the control and the multiple sclerosis groups as regard ICAM-1 levels:

Variable	Control group (n=35)	Multiple sclerosis group (n=50)	Mann whitney	P value
ICAM-1(ng/l):				
Median Range	559 310.4-750	367 116.1 – 744.1	6.5	<0.001 (HS)

P value <0.001

Table (5): ICAM-1 levels between the control, MS group without disability and MS group with disability.

Variable	Control group (n=35)	MS group without disability (n=25)	MS group with disability (n=25)	Kruskal wallis test	P value	Post hoc
ICAM-1(ng/l):						
Median Range	559 310.4-750	293 116.1-404.4	432 340.4-744.1	53.6	<0.001 (HS)	<0. 01 [1] <0. 01 [2] <0. 001[3]

p1: MS group without disability versus MS group with disability.
p2: MS group with disability versus Control group. P3: Control versus MS group without disability.

Table (6): Diagnostic performance of ICAM-1 in diagnosis of multiple sclerosis.

Sensitivity (%)	92%
Specificity (%)	85.7%
Positive Predictive Value (%)	94.1%
Negative Predictive Value (%)	89.5%
Accuracy (%)	92.8%

Table (7): Diagnostic performance of ICAM-1 in detection of disability

Sensitivity (%)	80%
Specificity (%)	64%
Positive Predictive Value (%)	75%
Negative Predictive Value (%)	88.8%
Accuracy. (%)	80%

Table (8): Laboratory findings between MS group without disability and MS group with disability:

Variable	MS group without disability (n=25)	MS group with disability (n=25)	t-test	P value
CRP (mg/l):				
Median Range	1.21 0.7- 2.02	13 7.1 – 20.2	Mann whitney test 6.07	<0.001 (HS)
IgM (g/l):				
Mean ± SD Range	1.11 ± 0.32 0.7-2.1	3.81 ±0 .87 2.3-5.5	14.53	<0.001 (HS)
TLC (x1000/uL):				
Mean ± SD Range Neutrophil range Lymphocyte range	8.26±1.70 5.4-14 3-10 1.5-3.1	8.49±1.74 6.8-14.12 4.8-10.7 1.5-2.2	0.46	0.646 (NS)
NLR:				
Mean ± SD Range	2.63± 0.29 2-3.1	3.8± 1.78 3.2-4.8	9.98	<0.001 (HS)

CRP : c reactive protein , Igm : total immunoglobulin M, TLC : total leucocytic count . NLR : neutrophil /lymphocyte ratio

Table (9): Correlation between Expanded Disability Status Scale , age, immunoglobulin-M, ICAM-1, C-reactive protein, and neutrophil lymphocyte ratio.

Variable	EDSS	
	R	**P**
Age:	0.108	0.455 (NS)
ICAM-1*:	0.54	<0.001 (HS)
CRP*:	0.77	<0.001 (HS)
IgM:	0.84	<0.001 (HS)
NLR:	0.83	<0.001 (HS)

EDSS : Expanded Disability Status Scale
r = correlation coefficient of pearson's correlation.

Table (10): Relation between site of lesion and ICAM ,CRP, NLR and IgM:

Variable	Brain stem lesions	Cerebellar lesions	Pyramidal lesions	Other sites lesio	ANO	P value	LSD
ICAM-1(mg/dl)							

Variable	Brain stem lesions	Cerebellar lesions	Pyramidal lesions	Other sites lesio	ANO	P value	LSD
Range Mean ± SD	605-744 679± 0.46	692-733 701±0.42	340-519 383±1.07	116.1-404.4 287±0.8	66.8	<0.001 (HS)	0.923[1] <0.001[2] <0.001[3] <0.001[4] <0.001[5] [6]
NLR (x1000/ul):							
Range Median	3.6–4.6 4.2	3.4 –4.5 3.9	3.2-4.8	2-3.1	KW 36.96	<0.001 (HS)	
CRP (mg/l):							
Range Median	12-19.2	10-20.2	7.1-18 10	0. 7-2.02 1.21	KW 38.73	<0.001 (HS)	
IgM(g/l):							
Range median	2.8-5.2	2.9-5.5	2.5-5.2	0.7-2.1 1.6	KW 68.73	<0.001 (HS)	

P value[1] for comparing brain stem lesion with cerebellar lesion

P value [2] for comparing brain stem lesion with pyramidal lesion

P value [3] for comparing brain stem lesion with other site lesions

P value[4] for comparing cerebellar lesion with pyramidal lesions

P value [5] for comparing cerebellar lesion with other sites lesions

P value[6] for comparing pyramidal lesion with other sites lesions

There is ascending increase in ICAM-1 concentration with Cerebellar, brain stem compared to other lesions.

There is high significant relation between site of lesion and NLR, CRP and IgM. There were increased of their levels in brain stem, cerebellar and pyramidal lesions while their levels were decreased in other sites lesions.

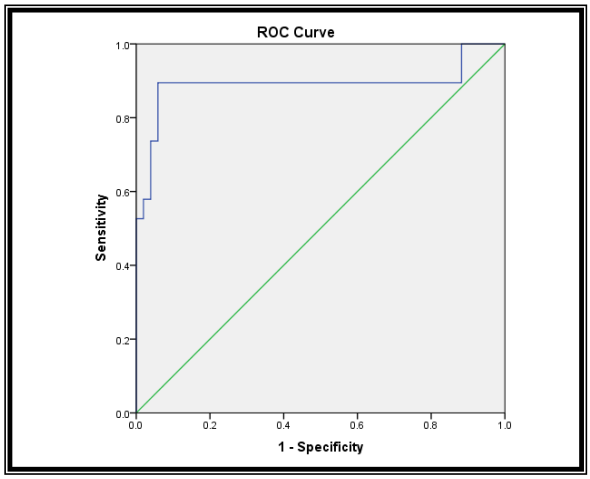

Fig. (1): ROC curve of Diagnostic performance of ICAM-1 in detecting the MS disease.

Area under the curve : 0.891

95% confidence interval : 0.769 – 1

Best cut off value : 650.54 mg/dl

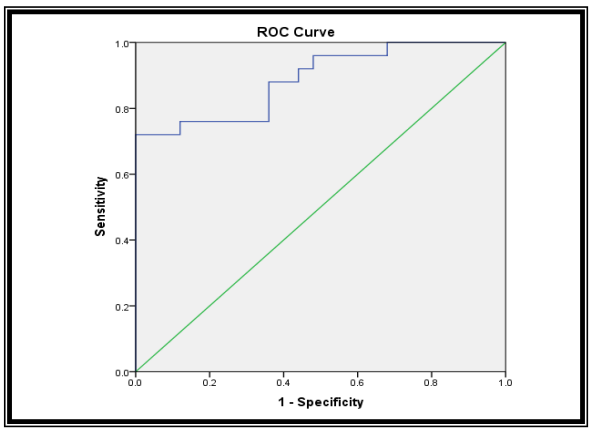

Fig. (2): ROC curve of Diagnostic performance of ICAM-1 in detecting the disability.

Area under the curve: 0.888.
95% confidence interval: 0. .797 – 0. .979.
Best cut off value: 374.12 mg/dl.

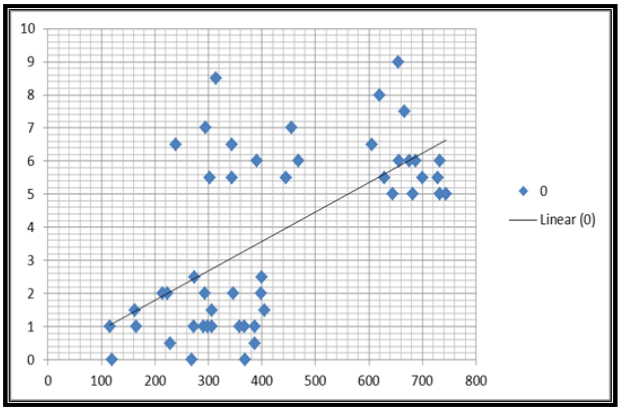

Fig (3): correlation of Expanded Disability Status Scale(EDSS) and ICAM-1.

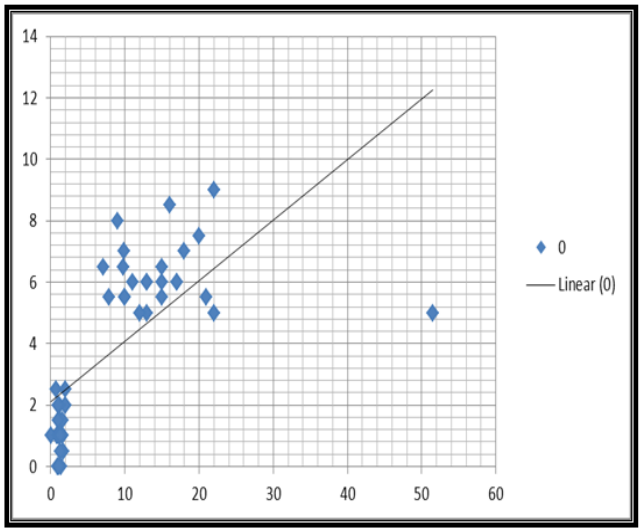

Fig (4): correlation of EDSS and CRP.

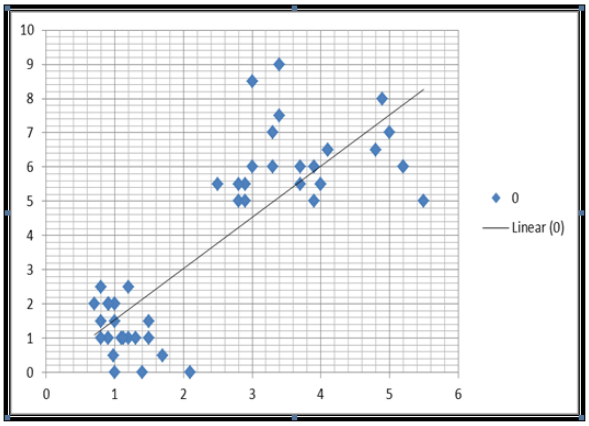

Fig (5): correlation of EDSS and IgM.

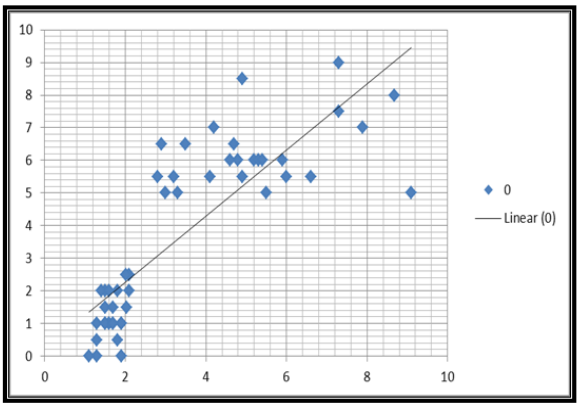

Fig (6): correlation of EDSS and NLR.

DISCUSSION

Multiple sclerosis is demyelinating, inflammatory and neurodegenerative disease of the central nervous system (CNS) and characterized by its chronicity. MS is a multifactorial, heterogeneous, auto-immune disease that is caused by complex gene environment interactions. **[11]**

Disability in MS patients either resulting from relapses or accumulating during the progressive phase of the disease, is partly a result of immune attack from adaptive and innate immunity. **[12]**

Soluble intercellular adhesion molecule-1 (sICAM-1) represents circulating form of ICAM-1 that is constitutively expressed or is inducible on the cell surface of different cell lines. It serves as a receptor for LFA-1 ,the lymphocyte function associated antigen. Interaction between ICAM-1, present on endothelial cells, and LFA-1 facilitates leukocytes adhesion and migration across the endothelial cells. **[13]**

The aim of this work is to assess ICAM-1 levels in remitting- relapsing multiple sclerosis during remission and to evaluate its correlation with neurological disability and then assess correlation of inflammatory markers (IgM, NLR, CRP) with neurological disability in multiple sclerosis patients.

There is high a significant difference between control group and patient group in remission as regard level of ICAM-1 as there was decreased levels of ICAM-1 in RRMS patients. This is due to the immunosuppression during the remission period in RRMS patients. **[3]**

Witkowska and colleagues reported that significant low levels of sICAM-1 during remission compared to those of healthy controls with a significantly varied pattern of ICAM-1 expression in patients with brain stem, pyramidal and cerebellar function disabilities . **[3]**

According to Sellner and colleagues there was reduced levels of ICAM-1 in RRMS during remission. (After a 12-month period of treatment with immunomodulatory therapy) **[14]**. But Alves and colleagues observed a continous increase in sICAM-1 levels in serum during remission also, suggesting that there is continuous inflammatory process within CNS of MS patients despite the regression of clinical signs of disease activity. **[15]**

Also according to Doerck and colleagues ,there is increased levels of ICAM-1 in remission as in relapse, and explained it due to cellular transmigration within BBB. Interaction between LFA-1 and ICAM-1 on brain endothelial cells is

important factor for transmigration of activated cells into the CNS. **[16]**

In this study, there was an increased levels of ICAM-1 in patients with neurological disability more than patients without disability with a positive correlation between ICAM-1 level and EDSS score .Also,there is increase of ICAM-1 concentration in Cerebellar and brain stem lesions compared to other lesions. These results were agreed with Witkowska and colleagues who reported a pattern of increasing sICAM-1 levels across the cerebellar and brain stem lesion. These findings were due to a relationship between sICAM-1 levels and worsening cerebellar and brain stem symptoms, as a result of increased facilitation of the movement of T cells across an impaired BBB to the CNS. So sICAM-1 may be used as a marker of cerebellar and brain stem deficits. **[3]**

This study also assesses relation of inflammatory markers (CRP, NLR , IgM) and neurological disability. For CRP, There is high significant difference between MS with disability and MS without disability. Farrokhia and colleagues reported that there is a correlation between CRP, neurological disability and disease progressive course. **[17]**

For IgM, there is also high significant difference between MS with neurological disability and MS without disability. These results are similar to that of Guzel and colleagues; as they found that IgM levels were higher in patients with high neurological disability according to EDSS. **[6]**

According to NLR, MS patients with disability show higher significant levels in contrast to MS patients without disability. Demirci and colleagues reported that high levels of NLR is positively correlated with EDSS and so can be used as a marker of disease progression and worsening of disability. **[18]**

Guzel and colleagues found that MS patient with low EDSS score showed no correlation with NLR, while MS patient with high EDSS score is correlated to disability and progression of the disease. This result may be due to neutrophil involvement of initial lesion formation in the pathologic process, prior to and early in the relapse and disappear without any role in chronic or progressive inflammation. **[6]**

In this study ,There were some limitations as low number of patients with moderate grades of disability and also low number of patients during remission in RRMS . Therefore ،there is a need to assess the benefit of serum sICAM-1 measurements in more extended studies with large samples of RRMS patients with different grades of neurological disability.

CONCLUSION

The ICAM-1 levels were decreased in MS patients in remission compared to healthy controls. Increase levels of ICAM-1 in MS patients with neurological disability compared to patients without disability especially in cerebellar and brain stem lesions. Increased levels of some inflammatory markers in MS patients with disability compared to patients without disability

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