Inflammatory Response in Multiple Sclerosis Patients

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Abstract: Background: Multiple sclerosis (MS) is a relapsing/remitting or chronic/ progressive disease of presumably autoimmune origin affecting mainly or exclusively the CNS, leading to demyelinisation and remyelinisation. Many pathogenic agents have been incriminated in being either directly involved in the pathogenesis or indirectly, i.e. by triggering an autoimmune process within the CNS. **Aim:** The aim of our study is to estimate serum levels of IL-15 and RANTES chemokine in MS patients either in relapse or remission state compared with age and sex matched healthy subjects. **Subjects and methods:** This case-control study was conducted on forty patients with clinically definite relapsing remitting MS according to 2010 Revisions of the McDonald Criteria. The patients were selected from Inpatient and outpatient Clinic of Neurology Department of Zagazig University Hospitals. The patients were divided into 2 main groups: (1) Twenty patients with MS in acute relapse stage (group I), (2) Twenty patients with MS in remission stage (group II) compared to 20 control healthy subjects. All patients were subjected to the following: Full history taking, Neurological assessment by Kurtzke Expanded Disability Status Scale (EDSS), MRI examination, serum IL-15 cytokine was assessed by enzyme like immunosorbent assay (ELISA) and serum RANTES chemokine assessed by (ELISA). **Results:** We found increased serum levels of IL15 and RANTES in MS patients compared with healthy controls with significant correlations with clinical disability scale. The elevated serum level of IL15 and RANTES is still elevated in remission compared to control and this indicates continuous subclinical pathology during remission. **Conclusion**: Our results suggest the possible role of cytokines/chemokines in the pathogenesis of MS, and their activity is inked more to relapse of the disease.

[Emad Latif Agban, Sawsan Abd EL Aziz Yousef, Dorriya Abd EL Fattah EL Sayed and Sabah Mohamed Lotfy. **Inflammatory Response in Multiple Sclerosis Patients.** *Nat Sci* 2016;14(7):140-148]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 19. doi:10.7537/marsnsj140716.19.

Keywords: Multiple sclerosis (MS), IL-15 cytokine and RANTES chemokine.

1. Introduction:

Currently, MS is considered to be an inflammatory immune-mediated disease of the central nervous system (CNS), the aetiology of which remains enigmatic. Perivascular mononuclear cell infiltration and activation of the immune system are considered to lead ultimately to demyelination and astrogliosis. Cytokines produced by infiltrating inflammatory cells and resident cells in the brain are proposed to play a major role in directing and regulating the immune response as well as mediating tissue damage [1].

There exists evidence showing dysregulation of proinflammatory cytokines, with an up-regulation of both T cell and macrophage-derived cytokines, not only systemically but also locally in the cerebrospinal fluid (CSF) and in MS brain lesions [2]. interleukin-15 (IL-15) is a characterized cytokine with biological functions resembling those of IL-2, of which induction of T cell proliferation might be the most important. The effects of IL-15 are mediated through the β- and γ-chains of the IL-2 receptor and a unique IL-15 receptor α-chain. Like IL-2, IL-15 induces T-cell proliferation and interferon-gamma (IFN-γ) production. In addition, IL-15 induces cytokine production by monocytes and polymorphonuclear cells[3]. Depending on the number of an intervening amino acid between the first two cysteines, chemokines are subdivided into four groups: a-CxC, b-CC, Cx3C and C. Regulated upon activation, normal T-cell expressed and secreted (RANTES) or also known as Chemokine (C-C motif) ligand 5 (CCL5), is a member of the CC- beta subfamily with strong chemoattractant activity for T lymphocytes and monocytes [4]. In MS, activated T lymphocytes migrate from the blood to CNS through chemoattraction and recruitment performing by chemokines [5].

Aim of Work

The aim of our study is to estimate serum levels of IL-15 and RANTES chemokine in MS patients compared with age and sex matched healthy subjects.

Also to find out the relationships between the serum levels of both IL-15 and RANTES with either clinical data using Expanded Disability Status Scale (EDSS) or radiological findings in our MS patients.

2. Subjects & Methods

This case-control study was conducted on forty patients with clinically definite relapsing remitting MS according to 2010 Revisions of the McDonald Criteria[6,7].The patients were selected from Inpatient

and outpatient Clinic of Neurology Department of Zagazig University Hospitals in the period from April 2011 to December 2014.

Patients Group:

This group included 40 patients with clinically definite MS according to Mac Donald criteria, revision 2010 [7]. They were 19 males (47.5%) and 21 females (52.5%). Their age ranged from 18 to 55 years with a mean age of 34.1±8.1 years.

The patients were divided into 2 main groups:

(1) Twenty patients with MS in acute relapse stage (group I).

Relapse was defined as the occurrence of one or more new symptoms or return of old symptoms of neurological dysfunction with duration of at least 24 hours or more and occurred at least 30 days after the last relapse in the absence of a change in core body temperature or infection [8].

(2) Twenty patients with MS in remission stage (group II).

Remission was defined as persistence of symptoms after duration of one month from the clinical attack and symptoms become stable [8].

The relapse group was 9 male (45%) and 11 females (55%) with e mean age of 35.8±8.3 years. The remitting group was 10 males (50%) and 10 females (50%) with a mean age was 32±7.7 years.

Written consents were taken from all patients or their caregivers.

Control group:

Twenty age and sex matched healthy subjects were chosen as a control group. They were 9 males (45%) and 11 females (55%) with a mean age of 31.85±6.8 years.

Exclusion Criteria:

We will exclude the following from the study:

- Patients not fulfilling McDonald's criteria for diagnosing MS.
- Patients with evidence of systemic inflammation on clinical examination.
- Patients with serum biochemical tests evidence of systemic inflammation (increased number of WBCs, elevated CRP or elevated ESR.
- Patients with collagen diseases, vasculitis, malignancies, autoimmune diseases, hematological diseases, severe hepatic or renal diseases.
- Patients who were on regular treatment of non steroidal anti-inflammatory drugs during the last 2 months before enrollment in the study.

All patients were subjected to the following:

1- **Full history taking:**

With special stress on the history of MS and treatments:

- Full analysis of each attack: Regarding
- Cranial nerves affection
- Consciousness
- Motor and sensory affections
- Sphincteric disturbances (autonomic)
- Other systems affections

2- **General examination**:

With special stress on pulse, blood pressure, temperature, weight, head and neck, chest, heart, abdomen, lymph nodes, skin and joints.

3- **Neurological assessment:**

Examination of patients according to neurological sheet of our department. The clinical severity was assessed according to Kurtzke Expanded Disability Status Scale (EDSS) [9]. This scale is a method of quantifying disability in multiple sclerosis. The EDSS quantifies disability in eight Functional Systems (FS) and allows neurologists to assign a Functional System Score (FSS) in each of these. The Functional Systems are:

- pyramidal
- cerebellar
- brain stem
- sensory
- bowel and bladder
- visual
- cerebral
- other

The patients were categorized according to this scale into; EDSS from 1.0 to 4.5 refer to people with MS who are fully ambulatory and EDSS from 5.0 to 9.5 were defined by the impairment to ambulation [9].

4- **MRI examination:**

5- **Laboratory investigations:**

- **IL-15 cytokine secreted by T helper cells:**

Blood sample were collected from patients and control groups. Not fasting blood samples were obtained from a peripheral vein and centrifuged within 1 hour. Serum concentrations of circulating IL-15 were measured by immunoassay using commercially available enzyme like immunosorbent assay (ELISA) kits (**Catalog No.** K0331260, KOMA BIOTECH, based in Seoul, Korea). Dilute the standards and samples in Assay Diluent at 1:2 serial dilutions and assayed according to manufacturer's protocol. Optical densities were determined by means of an ELISA processing system (Stat Fax system USA). Values were calculated by comparison with a standard curve that was generated with IL-15 standards. The **Standard range** is 16-1000 pg/ml.

- **RANTES chemokine with chemoattractant activity:**

Serum concentrations of RANTES were measured by commercially available ELISA kits (**Catalog No.** K0331221, KOMA BIOTECH, based in Seoul, Korea). Dilute the standards and samples in Assay Diluent at 1:2 serial dilutions and assayed according to manufacturer's protocol. Optical

densities were determined by means of an ELISA processing system (Stat Fax system USA.). Values were calculated by comparison with a standard curve generated with serum RANTES standards. The **Standard range** is 16-1000 pg/ml.

We collected two samples from each Patient in group I (relapse), the first sample before administration of corticosteroids therapy. Second after 5 days therapy with corticosteroids. To compare both IL15 and Rantes before and after corticosteroids therapy.

We collected one sample from patients in group II (remission).

3. Results

The results are shown in the following Tables and Figures.

Table (1). Clinical data in both groups of patients

	Relapse N=20	Remission N=20	t	p
Age of onset Mean±SD (Range)	**32±7.5(17-44)**	**26.5±6.6(16-44)**	**2.46**	**0.018***
Duration of disease Mean ±SD (Range)	**3.9±3 (0.5-11)**	**5.8±3.8 (1.5-15)**	**1.8**	**0.07**
Number of previous attacks Mean ±SD (Range)	**3.25±2.1 (1-8)**	**7.2±3.7(2-16)**	**4.13**	**< 0.001****
MMSE Mean ± SD(Range)	**26.25±1.4(24-30)**	**27.35±1.98(24-30)**	**2.04**	**0.048***
EDSS Mean ± SD(Range)	**3.95±1.8 (1-6.5)**	**3.8±1.9 (1-6.5)**	**0.3**	**0.76**

* Significant; ** highly significant

Table (2). Comparison between IL 15 and RANTES level between All cases and control

	Control N=20	Case N=40	t	P
IL 15	**25.0±9.23**	**56.07±20.88**	**-4.385**	**0.00****
RANTES	**18.2±3.62**	**35.37±14.1**	**-3.953**	**0.00****

Table shows highly significant increase in IL15 and RANTES in patient groups in comparison to control group.

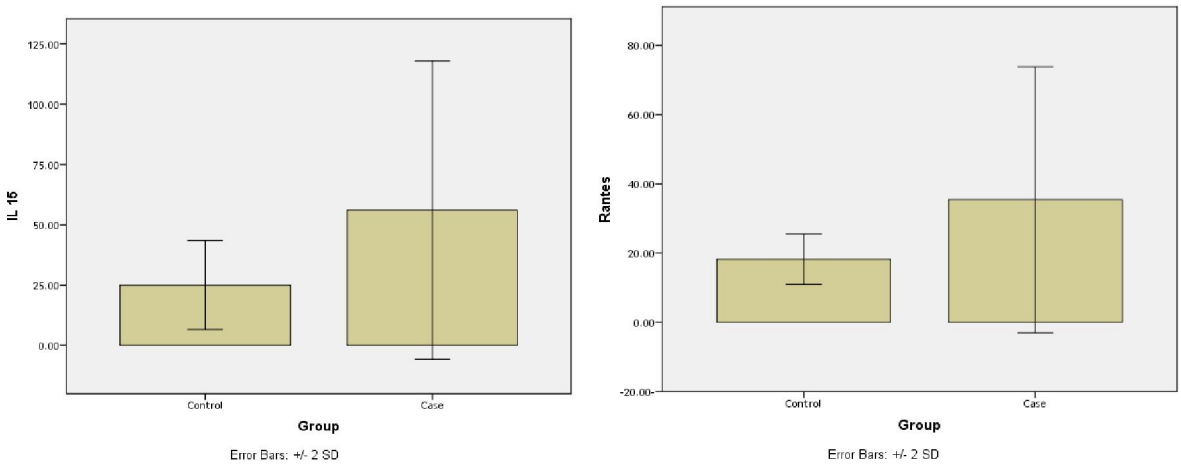

Fig.(1). IL 15 and Rantes level between cases and control

Table (3). Comparison between relapse group and remission group regard values of IL15 and Rantes

	Relapse N=20	Remission N=20	t	P
IL 15	**71.95±33.0**	**40.2±18.33**	**3.758**	**0.001****
Rantes	**46.25±19.9**	**24.5±10.4**	**4.323**	**0.000****

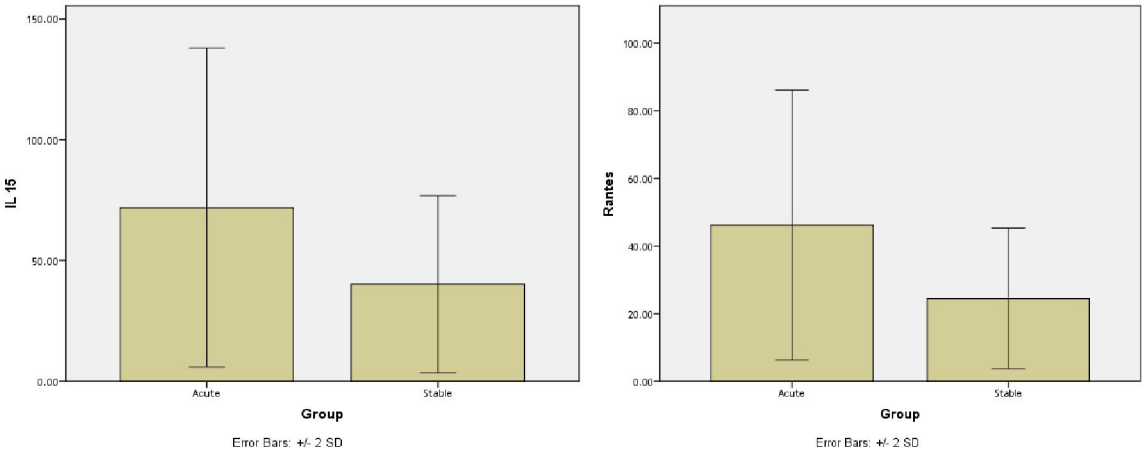

Fig.(2). IL 15 and Rantes level between the Relapse (Acute) group and Remission (stable) group

Table (4). Changes in IL15 and Rantes after corticosteroids Therapy in Relapse group

	Mean	Std. Deviation		
IL 15 before	**71.9500**	**33.03822**	**-1.32**	**0.21**
IL 15 after	**75.8000**	**38.11285**		
RANTES before	**46.2500**	**19.95225**	**4.81**	**0.00****
RANTES after	**36.5000**	**17.23369**		

** Highly sig.

Table (5). Correlation of MRI lesions to IL15, RANTES in our MS patients.

		IL 15	RANTES
Contrast enhancement	**R**	**.441****	**.451****
	P	**.004**	**.004**
Number of lesions	**R**	**.174**	**.176**
	P	**.284**	**.276**

** Highly sig.

Table (6). Correlation between IL15 with clinical variables in all Cases (relapse and remission groups)

Variable	IL 15	
	R	p
RANTES	**0.977****	**0.000**
Age of onset	**0.27**	**0.08**
Duration of disease	**-0.251**	**0.11**
MMSE	**-0.034**	**0.835**
EDSS	**-0.358***	**0.023**
Number of previous attacks	**-0.435****	**0.005**

*Significant correlation; ** Highly significant correlation; (-) means negative (inverse) correlation

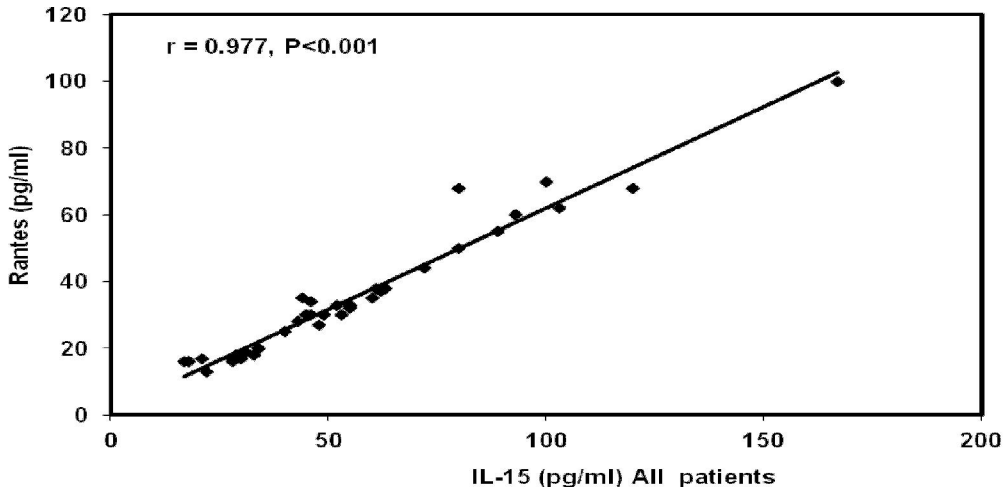

Fig. (3). Correlation between IL15 with RANTES in all Cases (relapse and remission groups)

Table (7). Correlation between RANTES with other variables in all Cases (relapse and remission groups)

Variable	RANTES	
	R	P
IL15	0.977**	0.000
Age of onset	0.33*	0.03
Duration of disease	-0.243	0.12
MMSE	-0.061	0.708
EDSS	-0.302	0.058
Number of previous attacks	-0.485**	0.002

*Significant correlation; ** Highly significant correlation; (-) means negative (inverse) correlation

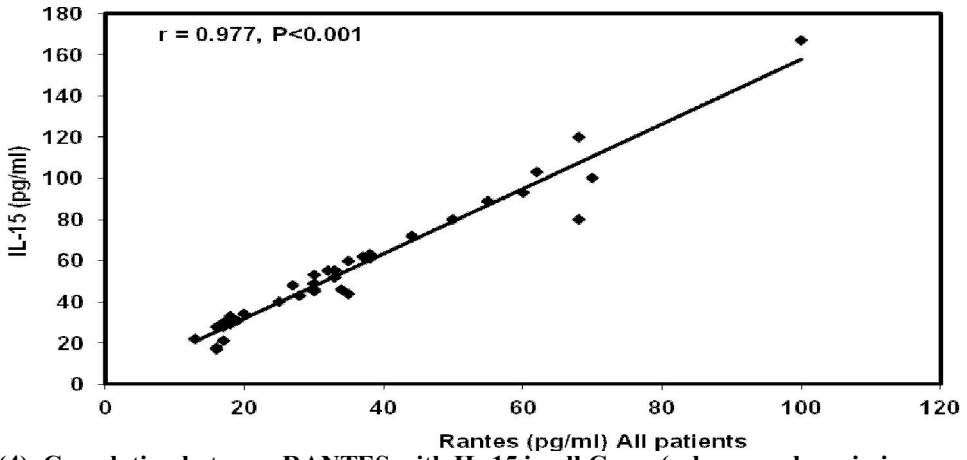

Fig.(4). Correlation between RANTES with IL-15 in all Cases (relapse and remission groups)

Table (8). Correlation between IL15 with other variables in relapse group

Variable	IL 15	
	R	p
RANTES	0.967**	0.000
Age of onset	0.135	0.570
Duration of disease	-0.262	0.264
MMSE	0.099	0.678
EDSS	-0.489*	0.029
Number of previous attacks	-0.391	0.088

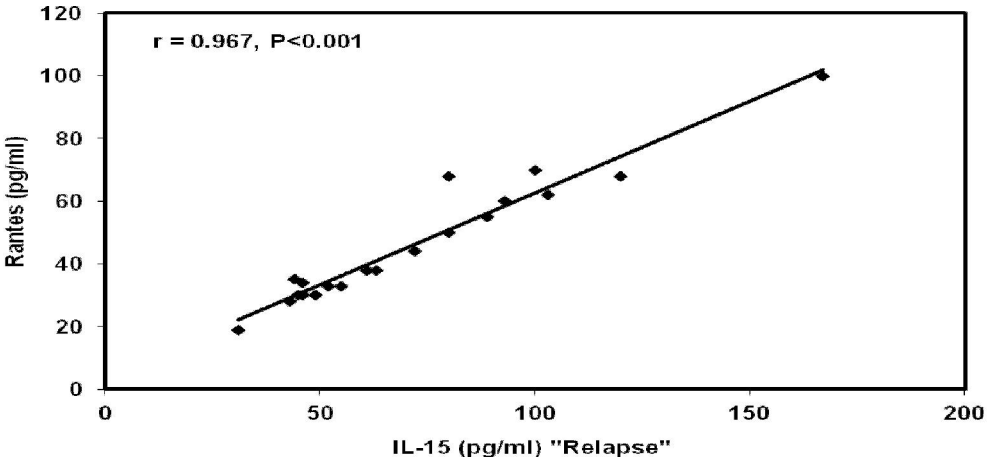

Fig. (5). Correlation between IL-15 and RANTES in relapse group

Table (9). Correlation between RANTES with other variables in relapse group

Variable	RANTES	
	R	P
IL15	0.967**	0.000
Age of onset	0.235	0.320
Duration of disease	-0.188	0.427
MMSE	0.101	0.670
EDSS	-0.472*	0.036
Number of previous attacks	-0.427	0.060

*Significant correlation; ** Highly significant correlation; (-) means negative (inverse) correlation

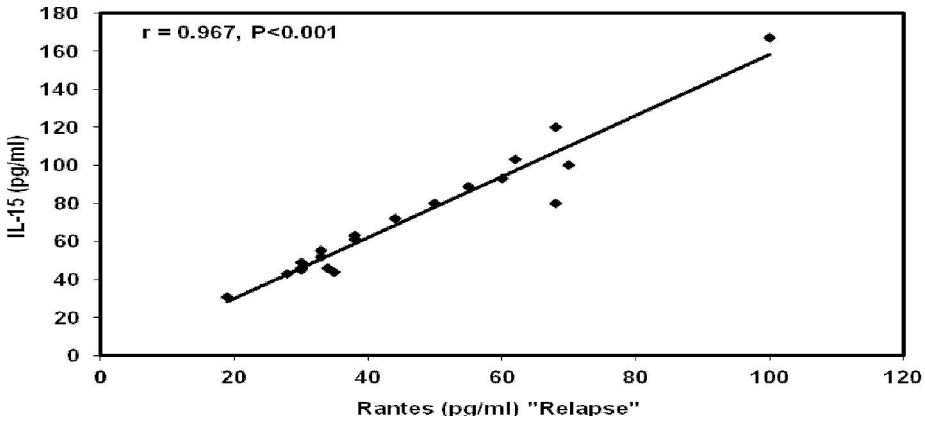

Fig.(6). Correlation between RANTES and IL-15 in relapse group

Table (10). Correlation between IL15 with other variables in remission group

Variable	IL 15	
	r	p
RANTES	0.979**	0.000
Age of onset	0.314	0.177
Duration of disease	0.039	0.869
MMSE	0.278	0.236
EDSS	-0.386	0.093
Number of previous attacks	-0.078	0.743

*Significant correlation; ** Highly significant correlation; (-) means negative (inverse) correlation

Table (11). Correlation between RANTES with other variables in remission group

Variable	RANTES	
	r	P
IL15	0.979**	.000
Age of onset	0.337	0.147
Duration of disease	-0.013	0.956
MMSE	0.269	0.251
EDSS	-0.334	0.151
Number of previous attacks	-0.131	0.581

*Significant correlation; ** Highly significant correlation; (-) means negative (inverse) correlation

4. Discussion

In the current study, we found that the mean age of onset of our MS patients was (34.1±8.1) years. This is near the figure reported by Yamout et al (2010) [30.2±10.2] [10] and Sidhom et al (2014) [30.3±9.5] [11]. Cognitive disturbances are increasingly being recognized as a prominent feature of MS; occurring in one third of patients with early relapsing remitting MS[12]. In the current study, we found that MS patients have a significant lower MMSE scores than control (26.25±1.4 Vs 29.13±1.01, respectively). Different authors (Jongen et al, 2012; Ruet, 2015; and Schoonheim et al, 2015) demonstrated the same results[13,14,15]. According to the EDSS criteria, our patients divided into people with MS who are fully ambulatory (EDSS steps 1.0 to 4.5), and those with the impairment to ambulation (EDSS steps 5.0 to 9.5). Death due to MS means (EDSS 10) [9]. We found 14 patients (70%) in remission group and 11 patients (55%) in relapse group, in the EDSS range of 1- 4.5. We found 6 patients (30%) in remission group and 9 patients (45%) in relapse group in the range of 5- 9.5, with no significant difference between the two groups. This result was against findings of Scalfari et al (2010) who found increase of disability scale in patients during relapse phase[16]. In our study, we found a significant increase in serum level of IL15 in our patients' groups compared to control. This finding is in concordance with that of Losy and Zaremba (2001), Blanco-Jerez et al (2002) who reported elevation of IL15 in MS patients [17,18]. On contrary, Hornig et al (2016) [27] could not discover a significant difference in serum IL15 in MS patients compared to control. However, it is not clear how exactly IL15 acts in the immune reactions of MS disease. Systemic origin of IL15 might be the result of infections triggering relapses of the disease [19]. It was previously thought to contribute to tissue damage by activating CD8-positive T cells [20]. Furthermore, IL15 attenuates the cytotoxicity of CD8-positive T cells via enhancement of the killer-inhibitory receptor CD94/NKG2A [21]. It is worth mention, that Wong et al (2015) mentioned that the elevated IL15 in MS patients suggested a Th2 cytokine profile and may serve to compensate for elevated Th1 cytokines levels and inflammation present in MS[28]. Regarding RANTES we found a significant increase in serum level in patients' groups in comparison to control group. This is in agreement with Iarlori et al (2000), van Veen et al (2007), and Rentzos et al (2010) who demonstrated elevated RANTES in MS patients(21,22&18) and disagreed with Kivisakk et al (1998) and Wong et al (2015) who found no evidence for elevated RANTES serum level in multiple sclerosis compared to control[28]. In the present study, there was a higher serum level of IL15 in relapse group patients compared to patients in remission group. Our results come to agree with Losy and Zaremba (2001) and Rentzos et al (2010)[5,16]. In contrast, Matsushita et al (2013) found that IL15 was levels were greater in the remission phase than in relapse phase [24]. RANTES serum level was higher among relapse group in comparison to remission group. This result goes in line with Iarlori et al (2000), Bartosik-Psujek and Stelmasiak (2005) and Rentzos et al (2010)[5,22,25]. Thus, the result of our work and other authors demonstrated that the chemokines are involved in the pathogenesis of MS and their activity is only linked to the relapse of the disease. The level of chemokines during a relapse maybe linked to a change in the lymphocytes Th1/Th2 activity (Bartosik-Psujek and Stelmasiak, 2005)[25]. We studied the changes in serum levels of IL15 and RANTES in relapse group patients after administration of corticosteroids mega dose. We found non-significant increase in serum level of IL15 after administration of corticosteroids, whereas a significant decrease in RANTES serum level was recorded after the same treatment. In accordance with our result, Rentzos et al (2010) found a significant increase of IL15 after corticosteroids administration in MS patients[5]. Furthermore, Matsushita et al (2013) found that during the relapse phase, IL15 levels were higher in their MS patients receiving prednisolone treatment than those without immunotherapy[24]. Therefore, they postulated that treatment with corticosteroids may convert the acute phase cytokines/chemokines profile towards the remission phase profile in relapsing remitting MS patients. On contrary, Blanco-Jerez et al (2002), in

their study mentioned that corticosteroids did not appear to affect IL-15 levels[18]. Regarding changes in serum level of RANTES after corticosteroid therapy, similar to our result, Bartosik-Psujek and Stelmasiak (2005) found a decrease in RANTES level immediately after steroid therapy[25]. In contrast, Rentzos et al (2010) found that corticosteroid treatment had no influence on serum levels of RANTES[5]. In our study we found that the IL15 serum level whether before or after steroids therapy in relapse group is significantly high in patients with EDSS less than 4.5. On the other hand, RANTES serum level had no significant relation to EDSS in relation to corticosteroid therapy. Rentzos et al (2010) didn't find any relation between IL15 or RANTES with the EDSS either before or after corticosteroid therapy[5]. In comparing MRI finding in our patient' groups, we found that the mean number of lesions in relapse group was 9.6 with SD 2.1 while in remission it was 8.6 with SD 3.1 with no significant difference. Regarding sites, the most common site in relapse and remission groups was juxta cortical, periventricular and spinal with a percentage of 40% and 45% of both groups respectively, with no significant difference. Nonetheless, a significant difference between both groups was recorded as regards contrast enhancement, which was higher in relapse group with mean of 3.5 while it was only 0.45 in remission group. This results was similar to findings of Gonzalez et al, (1987)[26]. Regarding the correlation of MRI lesions with IL15 and RANTES serum levels, we found highly significant correlations with contrast enhancement, whereas, no significant correlation was recorded as regards number of lesions in MRI with serum levels of IL15 and RANTES. These results were in line with Losy et al (2002)[17]. We studied in remission group, the correlation between IL15 and other clinical variables like age of onset, MMSE and number of previous attacks. We didn't find any correlation between this clinical data and IL15 in this patient group. This is in agreement with Rentzos et al (2010)[5]. We also correlated the IL15 with other clinical variables in patients of relapse group. In this group, we had a different correlation profile, as we found an inverse significant correlation with EDSS. On other hand, there was no correlation with age of onset, duration of the disease, and number of previous attacks. Regarding RANTES correlation with other variables in patients of relapse group, it was similar to that of IL15. As RANTES had inverse significant correlation with EDSS. On other hand, there was no correlation with age of onset, duration of the disease, MMSE and number of previous attacks. Bartosik-Psujek and Stelmasiak (2005), in their study demonstrated non significant correlations between RANTES levels and demographic parameters (age, sex) as well as clinical parameters (EDSS, duration of the disease, number of previous attacks)[25]. Furthermore, Van Veen et al (2007) observed a faster progression rate of disability in patients with the high producer allele for RANTES[23]. On the other hand, Rentzos et al (2010) found no correlation between RANTES serum levels and EDSS score or duration of the disease in patients with relapse[5].

5. Conclusion

We found increased serum levels of IL15 and RANTES in MS patients compared with healthy controls with significant correlations with clinical disability scale.

The elevated serum level of IL15 and RANTES is still elevated in remission compared to control and this indicates continuous subclinical pathology during remission.

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7/25/2016