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Correlation of Serum Levels of Interleukine-16, CCL27, Tumor Necrosis Factor-related Apoptosis-inducing Ligand, and B-cell Activating Factor with Multiple Sclerosis Severity

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ABSTRACT

The pathogenic roles of Interleukine-16 (IL-16), CCL27, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and B-cell activating factor **(**BAFF) has been shown in some autoimmune and inflammatory diseases. We aimed to correlate the circulatory changes of such factors with the severity of disease in patients with multiple sclerosis (MS).

This case-control study was conducted on 84 MS patients and 83 healthy controls. We measured the serum levels of IL-16, CCL27, TRAIL, and BAFF in all participants by enzyme-linked immune sorbent assay. Using the expanded disability status scale (EDSS), we evaluated the severity of MS. Finally, we assessed the correlation between serum levels of such factors with the severity of MS.

We found increased serum levels of CCL27, IL-16, and BAFF in patients with MS compared to those in healthy subjects. However, no difference was found in serum levels of TRAIL between the patients and controls. In addition, a significant positive correlation between serum levels of CCL27, IL-16, TRAIL, and BAFF with disease severity according to EDSS score was determined.

We showed higher serum levels of CCL27, BAFF, TRAIL, and IL-16 in MS patients with more severe disabilities than mild forms. Such finding may represent their contribution to the pathogenesis of MS. Blocking such molecules may yield new treatments for MS.

Keywords: B cell-activating factor; Chemokine CCL27; Multiple sclerosis; TNF-related apoptosis-inducing ligand

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INTRODUCTION

Multiple sclerosis (MS) is an autoimmune, inflammatory, and chronic central nervous system (CNS) disease[1] which causes multi-sensory and motor complications. The MS classification, based on clinical symptoms and severity, contains relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive relapsing MS (PRMS).[2] MS prevalence has increased all around the world[3,4] therefore; elucidating its associated mechanisms seems to be essential. Various cytokines such as tumor necrosis factor (TNF)-α,[5] interleukin (IL)-33, and IL-37[6] play important roles in the pathophysiology of MS. For example, TNF-α is associated with demyelination, oligodendrocyte cytotoxicity, and inflammation of CNS in MS disease;[5,7] and IL-33, as well as IL-37, are correlated with EDSS, criteria of disease severity in MS.[6]

IL-16, as an inflammatory and chemoattractant cytokine,[8] is produced by CD8+[9] as well as CD4+ T cells[10] and B cells.[11] Having activated after the cleavage of the C-terminal region of pro-IL-16,[12] IL-16 shows multiple functions. It leads to the elevation of other inflammatory cytokines such as IL-1β, IL-6, and Tumor Necrosis Factor (TNF)-α by monocytes.[13] Also, the overexpression of IL-16 leads to activation of CD4+ T cells in special inflammatory sites such as the respiratory tract.[14] The IL-16-induced migratory response is significantly increased with the accompaniment of its receptor, namely CCR5.[15] IL-16 is expressed in CNS and contributes to the distinction of developmental stages in microglial cells during fetal CNS ontogeny.[16] Therefore, it may be a valuable marker for microglial cell activation in CNS.[17] Also, IL-16 has an important role in the pathophysiology of CNS disorders such as brain tumors.[18]

Numerous cells such as astrocytes express chemokine ligand 27 (CCL27).[19] Having bound to its receptor, namely CCR10, CCL27 is induced by inflammatory cytokines including TNF and IL-1.[20,21] CCL27 produced by keratinocytes in which contributes to skin homeostasis[20] and T cell-mediated skin inflammation.[21] Also, The CCL27 and its receptors are expressed in microglia, oligodendrocytes, astrocytes, and neurons which it can have important roles the recruitment of T cells to CNS.[22,23]

Recent studies suggest that members of the tumor necrosis factor (TNF) protein family contribute to tissue inflammation and increase of co-morbidities in different immune-mediated diseases.[24,25] TNF-related apoptosis-inducing ligand (TRAIL), a member of the TNF superfamily,[26] has different roles in inflammatory diseases such as stroke,[27] trauma,[28] infections,[29] and MS.[30] The main mechanism of such role is the induction of apoptosis through Fas-associated protein in conjunction with death domain/death-inducing signaling complex (FADD/DISC)/caspase-8in several cell types such as oligodendroglia and neurons.[31]

B cell-activating factor (BAFF), the other member of the TNF superfamily produced by myeloid cells such as dendritic cells, monocyte/macrophages, and neutrophils,[32] has a significant role in several inflammatory diseases such as Sjogren's syndrome,[32] rheumatoid arthritis,[33] systemic lupus erythematosus,[34] and MS.[35] The main mechanism of this factor is through the interaction of BAFF to BAFF receptors which activates non-canonical and classical NF-κB signaling pathways[34,35] on different cells such as neurons.

Considering limited studies on serum levels of IL-16, CCL27, TRAIL, and BAFF cytokines in MS patients, we aimed to evaluate their serum changes in such patients. If our study confirms their correlation with the severity of MS, it may propose their prognostic as well as therapeutic values.

MATERIALS AND METHODS

Study Subjects

We performed our case-control study on 84 patients with MS in the remission phase for at least 3 months. MS was defined by a neurologist according to McDonald's Criteria 2017. Which uses MRI scan and clinical manifestations which fulfills dissemination in time and space. Expanded Disability Status Scale (EDSS) was used as a routine method for assessment of the disability in MS. It evaluates the severity of disability in 8 Functional Systems including pyramidal, cerebellar, brainstem, sensory, bowel & bladder, visual, cerebral, and other organs. Any other acute/chronic infectious, inflammatory, as well as autoimmune disease and pregnancy, was considered as an exclusion criterion. In addition, 83 healthy volunteers without a family history of RRMS were enrolled as the control group. Our study was approved by the local ethics committee (IR.KAUMS.REC.1395.78). Informed consent was obtained from each participant.

Experiments

Peripheral blood taken from each participant was used to measure the serum levels of CCL27, IL-16, TRAIL and BAFF using commercially available enzyme-linked immune sorbent assay (ELISA) kits [MyBiosource, USA for CCL27 (detection range: 313-20000 pg/mL) and IL-16 (detection range: 31.2-2000 pg/mL); R&D, USA for TRAIL (detection range: 15.6-1000 pg/mL) and BAFF (detection range: 62.5-4000 pg/mL)] according to manufacturer's instructions. Samples were analyzed in duplicates and mean the serum levels of TRAIL and BAFF reported in pg/mL in each group.

Statistical Analysis

The serum levels of CCL27, IL-16, TRAIL, and BAFF were analyzed by independent t and chi-square tests. We evaluated the normal distribution of all quantitative parameters by the Kolmogorov-Smirnov test. Correlations between variables were calculated by Spearman's correlation coefficient. The backward method of multiple linear regression analysis was used to explore the simultaneous effects of various factors on those cytokines. Adjusted R Squared was considered as a criterion of the goodness-of-fit test, and $p<0.1$ was determined as a criterion of exclusion from the model. Using area under curve (AUC) analysis, we determined the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) for each cytokine as a marker of MS diagnosis. ROC curve was drawn for each cytokine. $p<0.05$ was considered statistically significant.

RESULTS

Table 1 shows the clinical and laboratory characteristics of the patients and controls. The mean serum levels of CCL27, IL-16, and BAFF in patients with MS were significantly higher than those in healthy

Table 1. Basic and clinical characteristics of patients with multiple sclerosis (MS) and health subjects

		MS patients	Healthy subjects	*p*
Number of subjects		84	83	-
Male/female		15/69	35/48	**0.001**
Age (years)		35.21±12.04	35.49±10.56	0.061
Positive Family history		7 (8.3%)	-	-
Disease duration (years)		5.83±4.45		
Treatment duration (years)		3.15±3.31		
Kind of MS	CIS (%)	5(6)		
	RRMS (%)	69(82.1)		
	PPMS (%)	1(1.2)		
	SPMS (%)	7(8.3)		
	PRMS (%)	2(2.4)		
Drugs used	Cinovex	63(75)		
	Relief	10(11.9)		
	Betaferon	2(2.4)		
	Others	2(2.4)		
	No drug	7(8.3)		
EDSS	CIS	0.5±1.11		
	RRMS	2.07±1.45		
	PPMS	6		
	SPMS	4.93±1.43		
	PRMS	6.25±0.35		
CCL27 (pg/mL)		2804.05±3714.4	953.05±352.77	**<0.001**
IL-16 (pg/mL)		132.93±64.65	81.85±55.85	**<0.001**
TRAIL (pg/mL)		78.15±43.5	71.81 ± 34.52	0.297
BAFF (pg/mL)		68.23±15.88	17.78 ± 10.01	**<0.001**

subjects (p<0.001). However, there was no significant difference in serum levels of TRAIL in patients with MS compared with healthy subjects (p=0.297).

The correlation of serum levels of CCL27, IL-16, TRAIL, and BAFF with different parameters in MS patients is shown in Table 2. We found significant correlations between the serum levels of CCL27, IL-16, TRAIL, and BAFF with EDSS.

Using Linear regression coefficients for evaluating the factors affecting EDSS, we found that age, TRAIL, and BAFF serum levels had a significant positive correlation with EDSS (t=4.47, p<0.001; and t= 6.17, p<0.001, t=6.81, p<0.001; respectively) (Table 3).

Cut-off Points and Predictive Values

Using the ROC curve and AUC, we tried to determine the sensitivity and specificity of CCL27, IL-16, TRAIL, and BAFF as diagnostic markers of MS (Figure 1 and Table 4). BAFF had the most specificity, PPV, and NPV in the cut-off point of 28.65 as 92.9%, 91.5%, and 80.4%; respectively.

Table 2. Bivariate correlation between serum levels of chemokine ligand (CCL) 27, Interleukin (IL)-16, TNF-related apoptosis-inducing ligand (TRAIL), and B cell-activating factor (BAFF) with different parameters in multiple sclerosis (MS) patients

Variables	CCL27		IL-16		TRAIL		BAFF	
	CC*	*p*	CC*	*p*	CC*	*p*	CC*	*P*
CCL27	1.000	-						
IL-16	0.092	0.239	1.000	-				
TRAIL	0.269	<0.001	-0.040	0.609	1.000	-		
BAFF	0.595	<0.001	0.157	0.042	0.283	<0.001	1.000	-
Age	0.172	0.027	0.007	0.930	0.003	0.968	0.180	**0.021**
Number of relapses	0.433	<0.001	-0.148	0.179	0.500	<0.001	0.367	**0.001**
EDSS	0.827	<0.001	-0.228	0.037	0.659	<0.001	0.778	**<0.001**
Diseaseduration	0.496	<0.001	-0.045	0.685	0.236	0.031	0.257	**0.018**
Treatment duration	0.263	0.016	0.055	0.621	0.168	0.129	0.120	0.281

*CC=Spearman's Correlation coefficient

Table 3. Linear regression coefficients in evaluating the factors affecting the expanded disability status scale (EDSS) in patients with multiple sclerosis (MS)

Variables	Unstandardized Coefficients		Standardized Coefficients	***t	Sig.	Adjusted R Square
	*B	Std. Error	**Beta			
(Constant)	-2.531	0.400		-6.329	**<0.001**	0.715
Age	0.044	0.010	0.278	4.473	**<0.001**	
TRAIL	0.017	0.003	0.405	6.174	**<0.001**	
BAFF	0.055	0.008	0.464	6.818	**<0.001**	

*B: coefficient of multiple linear regression in our regression model in which "EDSS" and "AGE, TRAIL, BAFF" have been considered as dependent and independent variables, respectively. Such model could be demonstrated as: EDSS=Constant+0.044ˣAge+0.017ˣTRAIL+0.055ˣBAFF

**Beta: coefficient of multiple linear regression in our regression model without considering "Constant" value. Such model could be demonstrated as: EDSS=0.278ˣAge+0.405ˣTRAIL+0.464ˣBAFF

*** t: a statistic value related to our model which shows the significant effect of each variable presented by p-value.

Table 4. Sensitivity, specificity, and predicting values of interleukin (IL-16), chemokine ligand (CCL27), TNF-related apoptosis-inducing ligand (TRAIL), and B cell-activating factor (BAFF) serum levels in multiple sclerosis (MS) diagnosis

Variable	Cut point	Sensitivity	Specificity	Positive	Negative	Area under
IL-16	80.85	79.8	61.9	67.7	75.4	0.75
CCL27	1247.5	70.2	89.3	86.8	75	0.827
TRAIL	60	63.1	50	55.8	57.5	0.539
BAFF	28.65	77.4	92.9	91.5	80.4	0.872

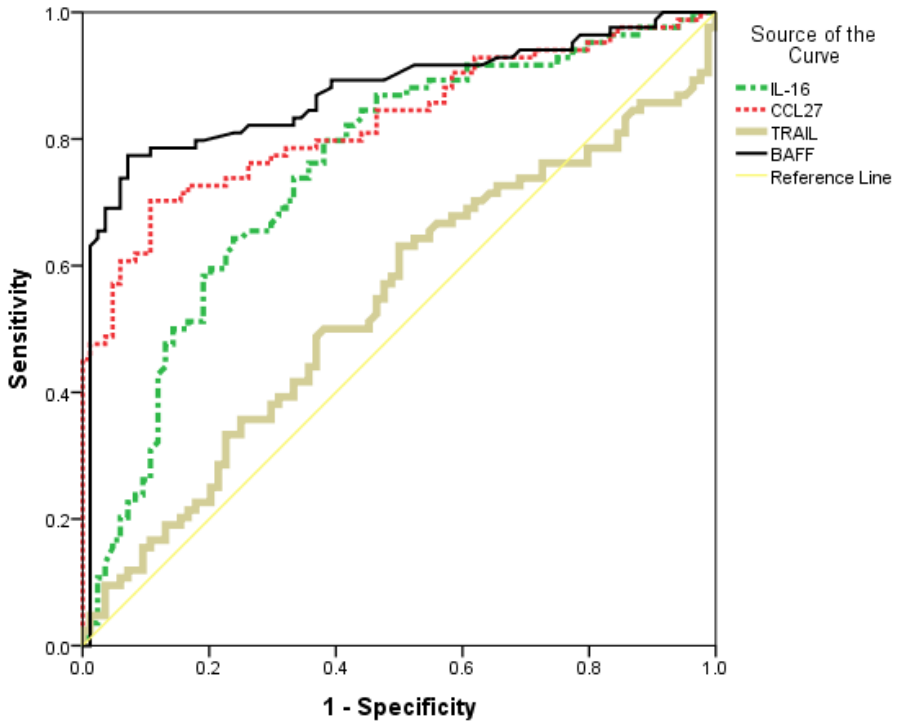

Figure 1. ROC curve demonstrating the sensitivity and specificity of interleukin (IL)-16, chemokine ligand (CCL) 27, TNF-related apoptosis-inducing ligand (TRAIL), and B cell-activating factor (BAFF) as diagnostic criteria of multiple sclerosis (MS) severity.

DISCUSSION

Our data indicated that there is a significant correlation between serum levels of CCL27, TRAIL, IL-16, and BAFF with the severity of MS. Such findings may reveal that some pathophysiology of MS is induced by these mentioned cytokines. Following our study, others also found increased serum levels of IL-16[36-38] or some of its polymorphisms[39]in MS patients which could be reduced by treatment with interferon β1a.[36] The CD4+ T-cell infiltration in the CNS is related to the elevation of IL-16 in MS brain lesions[37] which in turn can induce Th1 cell migration by CCR5.[13] In this way, we may consider that such a vicious cycle gradually worsens the MS condition.[15] Although inflammatory,[37] as well as apoptotic effects[40] of IL-16, may increase its serum levels in MS diseases, treatment may reverse such increased levels,[36] a phenomenon that may be

happening in our patients after more longitudinal periods of treatment duration.

In line with others,[40,41] our data demonstrate an increased serum level of CCL27 in patients with MS compared to healthy subjects. CCL27 may stimulate autoreactive T cell migration into brain tissue in MS disease, and lead to increased brain inflammation.[40] The CCL27 and its receptors are expressed in microglia, oligodendrocytes, astrocytes, and neurons and can contribute to neuronal death.[22] Interferon β as a treatment option in MS patients may inhibit the production of CCL27 and in this way inhibit CCL27 inflammatory effects.[23]

According to our results, BAFF serum levels were significantly higher in MS patients along with a significant positive correlation with the severity of the disease. In line with ours, the other study showed that basal BAFF serum levels of MS patients were significantly higher than those in the control group at least during the first six month-interferon β therapy.[42] In this regard, Dooley J et al, also showed that using drugs targeting BAFF levels such as interferon β and Fingolimod may lead to better control of MS from the point of decrease the relapses and the diseasing severity or progression.[43] Practical proof for a contributory link between high BAFF levels and B cell-dependent auto-immunities such as MS has been obtained in animal models.[44,45] Auto-reactive B cells appear to be particularly reliant on BAFF for survival and induce their pathology when more quantities of BAFF are existing.[46] Such elevated BAFF levels have also been demonstrated in cerebrospinal fluid of MS patients with a significant positive correlation with MS disability.[47]

Except ours, the only other study performed on the serum changes of BAFF and soluble form of TRAIL in MS patients showed its higher levels concomitantly with its lower surface expression on lymphocytes.[42] TRAIL may have its role in the pathogenesis of MS by inducing apoptosis in neurons and oligodendroglia.[31]

The main limitation of our study was that we did not correlate the changes of selected cytokines with the severity of disease during the cross-sectional times of the treatment period. Furthermore, we did not assess functional assays to clarify mechanisms by which such cytokines influence the fate of the disease. However, our study delivered a new cocktail of cytokines that have not been investigated enough yet in ambiguous pathology of MS.

Our data showed elevated serum levels of CCL27, BAFF, and IL-16 in MS patients correlated with more severe disability. Such finding may represent their contribution to the pathogenesis of MS and may also yield new prognostic as well as therapeutic biomarkers for MS.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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