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CEREBROSPINAL FLUID (CSF) IL-17A, IL-17F, IL-34 AND CXCL-13 LEVELS IN AMYOTROPHIC LATERAL SCLEROSIS (ALS/MND) PATIENTS

ABSTRACT

In this study, our clinic follow-up ALS/MND diagnose the cerebrospinal fluid of patients (CSF), IL-17A, IL-17F, IL-34 cytokines and CXCL-13 chemokine to evaluate the levels. that were determined by ELISA. In our study, significantly higher in the patient group and the proinflammatory cytokine, IL-17A and IL-17F of endothelial cells, fibroblasts and also known to be expressed in neurones. However, CXCL-13 level is considered among the patient group and the control group was not statistically significant difference. IL-34 also to be increased when compared to the patient group (n=4) than the control group (n=6), a recently described cytokine due to the IL-34 Th17 with modulating immune pathogenesis and immune with cytokines released from cells in a short time to be involved ALS/MND such as rare as to be made further studies for the diagnosis of a disease to a powerful new biomarker may and science has been suggested to contribute in this respect.

Keywords: ALS/MND, IL-17, IL-34, CXCL-13, Patient

1. INTRODUCTION

Amyotrophic lateral sclerosis/Motor Neuron Disease (ALS/MND) is a disease that affects the nerve cells in the brain and spinal cord, causing progressive weakening of extremity, respiratory and bulbar muscles, leading to loss of upper and lower motor neuron, weakness and spasticity characterized by degeneration of cortical, brain stem and spinal motor neurons (MNs), progressive and usually resulting in death within a few years [1 and 2]. Usually patients survive for 3-5 years after the initial diagnosis [3 and 4]. It has about 1-2 incidence per 100,000 person every year. Familial forms have been reported in approximately 10% of cases and sporadic [5]. ALS/MND is an adult-onset motor neuron disease with a risk of 1/400. It represents the third most common neurodegenerative disease after Alzheimer's and Parkinson's disease. Motor neurons extend from the brain to the spinal cord and from the spinal cord to the muscles. Progressive degeneration of motor neurons in ALS/MND results in death. Voluntary muscle movements are gradually affected, people lose their ability to talk, eat, move and breathe. Motor neurons that provide voluntary movements and muscle control are affected in ALS/MND patients [2 and 6].

Although the cause of ALS/MND is unknown, scientists have taken an important step in determining the cause in 1993 when they discovered that mutations in genes producing Cu/Zn superoxide

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dismutase (SOD1) enzyme were associated with some cases (about 20%). This enzyme is a powerful antioxidant that protects the body from damage caused by superoxide, a toxic free radical produced in mitochondria [7]. The first ALS linked gene is superoxide dismutase-1 (SOD1) [7]. In their 2011 study, Andersen and al-Chalabi concluded that at least fifteen genes involved in different cellular pathways were associated with ALS and that multiple cellular diseases contributed to pathogenic mechanisms [5]. These include oxidative stress, mitochondrial dysfunction, protein aggregation, impaired anterograd and retrograde transport, neuroinflamation, disregulated RNA signaling and glutamate (Glu) mediated excitotoxicity [8 and 9]. There is a lot of evidence in the ALS that shows mainly high levels of Glu-mediated excitotoxicity [10]. Glu-1 expression was decreased in the affected regions of the CNS and high levels of extracellular Glu were observed. The strategy applied in the clinic to slow the progression of disease in ALS is based on this basis [11 and 12].

In recent years, more than 20 genes were found to be associated with ALS according to the results of studies performed with ALS cases. It has been observed that these genes are especially associated with C9FOR72, TARDBP, FUS and SOD1 [13]. Charcot is known as the first scientist to describe ALS in 1869, but ALS/MND pathogenesis is unknown and effective treatments are still not available [14]. It is known that many studies are still needed to understand the cause of ALS, including the pathogenesis of ALS, inflammation/neuroinflammation during the disease, immune responses, immune mechanisms, and body response against to stress. Cytokines and chemokines are intracellular mediators that play a key role in inflammation and have been shown to increase in some inflammatory disorders of the brain [15 and 16]. Naive T cells differ to the Th1, Th2, Th17, Treg and Tfh cells depending on the nature of the antigenic stimulation and the cytokine environment. Cytokines and chemokines may play a role as a potential biomarker in a number of diseases by showing different properties despite the increase in many inflammatory diseases. As in our study, cytokine and chemokine studies in patients with ALS and cerebrospinal fluid remain limited [17 and 18].

Idiopathic intracranial hypertension (IIH) is defined as increased intracranial pressure in case of meningeal inflammation, venous occlusion and absence of any structural lesions. The incidence of this disease, which is more common in women, varies between 11-58 years. The pathogenesis is not known yet. Nevertheless, it is thought that the reasons such as drug use, exposure to toxic substances and underlying chronic disease are effective [19 and 20]. Studies of cytokines and chemokines (IL-1β, TNF, IL-17, IL-10, IP-10 etc.) in CSF and serum samples of IIH patients have been performed but have been limited [21]. Studies of cytokines and chemokines (IL-1β, TNF, IL-17, IL-10, IP-10) in CSF and serum samples of IIH patients have been performed but have been limited (Dhungana et al. 2009). Edwards et al in their study of the level of IL-17 CDIP, CIS, according to the IIH group have found higher in MS patients [22].

Interleukin-17 (IL-17) is a proinflammatory cytokine that plays a key role in host defense against extracellular bacterial and fungal infections. IL-17 was described in 1995 and plays a role in autoimmunity. T helper 17 (Th17) cells play an important role in the production of IL-17. Upregulation or elevation of IL-17 has been associated with various inflammatory disorders including psoriasis, psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis [23 and 24]. Although it is known to date that there are 6 homologues (IL-17A from IL-17F to IL-17F) among them, IL-17A and IL-17F are much more similar to each other as function and receptor [25].

Interleukin-34 (IL-34) is a novel cytokine identified in a comprehensive proteomic analysis as a tissue-specific ligand of the colony stimulating factor-1 (CSF-1) receptor (CSF-1R) in 2008. Structurally, IL-34 is a short-chain helical hematopoietic cytokine. Physiologically, IL-34 expression consists of Langerhans cells, endothelial cells, fibroblasts, and neurons. In any pathological condition; it is a cytokine that can be induced and regulated by a transcription factor which called nuclear factor kappa B (NF-κB). In addition to cellular adhesion and migration, it leads to activation of various signaling pathways that regulate major cellular functions including proliferation, differentiation, survival, metabolism and cytokine/chemokine expression. IL-34 is a specific cytokine that contributes to the development and preservation of brain microglia and Langerhans cells in the skin. In contrast to a newly entered cytokine in the interleukin family, and a hematopoietic cytokine, the role of neuroinflammatory is worth discussing [26]. IL-34 is also a cytokine capable of excreting IL-17 into Th17 cells. Therefore, IL-17 and Il-34 levels have been investigated in this study. CSF chemokine (C-X-C motif) ligand 13 (CXCL13) is an early marker of Lyme neuroboreliosis (LNB). It is known as chemokine ligand 13 (CXCL13) and is diagnosed as a B cell chemoattractant and supports the formation of B cell follicles that are important in the pathophysiology of Multipl Sclerosis (MS). CXCL13 increases in CSF of patients with various forms of MS, and its level appears to be correlated with disease activity. CXCL13 is a promising CSF biomarker for evaluating activity in CSF of patients with various forms of MS. However, studies are insufficient, and the results are not yet reliable enough to suggest its use in routine clinical practice [27 and 28].

2. RESEARCH SIGNIFICANCE

When the literature information is evaluated, our study is planned with the hypothesis that increasing IL-17 in many inflammation, increasing IL-34 causing secretion of IL-17 and CXCL-13 increase in MS patients also may be seen in ALS/MND patients. What role does the immune system play in the pathogenesis of ALS? For the answer to this question, how much more experimental and/or case studies should be done. It is a fact that the immune system and its components play a role in the pathogenesis of ALS, but the results of these cells, antibodies and cytokines are limited. In ALS, the diagnosis is based on clinical symptoms and the presence of biomarkers specific to ALS requires an early and definitive diagnosis and the development of medicines to treat the disease [29 and 30].

3. MATERIAL AND METHOD

This study was performed in accordance with the Declaration of Helsinki, having obtained approval (No: 2018/203) from the local ethics committee. Patients with ALS/MND diagnosed who were followed-up at the Neurology Clinic of Abant Izzet Baysal University Education Research Hospital and who had previously received CSF samples and were kept at -80°C were included in the study. IIH (n=6) and patients with ALS/MND (n=4) who were previously taken in Abant İzzet Baysal University Education and Research Hospital Neurology Clinic and who had previously taken CSF samples at -80°C were included in our study. In our study, IL-17A (Elabscience, USA), IL-17F (Cloud-Clone, USA) IL-34 (Elabscience, USA), cytokines and CXCL-13 (Euroimmun, Lubeck, Germany) chemokine levels (pg/mL) ELISA kit were determined by taking into consideration the manufacturer's recommendations. All CSF samples were kept at -80°C C until the working time. Levels of three cytokines (IL-17A, IL-17F and IL-34) (pg/mL) were investigated by ELISA

(Elabscience and Cloud-Clone, USA). Chi-square test was used for statistical analysis and T-Tests and non-parametric Mann-Whitney (Kolmogorov-Smirnov Z) tests were used for parametric tests. The significance level was determined as α=0.05. In both groups, CSF biochemical values of one case could not be reached.

4. RESULTS

The median age (min-max) of the patient with ALS/MND and the IIH group, respectively; 58 (37-73), 48 (36-58) and there was no statistically significant difference between the two groups (p=0.1) (Table 1). When comparing the differences between cytokine and chemokine levels (Figure 1), CSF biochemical parameters were also reviewed and summarized as in Tables 2 and 3.

Table 1. Age, cytokine and chemokine values between groups

Groups (n=10)	ALS/MND n=4	IIH n=6	p value
Age Median (min-max)	58 (37-73)	48 (36-58)	0.1*
IL-17A (pg/ml)	56 (47-86)	3 (1-4)	*0.02**
IL-17F (pg/ml)	14 (8-26)	2 (1-3)	*0.02**
IL-34 (pg/ml)	86 (69-130)	3 (2-11)	*0.02**
CXCL-13 pg/ml	2 (2-12)	3 (1-3)	0.6*

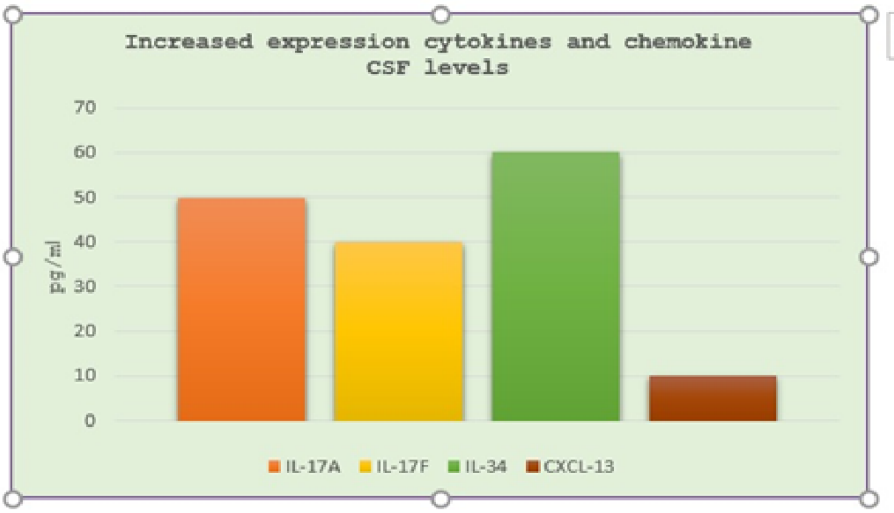

Figure 1. Cytokine and chemokine levels in CSF of ALS/MND patients

Table 2. CSF biochemical parameters

ALS/MND (n=4) IIH (n=6)	CSF Protein	Serum Protein	CSF Albumin	Serum Albumin	CSF Glucose	Serum Glucose
ALS/MND 1.	46.50	7.40	28.40	3.70	60.00	105.00
ALS/MND 2.	120.00	6.20	25.60	3.40	70.00	136.00
ALS/MND 3.	-		-	-	-	-
ALS/MND 4.	23.60	7.20	12.50	3.80	95.00	137.00
IIH 1.	24.30	6.80	13.50	4.30	63.00	117.00
IIH 2.	39.20	7.20	25.00	4.10	56.00	75.00
IIH 3.	-	-	-	-	-	-
IIH 4.	37.60	7.00	20.00	4.00	53.00	78.00
IIH 5.	17.00	7.50	7.80	4.00	71.00	92.00
IIH 6.	46.80	6.60	30.50	3.80	61.00	100.00

Table 3. Interleukin and chemokine values in CSF

ALS/MND (n=4) IIH (n=6)	IL-17A	IL-17F	IL-34	CXCL13
ALS/MND 1.	46.81	10.37	130.28	12.31
ALS/MND 2.	54.07	18.27	75.12	1.92
ALS/MND 3.	86.34	7.71	96.14	1.92
ALS/MND 4.	57.69	26.24	68.52	1.88
IIH 1.	1.73	1.44	6.81	1.94
IIH 2.	3.62	3.08	11.21	1.74
IIH 3.	3.31	1.34	3.61	2.22
IIH 4.	2.24	1.24	3.12	1.21
IIH 5.	1.12	2.78	2.01	1.15
IIH 6.	3.67	1.72	3.12	3.24

In the study, there was a statistically significant increase in IL-17A and IL-17F cytokines which are important in ALS/MND both in Th17 and IL-17F cytokines, which are important in the destruction of Th17 cells. for each three cytokines p=0.02). However, there was no statistically significant difference between CXCL-13 levels and the control group, which is known as an important marker in Lyme patients who were included in the neurological diseases group (p=0.6).

5. DISCUSSION

ALS/MND is a neurodegenerative disease that causes death within 3-5 years without a defined cause or effective treatment [31]. 90% of ALS/MND cases are sporadic (Sals), probably caused by exposure to environmental factors, while only 10 percent are familial (fALS). It has been reported by AL-Chalabi et al. that ALS appears to have a lot of similarity with cancer and that it occurs with the effect of multi-stage environmental factors as time progresses in genetically susceptible individuals [32 and 33]. How inflammation contributes to pathogenesis of various neurodegenerative diseases, including ALS [34], Alzheimer's disease (AD) [34 and 35], and Parkinson's disease (PD) [36] is still unclear and involves a very complex process. Inflammatory processes have been discussed in neuropathological studies on motor system of ALS patients [34, 37 and 38].

Neuroinflammation is increasingly recognized as an important mediator of progression in ALS/MND patients and is characterized by peripheral monocytes and lymphocytes that are associated with central nervous system (CNS) microglia and astroglia. Anti-inflammatory and neuroprotective factors trigger early stage of the disease, inflammation becomes proinflammatory and neurotoxicity occurs as the progression of the disease accelerates. In this way, motor neurons are damaged by multiple mechanisms arising from cell mutations and environmental factors. Damaged motor neurons secrete agents/agents/antigens that stimulate inflammatory processes produced by peripheral glial cells in the CNS, as well as environmental, neural and adaptive immune cells [29, 39 and 40]. In a recent study, sodium nitrite, known as NP001, has been shown to be an agent acting on inflammatory monocyte/macrophage in CNS and plays a role in slowing the progression of ALS [41]. Since cytokines and even chemokines, which are involved in inflammatory process/inflammation, present potential targets for ALS treatment, many studies have been done on their role in immune response. In particular, pro-inflammatory cytokines are known to be an important factor in ALS when the congenital immune system activation is thought [42 and 43]. Cytokines are key modulators of inflammation that participate in acute and chronic inflammations through a complex, sometimes seemingly

conflicting network of interactions. A better understanding of how these paths are arranged helps facilitate the more accurate identification of inflammatory agents and treatment of inflammatory diseases. It is possible to classify according to the structure of the immune response cytokines, each cytokines carry out special roles depending on the type and location of the cell [18, 44 and 45].

In many studies conducted with ALS pathogenesis and cytokines, proinflammatory cytokines, IL-17 released from Th17 cells showed an increase in serum samples of ALS patients compared to control groups (except for autoimmune diseases) [46]. In our study, as in serum samples, increased IL-17 level in CSF samples of ALS patients was found to be significant and it is consistent with the literature. In addition, the upregulation of IL-34 levels in ALS CNS samples, like IL-17, suggests that IL-34 may be a new biomarker and/or an agent for effective treatment of neurodegenerative diseases. However, there was no significant difference between the groups of patients and control subjects in the CXCL-13 chemokine, which is thought to be high in ALS CNS samples because of its high incidence in Multipl Sclerosis and Lyme patients. Until new studies, CXCL-13 continues to be a biomarker for Multipl Sclerosis and Lyme patients [34 and 37].

6. CONCLUSION

ALS is a neurodegenerative disease which is not known yet because of its treatment and pathogenesis. In addition to genetic factors, environmental factors such as vitamin deficiency may play a role in ALS mechanism. Especially the recent increase in autoimmune diseases suggests that this mechanism may be among the risk factors of ALS. Studies on cytokines suggest that a cytokine that is specifically known for a particular disease has increased in a different disease and may show a common feature between the two diseases. Therefore, in clinical cases, cytokine and chemokine measurements in samples such as CSF and serum may help to determine the pathogenesis and mechanism [47 and 51]. The results of the study showed that the high levels of proinflammatory cytokine IL-17A and IL-17F, which were significantly higher in ALS/MND, increased IL-34, which is also known to be expressed from endothelial cells, fibroblasts and even neurons were also increased in the patient group compared to the control group. Since it is a newly defined cytokine, IL-34 is known to play a role in immune pathogenesis and immune modulation with cytokines released from Th17 cells. Further studies are needed to diagnose a rare disease such as ALS/MND in a short time. It could be a new and powerful biomarker and it was thought that it would contribute to science.

NOTICE

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