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RESEARCH ARTICLE

Does cerebrospinal fluid IL-17F distinguish normal pressure hydrocephalus from dementia?

Şeyda Karabörk[1], **Hümeyra Çelik**[2], **Şule Aydın Türkoğlu**[3]

[1]Department of Medical Microbiology, Faculty of Medicine, Bolu Abant İzzet Baysal University, Bolu, Türkiye.
[2]Department of Physiology, Faculty of Medicine, Alaaddin Keykubat University, Antalya, Türkiye.
[3]Department of Neurology, Faculty of Medicine, Bolu Abant İzzet Baysal University, Bolu, Türkiye.

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ABSTRACT

Aim: The neurological disorder known as normal pressure hydrocephalus (NPH), which has an unknown cause, may be treatable, and is defined by a clinical triad of symptoms. A phenomenon known as dementia refers to a decline in cognitive performance that goes beyond what may be anticipated from the typical effects of biological aging. The symptomatic similarity between these two diseases causes problems in diagnosis. The objective of our study was to compare the concentrations of IL-17A, IL-17F, IL-34, and CXCL13 in the cerebrospinal fluid (CSF) of patients with NPH and dementia for an informative laboratory diagnosis.

Methods: The study included NPH and dementia cases (n=7, n=5, respectively) taken from the patients's CSF sample by lumbar puncture (LP). The levels of IL-17A, IL-17F, IL-34, and CXCL13 were measured in the CSF of patients' with NPH and dementia by enzyme-linked assay (ELISA) and compared between the two different groups.

Results: There was no difference in age between the NPH and dementia groups (p=0.5). There was no statistically significant difference was found in IL-17A (p=0.7), IL-34 (p=0.9), and CXCL13 (p=0.2) in the inflammatory marker analysis in the CSF. The groups had a statistically significant difference in IL-17F (p=0.04).

Conclusion: IL-17F can be an important laboratory marker used in the differential diagnosis of NPH and dementia.

Keywords: NPH, Dementia, IL-17A, IL-17F, IL-34, CXCL13

Corresponding author: Şeyda Karabörk **E-mail:** seydaozsoy20@hotmail.com
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INTRODUCTION

Neurodegenerative disorders are characterized by a continuous, progressive loss of neuronal structure leading to functional and cognitive deficits. Much research suggests that neurodegeneration is related to neuronal loss, protein aggregation, and immune system dysfunction-neuroinflammation (1). Neurodegenerative disorders include multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), dementia, Parkinson's disease (PD), and normal pressure hydrocephalus (NPH). The etiopathogenesis of neurodegenerative disorders is heterogeneous: endogenous, genetic, and environmental. Therefore, the exact cause of neurodegenerative diseases is unknown (2-4).

NPH is a progressive onset syndrome characterized by gait disturbance, urinary incontinence, and cognitive decline, radiologically defined by ventricular dilatation, and clinical improvement after shunting (5). NPH is a treatable condition. Early diagnosis of NPH may be difficult due to neuroimaging and symptomatic similarity with other neurological disorders like dementia. Prompt and accurate diagnosis plays an essential role in the potential treatment of NPH. To prevent NPH from progressing to the neurodegenerative process, the current symptomatic diagnostic criteria of NPH should be improved by adding new specific biomarkers in CSF (5-8). Like NPH, the etiology of dementia is a multifactorial condition associated with environmental and genetic factors. It can be challenging to determine the etiology of dementia; however, this etiological diagnosis is critical as it facilitates treatment management and informs the patients and their families about the prognosis. There is no specifically defined biomarker for clinically diagnosed dementia, and new studies are needed to increase the reliability of the diagnosis. Recent studies have reported that inflammation plays a vital role in the neurodegeneration of dementia, and it has been shown that some of the markers measured in body fluids are associated with the severity and progression of the disease (9,10).

Cytokines and chemokines are primarily produced by a few different cells, in addition to white blood cells and leukocytes, in response to diverse stimuli in pathological and physiological situations, acting as neuromodulators in the nervous system to control neuroinflammation (11,12). The profile of CSF cytokines allows the exploration of pathogenic mechanisms of different neurological diseases and therapeutic approaches. Members of the IL-17 cytokine family (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F) have diverse biological functions, supporting protective immunity against many pathogens and driving inflammatory pathology during infection and autoimmunity. IL-17A and IL-17F are produced by CD4+, CD8+, and γδ T cells and various innate immune cell populations (13,14). IL-34 has been suggested to have an essential role in maintaining CNS homeostasis through its effects on different cell types, including neurons, microglia, and endothelial cells. Recent researchers have found increasing evidence that IL-34 contributed to the pathogenesis of neurodegenerative disease and autoimmune disorders (15,16).

CXCL13 is known as B-cell attractant chemokine 1 (BCA-1) or B-lymphocyte chemoattractant (BLC) due to its strong chemotaxis to B cells. Studies of CXCL13 in CSF have shown that it is elevated, mainly in association with CNS-specific infectious conditions. In addition, CXCL13 has emerged as a trending chemokine in recent research on neurodegenerative diseases (17,18).

Determining the levels of various biomarkers in CSF may represent underlying neuropathological changes in the brain and may be crucial in identifying potential etiological pathways. In line with this recommendation, the determination of an up-to-date CSF marker in the diagnosis of difficult-to-diagnose neurological diseases such as NPH and dementia is essential for selecting the appropriate therapeutic approach and monitoring the effectiveness of treatment. Therefore, our study aims to compare the concentrations of IL-17A, IL-17F, IL-34, and CXCL13 in the CSF of patients with NPH and dementia to strengthen the laboratory diagnosis in addition to the patient's clinical findings.

METHODS

Ethical consideration and study population

The study was approved by the Clinical Ethics Committee of the Bolu Abant İzzet Baysal University (Number of approval: 2023/12). Seven NPH patients and five dementia cases of similar age and sex distribution were included by the BAİBÜ İzzet Baysal Training and Research Hospital Neurology Clinics, Bolu. The patients were diagnosed following the international NPH guidelines: Guidelines for Management of Idiopathic Normal Pressure Hydrocephalus (19), and dementia using the National Institute for Health and Care Excellence: Guidelines (20). Table 1 summarizes the clinical characteristics of NPH and dementia. Written informed consent was obtained from patients. As part of the diagnostic process for NPH and dementia, the CSF samples were obtained from the NPH and dementia patients via sterile lumbar puncture (LP) from the interspaces of lumbar 1-5. The CSF samples were defrosted just once to aliquot them before analysis. All CSF samples collected up until the time of the investigation were properly preserved at -80°C. The absence of both CSF samples was an exclusion criterion.

Measurement of cytokines with ELISA

For ELISA analysis of CSF samples, we used human IL-17A and IL-17F (Elabscience, USA), IL-34 (Cloud-Clone Corp., USA), and CXCL13 (Euroimmun, Lubeck, Germany) ELISA kits, which have been previously confirmed for CSF samples. Results were expressed as picograms per milliliter (pg/mL) according to the manufacturer's recommendations. The manufacturer's recommendations served as the basis for defining the specificity and sensitivity of the cytokines (specificity: except in IL-17A cytokine measurements, in which cross-reactivity with human IL-17F was negligible, and non-cross-reactivity was observed).

Statistical analysis

Data were analyzed using the statistical package program IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) Descriptive statistics are presented as mean ± standard deviation (x±SD) and median (min-max); "n" corresponds to the number of cases. The normal distribution of the data of numerical variables was evaluated with the Shapiro-Wilk test since the sample size was small. For normally distributed data, an unpaired two-tailed T-test was conducted. For non-normally distributed data, the Mann-Whitney U test was performed. A p-value of <0.05 was considered statistically significant.

RESULTS

We compared CSF cytokine levels between the two groups in NPH (n=7) and dementia (n=5) patients in 12 CSF samples. The mean age of the patients with NPH and the dementia groups was 64 (±11) and 59 (±15) years, respectively, and there was no

Table 1. The clinical characteristics of NPH and Dementia

	NPH	Dementia
Clinical traits/features (According to DSM)	• Cognitive dysfunction • Urination problems/incontinence	Decreasing: • Complex attention • Executive functions • Learning and memory • Language • Perceptual motor functions • Social cognition
Diagnostic criteria	• Usual opening pressure for CSF • MRI modifications: Ventricular system enlargement with or without cortical modifications • After a CSF spinal tap, neurological problems are reversed.	• For etiological background; Vitamin B12 level, complete blood count, thyroid function tests, serum electrolytes, liver and kidney function tests, • For imaging; MRI and CT

*CSF: Cerebrospinal fluid; CT: Computer tomography; DSM: Diagnostic and statistical manual of mental disorders; MRI: Magnetic Resonance Imaging

Table 2. Comparison of mean and p-values of variables between groups

	Dementia (n=5) Mean (±SD) Median (min-max)	NPH (n=7) Mean (±SD) Median (min-max)	p value
Age (year)	59 (±15)	64 (±11)	0.50*
	58 (36-78)	68 (46-79)	
Gender	1 Female	2 Female	0.2°
	4 Male	5 Male	
IL-17A (pg/ml)	38 (±27)	76 (±84)	0.70∞
	48 (8-73)	48 (3-256)	
IL-17F (pg/ml)	5 (±2)	12 (±6)	0.04*
	5 (3-8)	10 (6-23)	
IL-34 (pg/ml)	4 (±1)	6 (±5)	0.90∞
	3 (2-5)	3 (3-16)	
CXCL13 (pg/ml)	10 (±7)	5 (±3)	0.20*
	11 (1-18)	4 (1-11)	

NPH: normal pressure hydrocephalus, ∞: Mann Whitney U test used, *: Independent sample t-test used, °: Chi-square used, p<0.05: there is a significant difference between the NPH and Dementia groups.

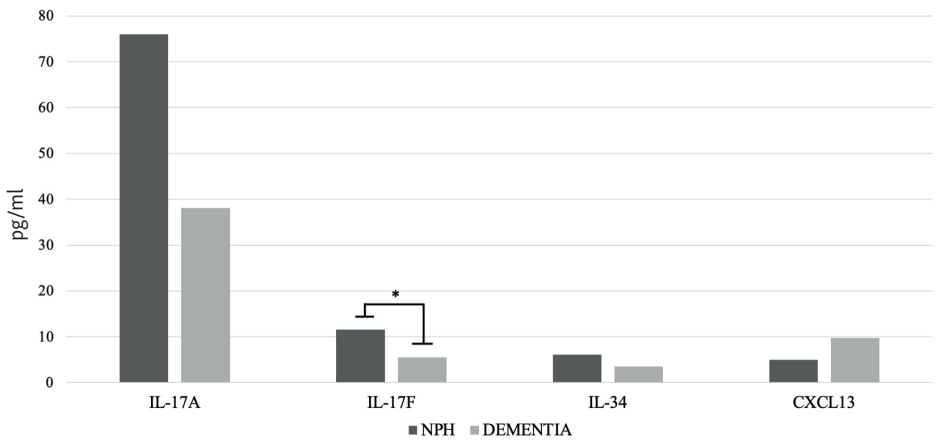

Figure 1. Cytokine and chemokine levels in CSF of NPH and dementia patients.

statistically significant difference between the two groups (p=0.5). In addition, there was no statistically significant difference between the groups regarding gender (p=0.2) (Table 2). In addition, there was no statistically significant difference between IL-17A (p=0.7), IL-34 (p=0.9), and CXCL13 (p=0.2) groups in the analysis of inflammatory markers in CSF. Contrary to the fact that there was no significant difference in IL-17A, IL-34, and CXCL-13 levels between the groups, IL-17 in CSF samples from NPH patients was statistically significantly higher than in the dementia group (p=0.04) (Table 2, Figure 1).

DISCUSSION

In this study, we found that IL-17F in CSF was high in dementia patients and no statistically significant difference was found between the CSF IL-17A, IL-34, and CXCL13 groups. We further revealed their clinical relevance in NPH patients, suggesting that different IL-17 family members may play different pathogenic roles in NPH.

Diagnosing neurological diseases can be challenging due to the overlapping symptoms, progressive nature, limited diagnostic tools, rarity, and patient variability, in spite of the fact that diagnosis of neurological diseases often requires a combination of physical examination, imaging, and laboratory tests. Nevertheless, detecting certain illnesses can be challenging because there are no conclusive diagnostic tests available. Therefore, in order to make an accurate diagnosis, healthcare professionals must do a comprehensive examination and order the necessary tests (21).

The symptoms of dementia and NPH can be identical, making diagnosis challenging because there are no distinct diagnostic tests or coexisting prerequisites for both neurological disorders. Healthcare professionals may employ a variety of diagnostic techniques, including lumbar punctures to test CSF pressure, brain imaging, and cognitive and gait assessments, to differentiate between NPH and dementia. Furthermore, a brief CSF drainage test may be performed in patients with suspected NPH to determine whether the removal of extra fluid improves their symptoms (6,10,19). Despite the need, the CSF biomarker profile in NPH and dementia has not yet been conclusively determined since IL-17, IL-34, and CXCL13-cytokines and chemokines that are now being assessed in the pathophysiology of neuroinflammatory diseases may direct the differentiation process between NPH and dementia.

IL-17F is essential for the immune system's reaction to a range of infections and inflammatory conditions. The brain's glial cells, which support and shield neurons, have also been linked to the regulation of IL-17F (13). According to recent research, there may be a connection between IL-17F and NPH, suggesting that it is produced in reaction to the accumulation of CSF (22). The development of NPH has been associated with abnormal glial cell function and IL-17F is a cytokine that contributes to this process by regulating glial cell activity. Moreover, it has been demonstrated that IL-17F stimulates the synthesis of matrix metalloproteinases (MMPs), which are enzymes that break down extracellular matrix proteins. MMPs play a role in the pathogenesis of NPH by damaging brain tissue and causing ventricular enlargement. While research on the active role of IL-17F in the development of NPH continues, there is increasing evidence indicating that IL-17F may also play a role in the disruption of glial cell functions and immune response in this process (13,22,23). There are two subtypes of IL-17, IL-17A, and IL-17F, with 50% homology. When literature data were evaluated, IL-17A and IL-17F were accepted as more potent inducers of inflammation than IL-17F, although they have similar biological properties (23). It has been demonstrated that IL-17F is a cytokine more involved in acute inflammation and produces more substantial neutrophil aggregation than IL-17A. However, it is known that the most prominent Th17-related cytokine in chronic inflammation is IL-17A, and studies report that IL-17A concentration increases, especially in Alzheimer's (23). Therefore, although IL-17A and IL-17F are homologous, it is appropriate to evaluate these two cytokines differently (14). In our study results, IL-17F showed a significant increase in NPH cases compared to dementia cases, while IL-17A showed a non-statistical numerical increase in NPH cases with similar homology. This is supported by the fact that CSF samples have been studied in the acute phase, confirming that NPH is an acute inflammatory disease.

Evaluating our results, IL-17F as in CSF examination may be a new diagnostic approach-biomarker for NPH and Dementia, which are difficult to differentiate in the acute phase. In addition, IL-17A, IL-17F, and IL-34 show a higher trend in NPH than in dementia in a numerically consistent manner without statistical significance, indicating that this pathway works in favor of NPH in the acute phase. CXCL13, another chemokine we evaluated in the study, is now known to be a prominent protein in Lyme neuroborreliosis (LNB) (17,18). Still, the low levels of CXCL13 in NPH cases may suggest that it can be used to exclude NPH Lyme neuroborreliosis. When we compare CXCL13 in

NPH and dementia cases, the high level of CXCL13 in the dementia group may suggest the coexistence of dementia and Lyme neuroborreliosis. We recommend that other serological diagnostic parameters be evaluated to exclude Lyme in patients with a pre-diagnosis of dementia.

It is a current approach that serum is not suitable for sample selection for the detection of neurological diseases and central tissues such as CSF are more diagnostic. In the 2014 study by Sosvorova et al., in which NPH cases were measured at pro and anti-inflammatory cytokines in CSF and plasma samples, it was concluded that there was not much change in plasma samples. However, cytokine levels increased significantly in CSF samples compared to the control group. According to the data obtained from the study, it was also stated that CSF samples could better show neurodegenerative changes in the brain and that specific cytokines could help clinicians diagnose NPH (7). In the review by Zhang et al., in which they compiled the markers in CSF samples of NPH patients, the markers in CSF samples of Alzheimer's patients were also mentioned because of the overlap/similarity in symptomatic and neuroimaging of NPH (6). The fact that our study was directly investigated in CSF samples proved these similar results and gave our study superiority.

The present data indicate that IL-17F may play a role in the pathogenesis of NPH. The level of IL-17F cytokine in CSF has the potential to be a specific biomarker to be used in the acute phase in the differential diagnosis of the two diseases in patients with NPH and dementia. This is especially important for NPH cases, progressing to dementia if not diagnosed early. In conclusion, this study has some limitations. The number of cases was few and the cases did not have clinical or biochemical parameters. For this reason, further studies should be conducted to examine the pathogenic role of IL-17F in NPH to reflect the underlying neuropathological changes in the brain and to reveal possible etiological mechanisms.

CONCLUSION

Based on our data, it is thought that targeting IL-17F as a biomarker may represent a potential therapeutic strategy in the early diagnosis and treatment of neurodegenerative diseases such as NPH and dementia. However, more research is needed to fully understand the mechanisms underlying the association between IL-17F and NPH and dementia.

Ethical approval

This study has been approved by the Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (approval date 17/01/2023, number 2023/12). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: ŞAT; Concept: ŞK; Design: ŞAT, ŞK; Data Collection or Processing: ŞAT, ŞK; Analysis or Interpretation: HÇ; Literature Search: ŞK, HÇ; Writing: HÇ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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