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CLINICAL STUDY

Is increased activator protein 1 in cerebrospinal fluid as a potential biomarker that distinguishes idiopathic intracranial hypertension from multiple sclerosis?

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ABSTRACT

OBJECTIVES: To distinguish whether idiopathic intracranial hypertension (IIH) is a condition predisposing to multiple sclerosis (MS) or an isolated disease, the current gene transcription factor Activator Protein-1 (AP-1) was evaluated with its potential to differentiate both diseases.

BACKGROUND: The aim of this study was to investigate the use of AP-1 as biomarkers for the discrimination of IIH and MS.

METHODS: AP-1, TNF-α, and IL-6 protein values in the CSF of the cases were evaluated by the ELISA method. The numerical measures of the groups and the ability of AP-1 to distinguish the groups were analyzed with the ROC curve.

RESULTS: There was no difference between the groups in CSF TNF-α, IL-6, CSF, and serum biochemistry analyses. However, it was determined that the AP-1 concentration (pg/ml) was significantly higher in the IIH group, the sensitivity of AP-1 in separating those with IIH was 75%, and the specificity in separating those with MS was 60% in those with an AP-1 concentration of 606.5 and above.

CONCLUSION: According to our results, the fact that CSF TNF-α and IL-6 values did not differ in IIH compared to MS revealed that IIH could not methodologically control MS, and AP-1 was a supportive parameter in differentiating both diseases *(Tab. 2, Fig. 1, Ref. 31)*. Text in PDF *www.elis.sk*

KEY WORDS: multiple sclerosis, idiopatic intracranial hypertension, activator protein-1, cerebrospinal fluid, inflammation.

Introduction

Multiple sclerosis (MS) is the most common autoimmune, inflammatory, neurodegenerative, demyelinating disease of the central nervous system (CNS) that starts with episodic neurological deficits and occurs most frequently in the young adult population (1), is diagnosed in 900,000 cases in the United States. **I**t affects over 2 million worldwide (2). Like most autoimmune diseases, the triggering event in MS is unknown (3). MS brains have some neuropathological hallmarks, such as numerous inflammatory demyelinated plaques distributed throughout the neuroaxis and characterized by infiltrating T cells, activated microglia and astroglia, synaptic loss, and neurodegeneration (4, 5). Such activated and autoreactive lymphocytes can enter the CNS. There, they start the myelin and neuronal damage and then feed it. **I**nfiltrating lymphocytes are further primed by the release and diffusion of a number of cytokines, such as tumor necrosis factor-α (TNF-α), which activates local microglia (4) and continue inflammation.

Idiopathic intracranial hypertension (IIH), among the neuroinflammatory diseases, is a disease whose pathophysiology remains unclear, characterized by obstruction or disruption of intracranial venous drainage in CSF absorption and inflammatory changes in this deterioration (6). Although increased intracranial pressure is clinically characterized by headache, papilledema, vision loss, and pulsatile tinnitus, no explanatory cause can be detected in radiological imaging and CSF examinations (7). Overall, the neuroinflammatory pathogenesis of IIH is complex and involves multiple factors. For example, neuroinflammatory processes can disrupt the blood-brain barrier (BBB), which normally regulates the movement of fluids and cells between the brain and the rest of the body. This disruption can lead to an increase in fluid and inflammatory cells within the brain, further exacerbating the pressure and damage (8). Neuroinflammation can cause damage to the myelin sheath, this damage can lead to a range of neurological symptoms.

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Inflammation, which plays a role in the pathophysiology of MS (9) and IIH (8), initiates the production and release of various cytokines and chemokines by stimulating the proinflammatory cytokines of the immune cells of the innate and/or adaptive immune system (10, 11). Activator protein 1 (AP-1), a transcription factor, participates in many cellular processes, including proliferation, apoptosis, differentiation, and transformation. Neurotransmitters, proinflammatory cytokines (TNF-α, IL-1, IL-6), UV radiation, and bacterial and viral infections induce AP-1 activation via Jun and Fos gene transcription and MAPKinases (12, 13, 14). AP-1 undergoes post-translational modification (15). Subsequently, AP-1 induces the production of cytokines such as TNF-α and IL-6 in microglia, neurons, and astrocytes in the central nervous system (16). The data obtained from the literature indicate that AP-1 plays a vital role in the initiative and development of inflammatory disorders, that determining its role in the pathophysiology can be a therapeutic strategy, and that AP-1 has the potential as a biomarker in inflammatory diseases (17). CSF sampling is used in the diagnosis of MS, healthy CSF is needed in studies, and IIH is studied as the control group of MS since CSF intake from healthy individuals is not ethical (18). Clinical studies have shown that IHH has a neurodegenerative inflammatory background (19, 20, 21), and the use of IIH as control patients of MS have been discussed. In this case, there is a need for new research that will distinguish between MS and IIH, develop new diagnostic biomarkers, and reveal the inflammatory picture of IIH.

The best of our knowledge, in our study, in newly diagnosed patients who did not use drugs, we compared both the CSFs of IIH with MS cases and whether IIH is the control of MS and whether AP-1, which is a transcription factor, both in the early period. In addition, the potential to differentiate the disease will be evaluated.

Materials and methods

Ethical approval and participants

Ethics committee approval of the study was obtained from Bolu Abant İzzet Baysal University Clinical Research Ethics Committee with the decision number 2022/221. Our research was conducted in vitro conditions in Bolu Abant İzzet Baysal University (BAIBU) Molecular Biology and Microbiology Laboratory. In this study, 22 MS and 16 IIH cases were included in the Neurology Clinic of BAIBU Training and Research Hospital, who did not start using drugs that meet McDonald's diagnostic criteria. Working groups were formed due to detailed system inquiries and clinical examinations. All patients were included in the study by signing an informed consent form. The data of the patients were analyzed retrospectively and prospectively. Demographic and clinical data of the patients were obtained from patient information and patient files registered in the BAIBU Medical Faculty Hospital database. CSF samples of the cases included in the study, which required indication and was taken by Lumbar Puncture (LP), were stored at –80 °C until the study time. While volunteers aged 18–65 years, diagnosed with MS according to McDonald's criteria for MS cases, and those followed in the clinic with the diagnosis of IIH were included in the study; individuals who were not volunteers, were outside the age range and had another autoimmune disease (Diabetes, Systemic lupus, etc.) were excluded from the study, as cross-reactions could occur.

ELISA step

TNF-α, IL-6 and AP-1 (Lot number: 20220510, Sinogeneclon, China) values in CSF samples measured by ELISA method according to company recommendations. After, 100 µL of sample or AP-1 (pg/ml), IL-6 (ng/L), and TNF-α (ng/L) standard was added to wells of a 96-well plate. The plate was incubated for 1.5 h at 37 °C. Next, the liquids in the plate were removed, and instantly 100 µL biotinylated detection Ab solution was added to the wells, and the plate was incubated for 1 h at 37 °C. Next, the plate was washed 3 times with the wash buffer, 100 µL HRP conjugate was added to the wells, and the plate was incubated for 0.5 h at 37 °C. Next, the plate was washed 5 times with the wash buffer, 90 µL substrate solution was added to the wells, and the plate was incubated for 15 min at 37 °C. Then, 50 µL of stop solution was added to the wells. The optical density was determined at 450 nm in the microplate reader (Epoch BioTek Instruments, Inc. Highland Park) and the final color's intensity is related to the amount of our parameters contained in the sample.

Statistical analysis

The descriptive statistics of measurements were calculated as arithmetic mean, standard deviation (SD), median, and 25th and 75th percentiles. The conformity of numerical type measurements to the normal distribution was examined with the Shapiro-Wilks test, and it was determined that they did not show normal distribution. Relationships between categorical features and groups were analyzed with Pearson chi-square or Fisher–Freeman–Halton test. The Mann–Whitney U test was used to compare the groups regarding numerical measurements. In addition, the success of AP-1 in distinguishing groups was also assessed with ROC (Receiving Operating Characteristics) curve analysis. The $p \leq 0.05$ level was considered statistically significant in the calculations, and the SPSS (ver. 23) program was used.

Results

A total of 38 people, 22 of whom had MS and 16 of whom had IIH, were included in the study. The number of women/men in the MS group was 16/6, and the number of women/men in the IIH group was 14/2. Therefore, the groups were observed to be similar in gender distribution ($p=0.270$). In addition, no statistically significant difference was found between the mean age of the MS group (34.9±10.1) and the mean age of the IIH group (38.7±12.5) ($p=0.298$). According to this result, it can be said that the demographic structure of the two groups is similar in terms of age and gender. Table 1 shows the descriptive statistics of the two groups in terms of numerical characteristics.

When Table 1 is examined, It was determined that the AP-1 concentration was significantly higher in the IIH group, the both mean CSF LDH ($p=0.029$) and the mean IgG Index ($p=0.001$) were increased in the MS group. However, apart from these three

Tab. 1. Descriptive statistics of numerical characteristics of MS and IIH.

	MS						IIH					
		Mean	SD	Percentiles				Mean	SD	Percentiles			
	n			25th	Median	75th	n			25th	Median	75th	p*
AP-1 (pg/ml)	22	611.05	299.81	425.25	576.50	647.75	16	656.19	98.26	571.50	669.00	700.25	**0.036**
IL-6 (ng/L)	22	2.47	1.28	1.95	2.22	2.64	16	1.99	.51	1.55	1.92	2.17	0.064
TNF-α (ng/L)	22	83.69	43.02	60.09	76.91	89.64	16	62.36	27.59	40.77	59.18	80.55	0.089
CSF Leucocyte	19	1.05	3.57	.00	.00	.00	15	4.13	9.30	.00	.00	4.00	0.286
CSF albumin	19	149.49	65.53	114.00	134.00	169.00	15	137.27	73.67	87.00	114.00	183.00	0.430
CSF glucose	19	64.37	9.47	58.00	60.00	74.00	15	63.53	8.87	58.00	62.00	66.00	0.891
CSF chlor	19	123.95	2.32	123.00	124.00	126.00	14	124.71	2.20	123.75	124.50	126.00	0.321
CSF LDH	19	14.53	4.43	13.00	15.00	17.00	14	11.21	4.85	6.75	11.50	13.50	**0.029**
CSF Protein	19	293.32	114.51	237.50	261.30	316.20	15	250.13	114.98	161.10	247.50	299.30	0.256
CSF IgG Index	17	1.06	.55	.69	.91	1.21	7	.52	.07	.45	.51	.59	**0.001**
Serum albumin	19	45.55	4.71	41.70	46.00	50.00	15	43.47	3.40	40.00	44.00	47.00	0.179
Serum glucose	19	95.47	18.97	85.00	90.00	106.00	15	95.87	23.88	79.00	89.00	110.00	0.784
Serum chlor	19	106.16	2.14	105.00	107.00	108.00	14	105.50	2.95	103.75	106.00	108.00	0.679
Serum LDH	19	232.68	132.90	166.00	196.00	251.00	14	217.71	100.35	171.00	197.00	215.00	0.928
Serum Homocystein	17	9.82	5.89	6.68	8.74	10.45	10	8.65	3.03	6.81	8.60	11.25	0.980

* Mann–Whitney U test

measurements, the two groups were similar regarding other characteristics in given Table 1.

When evaluated with the curve of AP-1 concentration, the ROC curve given in Figure 1 was obtained. The area under the curve, AUC, is 0.702±0.086 (p=0.036). The best cutoff point was found to be 606.5. When this cut-off point is taken, the AP-1 is 0.75 sensitive and 0.60 selective.

The relations between groups and categorical characteristics are given in Table 2. When the table is examined, oligoclonal band (OCB) positivity is significantly higher in the MS group. When the OCB type distribution is reviewed according to the groups, Type 1 is significantly higher in the IIH group, and Type 2 is significantly higher in the MS group. The number of Type 3 and Type 4 patients is only one each. Among our results, the high CSF IgG Index, OCB positivity, and Type 2 OCB positivity in our MS group supported the suitability of the patients we selected according to McDonald's criteria with laboratory findings. Apart from that, Lyme IgG and IgM positivity were found at similar rates in both groups.

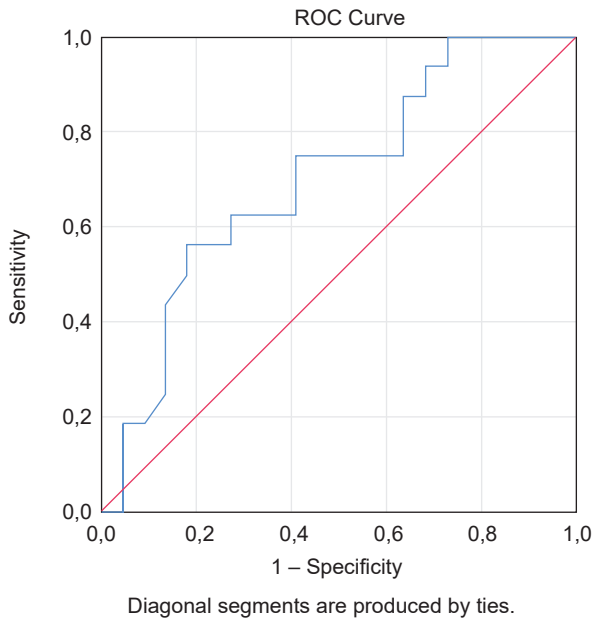

Fig. 1. Success of AP-1 in separating MS and IIH groups (ROC curve).

Discussion

According to our study results, although there was no difference between the CSF TNF-α, IL-6, and biochemical analysis values of MS and IIH, AP-1 was higher in the IIH group. When evaluated together with OCB negativity, the success of AP-1 in distinguishing between MS and IIH was found to be 75%.

Recent studies have determined that IIH patients return to demyelinating diseases such as MS in the long term. Whether IIH is an isolated inflammatory demyelinating disease, a transi-

Tab. 2. Relationships between groups and categorical features.

		Diagnosis				Total	
		MS		IIH			
		n	%	n	%	n	p
OCB	Negative	2	12.5	7	100.0	9	**0.001**
	Positive	14	87.5	0	0.0	14	
OCB Type	Type 1	2	12.5	6	85.7	8	**0.001**
	Type 2	13	81.3	0	0.0	13	
	Type 3	1	6.3	0	0.0	1	
	Type 4	0	0.0	1	14.3	1	
Lyme IgG	Negative	12	75.0	10	76.9	22	0.904
	Positive	4	25.0	3	23.1	7	
Lyme IgM	Negative	15	93.8	13	100.0	28	0.359
	Positive	1	6.3	0	0.0	1	

tional form predisposing to other demyelinating diseases has been considered. In samples, a 33-year-old female patient with visual disturbances and hypertension accompanying headache, applied to the ophthalmology clinic and was diagnosed with IIH, and her complaints regressed with treatment. However, after three months, the patient was admitted to the ophthalmology department with an increasing headache. High pressure after LP in neurological examination, presence of lesions in MRI, OCB positivity in CSF analysis, and presence of lymphocytosis turned the diagnosis in favor of MS (22). Similarly, there are publications in which the conversion of IIH to MS was observed in different case series (23). This situation creates a disadvantage for people with MS who are diagnosed with IIH and whose treatment is delayed. On the other hand, in cases where the transformation of IIH to MS is observed or coincides, it may be necessary to consider cases where the etiological factor may be completely different. Lyme disease mimics symptoms in other autoimmune and neurologic disorders, such as MS, demyelinating diseases, and rheumatoid arthritis (24). The similarity of both positivity and negativity of Lyme IgM and Lyme IgG between MS and IIH groups, which are included in our study results, also supports this approach. The difficulty in distinguishing between MS and IIH and the fact that the transformation into each other is observed in our clinic and causes some problems shows that there is a need to develop new diagnostic markers to differentiate MS and IIH from each other. In selecting biomarkers of neuroinflammatory diseases, inflammatory markers associated with the pathogenesis of the disease are preferred. For this purpose, there are new studies in which AP-1, which plays a role as a transcription factor in the regulation of various physiological and pathological cellular processes such as inflammation, apoptosis, cell migration, and transformation, is studied as a biomarker in neurodegeneration (25, 26), neurogenesis (26), neuroinflammation (27) processes. AP-1, which we evaluated with the idea of whether it could be a new biomarker for IIH, was found to be significantly higher in CSF compared to MS in IIH, in addition to OCD negativity. The 75% sensitivity in the ROC analysis suggests that AP-1 may be a biomarker that will distinguish IIH from MS. Another situation between MS and IIH is that since CSF sampling is used in diagnosing MS, healthy CSF is needed in studies, and IIH is evaluated as the control group of MS since CSF intake from healthy individuals is unethical (18). However, studies conducted in recent years have discussed the accuracy of IIH as a control phenomenon because current studies showing that some conditions characterized in inflammatory demyelinating diseases are also present in IIH have shown that pericyte degeneration, BBB dysfunction (28), and AQP4 perivascular expression, which are specific to chronic degenerative diseases, are also increased in IIH. For this reason, it is said that IIH is not innocent (29), and is a more neurodegenerative severe disease compared to previous findings (30). In addition, high levels of neurofilament in the cytoskeleton of neurons (21), which predict future relapses in MS, were also shown in IIH cases (31). However, in our study results supporting these approaches, no difference was found between MS and IIH groups regarding CSF TNF-α, CSF IL-6, and both CSF and serum biochemical parameters such as Lyme IgM, Lyme IgG, IgG index, albumin, leucocyte, glucose, chlorine, LDH, protein, homocysteine.

At this stage, we think studying IIH as a control group would be an incorrect methodological choice for future studies. Including IIH as a different neurodegenerative disease group would be more appropriate rather than the control of MS neurodegenerative diseases.

Our limitations were the need for simultaneous serum evaluation with the CSF evaluation of inflammatory markers, the inability to confirm with molecular methods, the absence of healthy controls, and the small number of samples. Our superiority is that we have studied CSF samples of newly diagnosed cases who have not yet used drugs, that AP-1 was evaluated for the first time in IIH with biochemical parameters in CSF samples, and that the evaluation of IIH as the control of MS was a methodological error.

Conclusion

The results of our study, in which we compared the CSF findings of MS and IIH cases, were consistent with previously published reports that IIH is not a benign condition considering a control. In addition, we believe that AP-1, with its oligoclonal band negativity, maybe a potential biomarker candidate for IIH supporting rapid diagnosis from CSF samples in the early period and distinguish IIH from MS. Studies evaluating the relationship of AP-1 with the broad cytokine profile in IIH and MS will be helpful to illuminate the process.

Learning points

* PTS is not a benign condition that can be used in scientific research as a control group of MS.

* AP-1 may be a biomarker distinguishing IIH from MS with OCB negativity.

* IIH is not an innocent condition with inflammatory CSF findings.

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