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ORIGINAL ARTICLE

Role of tumor necrosis factor-alpha in the pathophysiology of idiopathic intracranial hypertension

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Background: Although the pathogenesis of idiopathic intracranial hypertension (IIH) is still poorly understood, the contribution of inflammatory mechanisms has been proposed in its pathophysiology.

Objective: This study aimed to measure serum tumor necrosis factor-α (TNF-α) levels in patients with IIH and to examine its relationship with clinical and ophthalmological parameters and cerebrospinal fluid (CSF) opening pressure.

Subjects and methods: Thirty-six IIH patients and 30 healthy subjects were enrolled in the study. Patients were subjected to complete neurological, general, and ophthalmological assessments. Serum TNF-α levels were measured for patients and controls using the enzyme-linked immunosorbent assay.

Results: Serum TNF-α levels were significantly higher in IIH patients compared to healthy controls (p value <.001). Serum TNF-α level was significantly negatively correlated with grade of perimetry and CSF opening pressure (r = −.36, p value = .02), (r = −.37, p value = .02) respectively. However, serum TNF-α was not significantly correlated either with age at onset, disease duration, BMI, headache severity, relapse rate, visual acuity, or papilloedema grade. Serum TNF-α was found to be a significant predictor of the severity of the visual field affection in IIH patients, as one-grade increase of the perimetric grading was associated with a decrease in serum TNF-α by 13.96 ng/ml.

Conclusion: Altered serum TNF-α levels may suggest the potential involvement of pro-inflammatory mechanisms in the pathogenesis of IIH. Serum TNF-α level may be an indicator of the severity of the visual field affection in IIH.

KEYWORDS
CSF opening pressure, idiopathic intracranial hypertension, obesity, TNF-α

1 | INTRODUCTION

Idiopathic intracranial hypertension (IIH) is a disorder characterized by increased intracranial pressure (ICP) of unknown etiology without any clinical, laboratory, or radiological evidence of intracranial pathology on conventional imaging. It is predominantly observed in women of childbearing age and is associated with a history of recent weight gain.[1]

There is growing evidence that the incidence and prevalence of IIH are rising, which is likely related to the increasing prevalence

of obesity worldwide. The World Health Organization (WHO) indicated a two-fold increase in the UK between 1997 and 2002 and a three-fold increase in the USA between 1990 and 2006.[2]

The underlying pathophysiological mechanisms of IIH have not been established. Disorders in cerebrospinal fluid dynamics (overproduction or under drainage) are likely a result of an initial trigger or ongoing insult. The role of cerebral venous sinus stenosis in the disease pathophysiology is still uncertain.[3] Moreover, a link has been suggested between IIH and metabolic dysregulation.[4] Adipose tissues secrete pro-inflammatory cytokines, chemokines, adipokines, and hormones that may be involved in IIH pathogenesis.[5]

Tumor necrosis factor α (TNF-α) is a key component of the innate immune system and one of the pro-inflammatory cytokines. TNF-α expression had a strong positive correlation with the degree of obesity and the level of hyperinsulinemia and a negative correlation with the adipose tissue lipoprotein lipase activity. This contradiction might be explained by the differential obesity-related pathway regulation in IIH patients through insulin-resistant mechanisms and the overproduction of its mRNA in obese patients and due to the accession of blood products to the CSF.[6]

Previous studies have shown that TNF-α levels were altered in IIH patients compared to healthy controls. This alteration in serum TNF-α levels may support the role of inflammatory mechanisms in the pathophysiology of IIH.[7,8]

The current study aimed to measure the serum TNF-α levels in a sample of Egyptian IIH patients in comparison to healthy control subjects and to examine the correlation between TNF-α level and certain clinical (age at onset, disease duration, body mass index, relapse rate, and disease severity) and ophthalmological parameters and CSF opening pressure.

2 | SUBJECTS AND METHODS

2.1 | Participants

This was a case–control study involving 66 subjects (36 patients diagnosed as IIH and 30 healthy matched controls). The study was conducted at the neurology department of Cairo University Hospitals in the period from August 2018 to January 2019. Patients were selected from those admitted at the neurology department or attending the neurology outpatient clinic of Cairo University hospitals. The control subjects were recruited from nurses, workers, and relatives of patients in the neurology department. The aim and procedures of the study were explained to every participant and an informed consent was obtained from each participant before being enrolled in the study. The study was approved by the ethical committee of the Department of Neurology, Faculty of Medicine, Cairo University.

The study included two groups:

- *Group A*: included 36 IIH patients.
- *Group B*: included 30 healthy control subjects matched for age, gender, and body mass index (BMI).

2.2 | Inclusion criteria

- Patients (of both sexes) with idiopathic intracranial hypertension (IIH) according to the criteria of Headache Classification Committee of the International Headache Society (IHS), (2018).[9]
- Age range from 20 to 45 years.

2.3 | Exclusion criteria

- Patients with neurological disorders causing secondary increased intracranial pressure (ICP) such as venous sinus thrombosis, Behcet disease, systemic lupus erythematosus, or rheumatoid arthritis.
- Drugs that might increase intracranial tension such as oral contraceptive pills or vitamin A supplements.
- Patient with co-morbid medical or ocular conditions that can functionally or structurally affect the visual pathway (e.g., diabetes mellitus, hypertension, glaucoma).

2.4 | Methods

Patients were submitted to the following:

- Thorough clinical assessment.
- Clinical evaluation of headache and assessment of headache severity using the comparative pain rating scale.[10]
- Evaluation of relapse: According to (Yri et al, 2012),[11] relapse was defined as the recurrence of either a previously resolved papilledema or symptoms of raised ICP such as pulsatile tinnitus, transient visual obscuration (TVO), blurred vision, and diplopia that required urgent management by lumbar puncture (LP) or shunt; however, headache is heterogenic and unrelated to relapse and is therefore a poor marker of disease activity.
- Classification of obesity according to the body mass index (BMI) into: Overweight: BMI (25–29.9); Class I obesity: BMI (30–34.9); Class II obesity: BMI (35–39.9); Extreme obesity: BMI ≥40.[12]
- Ophthalmological Assessment
  1. *Visual Acuity Measurement* using the Snellen chart. Visual acuity was classified according to the World Health Organization classification of visual impairment, 2018.[13]
  2. *Fundus examination* by direct and indirect ophthalmoscopy: to detect signs of papilledema. Grading of the papilledema was done according to the criteria of the Modified Frisen Scale.[14]
  3. *Assessment of the peripheral visual field*: Automated perimetry was used for the assessment of the peripheral visual field. In automated perimetry, a computer program is selected. The most commonly used one tests the central 30° of the visual field using a six-degree spaced grid. This is accomplished by keeping the size and location of a target constant and varying the brightness until the dimmest target that the patient can see at each of the test locations is found. These maps of visual

sensitivity, made by either of these methods, are very important in diagnosing diseases of the visual system. Grading of the perimetry was done.[15]

- Imaging studies: Magnetic resonance imaging and magnetic resonance venography of the brain were performed for all patients at the diagnostic Radiology Department of the Cairo University Hospitals. Magnetic resonance imaging was performed on the 1.5 Tesla Phillips Intera scanner at the Magnetic Resonance Unit (Radiodiagnosis Department, Kasr AL Ainy hospital) to exclude secondary causes of increase intracranial pressure. MRI images were analyzed regarding hydrocephalus, intracranial masses, meningeal disease and dural venous sinus thrombosis, and presence of an empty sella sign. Magnetic resonance venography (MRV) was performed to detect abnormalities of the venous system including thrombosis, irregularities, attenuation, or filling defects in venous sinuses.[16]
- CSF opening pressure measurement: Opening CSF pressure was measured for all patients by lumbar puncture (LP) using an LP needle. CSF pressure is measured in naïve patients prior to treatment. LP was performed under complete aseptic conditions with the patient lying in the lateral decubitus position and legs extended during the pressure measurements. LP needle was introduced into the thecal space between L3–4 vertebrae at the level of the superior iliac crest. The reference range for IIH diagnosis: cerebrospinal fluid (CSF) pressure exceeds 250 mm CSF.[9]
- Laboratory Workup included:
  1. Antinuclear antibodies, lupus anticoagulant, antiphospholipid antibodies. Factor v Leiden, protein S, protein C, Antithrombin III to exclude secondary causes of increased intracranial pressure.
  2. Hormonal profile: including FSH, LH, TSH, GH, prolactin, and ACTH.
  3. *Measurement of serum levels of tumor necrosis factor* α by enzyme-linked immune assay (ELISA). It was performed at the Biochemistry department of the faculty of medicine, Cairo University. Blood samples were collected from antecubital veins of all participants at 8:00 a.m. after eight hours of fasting in order to achieve standardization. Samples were centrifuged and prepared sera were stored at −80℃ for later use. Repeated freeze/thaw cycles were avoided.

2.5 | Statistical analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 21. Data were summarized using number and percentage for qualitative variables, mean and standard deviation for quantitative variables that are normally distributed, and mean and interquartile range were used in quantitative variables that are not normally distributed. Comparisons between groups were done using chi-square ($\chi 2$) test for qualitative variables, non-parametric Kruskal–Wallis test and Mann–Whitney test were used in quantitative variables that are not normally distributed. Correlations were done to test for the linear relationship between variables. Linear regression analysis was done to test for significant predictors of TNF-α. *p* Values less than .05 were considered as statistically significant.

TABLE 1 Age, sex, and BMI of the studied groups

	Patients	Control	*p* Value
Age			
Range	18–58 years	18–58 years	.9
Mean ± SD	36.25 ± 8.23	35.93 ± 8.67	
Sex *n* %			
Females	35 (97.2%)	29 (96.6%)	1
Males	1 (2.8%)	1 (3.33%)	
BMI (Kg/m^2)			
Mean ± SD	36.07 ± 7.92	36.57 ± 8.59	.9
Normal weight	1 (2.8%)	1 (3.3%)	
Overweight	6 (16.7%)	5 (16.7%)	
Class I obesity	9 (25%)	8 (26.7%)	
Class II obesity	13 (36.1%)	8 (26.7%)	
Extreme obesity	7 (19.4%)	8 (26.7%)	

Abbreviation: BMI, Body mass index.

3 | RESULTS

3.1 | Descriptive data

3.1.1 | Age, sex, and Body Mass Index

Age, sex, and Body Mass Index (BMI) are illustrated in Table 1.

3.1.2 | Clinical characteristics of patients group

Age at onset and Duration: The age at onset of IIH ranged from 16 to 52 years with a mean of 31.42 ± 8.22 years. Disease duration ranged from 1 month to 240 months with a mean duration 62.17 ± 63.483 months.

History of relapse: Two patients (5.5%) did not experience any relapse during the course of the disease, 8 patients (22.2%) had one relapse, 14 patients (38.8%) had two relapses, 5 patients (13.8%) had three relapses, 5 patients (13.8%) had four relapses, and 2 patients (5.5%) had more than 5 relapses.

Menstrual history: Twenty-seven patients (27%) had regular menses. Menstrual irregularities were reported in eight patients (25.1%), in the form of oligohypomenorrhea and metrorrhagia. Two patients had amenorrhea (5.5%) and one patient (2.7%) was menopausal.

Treatment: Thirty-five patients (97.2%) used medical treatment in the form of acetazolamide with different dosages, and 1 patient

TABLE 2 Comparison of mean serum TNF-α between the study groups

		Mean ± SD	Median	IQR	*p* Value
Serum TNF-α (ng/ml)	Patients	116.95 ± 43.43	105	90.35–127.13	<.001*
	Controls	43.32 ± 17.79	36.85	32.23–46.30	

Abbreviations: IQR, interquartile range; TNF-α, tumor necrosis factor alpha.
*Highly significant.

(2.8%) did optic nerve fenestration in her right eye and was prepared to do fenestration in her left eye.

Headache characteristics: Headache was reported by 29 patients (80.55%). According to the comparative pain rating scale, the headache was severe in 17 patients (47.2%), moderate in 9 patients (25.0%), and mild in 10 patients (27.8%). Headache was diurnal in 12 patients (29.7%) and nocturnal in 14 patients (37.8%) and it shows no variation in 10 patients (27.8%). Headache was related to vertex in 11 patients (30.6%), occipital in 10 patients (27.8%), whole cranium in 9 patients (25%), bitemporal in 4 patients (11.1%), bifrontal in 1 patient (2.8%) and temporal in 1 patient (2.8%). The headache was bursting in 9 patients (25.0%), pressing in 8 patients (22.2%), dull aching in 6 patients (16.7%), throbbing in 5 patients (13.9%), band like in 5 patients (13.9%), and burning, tight band and lancinating in one patient for each.

Results of the ophthalmological assessment

Visual symptoms were reported as a primary complaint in seven patients (19.5%), and in association with headache in 29 patients (80.5%). The visual symptoms were in the form of blurring of vision in 13 patients (36.1%), TVOs in 12 patients (12%), diminution of vision in 8 patients (22.2%), photophobia in 4 patients (11.1%), and diplopia in two patients (5.6%).

Eleven patients (30.6%) had a normal visual acuity, 17 patients (47.4%) had mild visual impairment, four patients (11.1%) had moderate visual impairment, three patients (8.3%) had severe visual impairment, and one patient (2.8%) had hand movements.

Twenty-eight patients (77.8%) had papilledema with different grades, six patients (16.7%) had post papilledemic optic atrophy, and two patients (5.5%) had a resolved papilledema.

Ten patients (27.7%) had mild field changes (grade 1), 11 patients (30.5%) had moderate field changes (grade 2), nine patients (25%) had severe field changes (grade 3), and six patients (16.6%) had tubular scotoma (grade 4).

3.1.3 | CSF opening pressure

The opening CSF pressure in the patients ranged from 150 to 770 mmH_2O with a mean 398.75 ± 133.798 mmH_2O.

3.1.4 | MRI and MRV of the brain

Thirty patients (81.1%) had a normal brain MRI, three patients (8.1%) had partially empty sella turcica, one patient (2.7%) had a mega cisterna magna, and one patient had a prominent sulci (2.7%). MRV was normal in 35 patients (97.3%), and one patient had an attenuation in the transverse sinuses (2.7%).

3.1.5 | Serum TNF-α levels

In the patients group, serum TNF-α ranged from (53.60–225.40 ng/ml) with a median of 105.00, while in control subjects, it ranged from (26.30–91.30 ng/ml) with a median of 36.85 ng/ml.

3.2 | Comparative results

3.2.1 | Comparison of serum TNF α levels between the studied groups

There was a statistically significant difference between patients and controls with regard to the mean serum TNF-α level, being significantly higher in patients compared to controls (p value < .001) Table 2.

3.2.2 | Comparison of serum TNF-α levels between patient subgroups distributed according to BMI

There was no statistically significant difference between patients subgroups in terms of the mean serum TNF-α level (p value = .9).

3.2.3 | Comparison of serum TNF-α levels between patient subgroups distributed according to headache severity, relapse rate, and CSF opening pressure

There was no statistically significant difference between patient subgroups distributed according to headache severity, number of relapses or CSF opening pressure as regards mean serum TNF-α level (p value = .16, .92, .18 respectively).

3.2.4 | Comparison of serum TNF-α levels between patient subgroups distributed according to visual acuity, papilledema grading, and perimetry

There was no statistically significant difference between patients subgroups distributed according to visual acuity as regards mean

serum TNF-α level (*p* value = .23 for the right eye and .32 for the left eye). Also, no statistically significant difference was found between patient subgroups distributed according to the papilledema grade or perimetry as regards mean serum TNF-α level (*p* value = .44, .12) respectively.

3.3 | Correlations

A statistically significant negative correlation was detected between serum TNF-α level and CSF opening pressure and grade of perimetry ($r = -.37$, *p* value = .02), ($r = -.36$, *p* value = .02), respectively (Figures 1 and 2). However, no significant correlation was detected between age at onset, disease duration, BMI, headache severity, or relapse rate and serum TNF-α level ($p > .05$). No significant correlation was also detected between serum TNF-α level and visual acuity and grade of papilledema ($p > .05$) Table 3.

3.4 | Regression analysis

Stepwise linear regression analysis was done to test for significant predictors of TNF α among IIH patients. Papilledema grade, perimetry grade, and CSF opening pressure and perimetry degree were entered in the regression analysis model. Only perimetry grade was found to be a significant predictor for TNF-α, a one-unit increase in perimetry grading is associated with a decrease by 13.96 ng/ml in the mean serum TNF-α level, Table 4.

4 | DISCUSSION

The exact pathophysiological mechanisms of IIH remain controversial. Although pressure dynamics of CSF seem to have a role in the etiology, the contribution of inflammatory mechanisms and changes in cytokine levels have been proposed.[3,17]

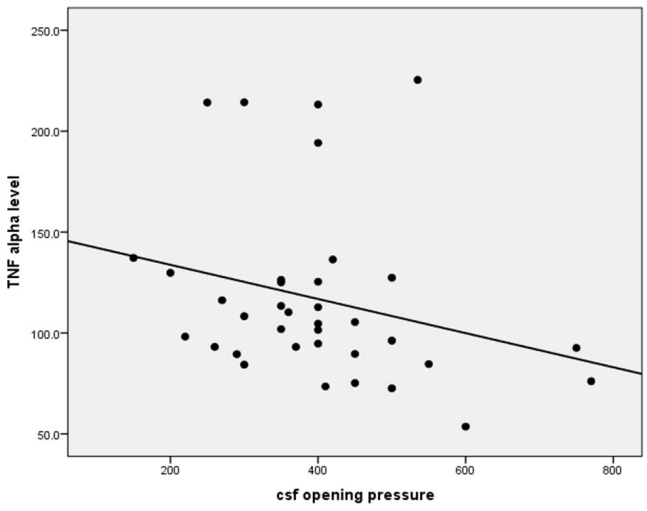

FIGURE 1 Correlation between serum TNFα level and cerebrospinal fluid (CSF) opening pressure

In the present study, mean serum TNF-α levels were significantly higher in IIH patients compared to healthy controls. This was in agreement with Altıokka-Uzun and colleagues, 2015,[18] who reported that patients with IIH had significantly elevated levels of TNF-α and other cytokines (IFN-g, IL-4, 10, 12, 17) in their sera compared to healthy controls and patients with relapsing-remitting multiple sclerosis (MS) in a study performed on 26 IIH patients, 13 multiple sclerosis patients, and 20 healthy subjects. Moreover, TNF-α and IL-17 showed higher CSF than serum concentrations in IIH patients indicating the presence of intrathecal cytokine-producing immune cells. They concluded that the presence of elevated cytokine levels in IIH patients may indicate a non-antigen-driven generalized pro-inflammatory state and support an immunologic background in the pathophysiological pathway of this disorder.

On the contrary, Edwards et al, 2013,[17] analyzed the concentrations of 14 cytokines in the serum and cerebrospinal fluid (CSF) of 17 patients with IIH and 53 patients with other neurological conditions (multiple sclerosis, inflammatory neurological conditions, and non-organic/non-inflammatory neurological conditions). No significant differences were seen in serum cytokine levels between the patient groups. In IIH patients, levels of IL-2, 8, and 17 were significantly higher in CSF than serum; levels of (IL-1β, 4, 22), IFN-γ, and TNF-α were significantly higher in serum than in CSF, indicating the intrathecal synthesis of these cytokines in IIH. The discrepancy between results may be attributed to the difference in sample size, inclusion criteria, and methodology.

Samanci, et al, 2016[19] also reported that TNF-α levels were significantly lower in IIH patients compared to healthy control subjects in a study including thirty-nine IIH patients and 40 age-, gender-, and BMI-matched healthy subjects. Serum TNF-α levels were significantly lower in IIH patients with relapse compared to healthy controls. They also reported that patients who showed good response to treatment had higher levels of TNF-α, suggesting that this marker might be used in predicting the prognosis of IIH.

Although obesity is one of the main risk factors of IIH, the involvement of this association with IIH pathogenesis is not clear. Obesity is recognized as a pro-inflammatory state and is associated with the increased expression of a number of adipokines and cytokines including leptin, IL-6, and TNF-α.[7] Di Gregorio et al, 2005[20] proved that inflammatory cells infiltrate fat cells within the adipose tissue and activate adipocytes to produce inflammatory mediators and adipocytokines involving TNF-α, leading to a vicious circle of inflammation related to obesity. Moreover, Sinclair et al (2008)[3] reported elevated levels of TNF-α in adipose tissues of humans and rats.

In the current study, no relationship was found between BMI and serum TNF-α level. This was in accordance with previous studies that found no correlation between cytokine/adipokine levels in serum and BMI.[18,21] Moreover, Samanci et al, 2016[19] reported the lack of correlation between BMI and serum TNF-α level, suggesting

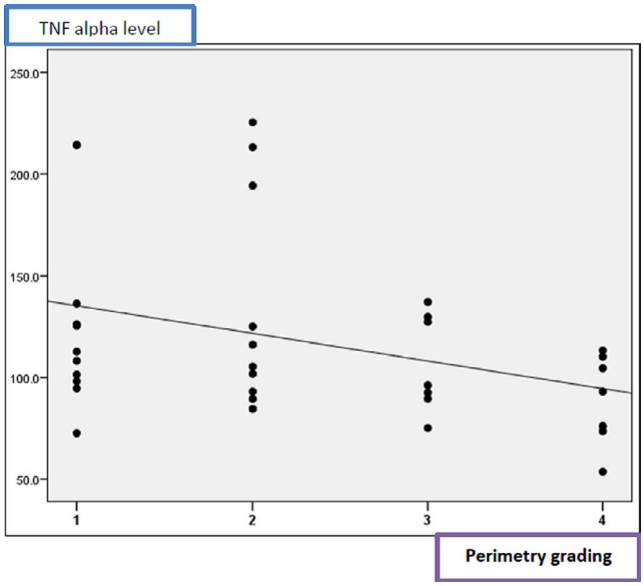

FIGURE 2 Correlation between serum TNFα level and perimetry grade

that TNF-α does not depend only on the adipose tissue. They also failed to show significant alterations of adipokine levels in IIH patients compared to matched controls, and there were no correlations between adipokine levels and clinical features of IIH subgroups, suggesting that inflammatory findings observed in IIH patients are not simply mediated by adipose tissue.

In this study, serum TNF-α level was statistically negatively correlated with CSF opening pressure and perimetry grade. This might be explained by the differential obesity-related pathway regulation in IIH patients. Serum TNF-α levels of IIH patients were found to be paradoxically decreased as compared to overweight healthy individuals. IIH patients showed relatively reduced leptin and relatively increased IGF-1 levels. Leptin and IGF-1 are known to enhance and suppress TNF-α production, respectively.[22,23] However, Edwards et al, 2013[17] found no correlations between TNF-α levels and CSF opening pressure in IIH patients. This discrepancy may be attributed to the small cohort of IIH patients (17 patients) included in the study by Edwards et al. To the best of our knowledge, this is the first study assessing the relationship between perimetry grading and TNF-α level.

In the present study, serum TNF-α level was not significantly correlated with either headache severity, relapse rate, visual acuity, papilledema grading, a finding which agreed with Samanci et al, 2016,[19] who found no correlation between TNF-α level and clinical parameters such as headache severity, relapse rate, visual loss, or papilledema.

In this study, 34 patients (94.5%) had previous relapses. Samanci, et al, 2016[19] reported that the detection of higher levels of pro-inflammatory IL-8 and TNF-α in patients without relapse and IL-1b in patients with relapse suggests that chronic low-level inflammation might have a protective role in IIH. The mechanisms by which inflammation reduces the neuronal damage induced by increased intracranial pressure in IIH need to be further studied. Pro-inflammatory

TABLE 3 Correlation of serum TNF-α with clinical, ophthalmological parameters and CSF opening pressure

TNF-α serum level (ng/ml)	Age at onset (years)	*R*	−.14
		p Value	.41
	Duration (months)	*R*	.22
		p Value	.19
	BMI	*R*	.07
		p Value	.65
	Relapse frequency	*R*	−.02
		p Value	.22
	Headache severity	*R*	.1
		p Value	.53
	Right visual acuity	*R*	−.16
		p Value	.34
	Left visual acuity	*R*	−.1
		p Value	.54
	Papilloedema grade	*R*	−.09
		p Value	.6
	Perimetry grade	*R*	−.36
		p Value	.028*
	CSF opening pressure (mmH_2O)	*R*	−.37
		p Value	.025*

Abbreviations: BMI, body mass index; CSF, cerebrospinal fluid; TNF-α, tumor necrosis factor alpha.
*Significant.

TABLE 4 Significant predictors for serum TNF-α among IIH patients

	p Value	B (regression coefficient)	95% C1 for B
Perimetry grading	<.001	149.53	117.71: 181.35
	−.027	−13.96	−26.24: −1.69

cytokines are well known to activate multiple survival pathways and to enhance the proliferation capacity of endothelial and smooth muscle cells.[24] Mildly elevated pro-inflammatory cytokine levels might attenuate the vascular damage inflicted by increased intracranial pressure, improving the nourishment of the neuro-axonal structures, and thus ameliorating the visual disturbance.[18] In view of this, we may suggest that the recurrent relapses in most of our IIH patients enhanced the chronic inflammatory protective mechanisms that result in increased TNF-α levels during the remission period. The cumulative effect of this chronic inflammation may explain the high levels of serum TNF-α in our patients compared to controls. It may also clarify the contradiction with Samanci, et al, 2016,[19] who reported low level of TNF-α in their patients, as relapses were found only in 12% of their patients.

Stepwise linear regression analysis revealed that a one-degree increase in perimetry grading was associated with a decrease by 13.96 ng/ml in TNF-α level, which means that TNF-α level is an indicator of the severity of the visual affection in IIH patients.

Previous researchers have suggested the key role of inflammation in the pathogenesis of IIH. Dysregulation of inflammatory cytokines and adipokines may drive aberrant 11β-HSD1 (11β-hydroxysteroid dehydrogenase type 1) activity in IIH. This may lead to altered CSF dynamics.[25] Moreover, neuroinflammation is associated with persistent reactive gliosis, which may impair glymphatic pathway function.[26] Lenck et al[27] hypothesized that IIH may be triggered by an initial impairment in interstitial fluid (ISF) transport from the glymphatic system to the dural venous sinuses. It seems that TNF-α induced neuroinflammation could be associated with impairment of CSF circulation (overproduction or under drainage), possibly through TNF-α-mediated glucocorticoid dysregulation. TNF may also account for veno glymphatic pathway dysfunction. Both altered CSF dynamics and veno glymphatic pathway dysfunction may contribute to the pathophysiology of IIH.

The main limitation to this study is the variations in serum TNF-α level during disease stages (relapse and remission). So, repeated measurement of its level is recommended to realize the variance over time. Another limitation was that we did not have the opportunity to analyze other inflammatory biomarkers in both serum and CSF.

In view of the previous findings, it could be concluded that altered serum TNF-α levels may support the role of inflammatory mechanisms in the pathophysiology of idiopathic intracranial hypertension (IIH) and that serum TNF-α level can be used as a prognostic marker for disease severity. However, the relationship between inflammation and IIH needs further elucidation as to whether it reflects a disease-causing immunological mechanism or is a phenomenon caused by non-inflammatory secondary causes such as stagnation of CSF and compression of the neural tissue due to elevated CSF pressure. Consequently, future studies are warranted to investigate whether IIH patients may benefit from either immunotherapy that modulates TNF-α levels to decrease disease severity and prevent the occurrence of relapses or the removal of adipokine-producing fat tissue by liposuction.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in absence of any commercial relationships that could be constructed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Ebtesam Mohamed Fahmy: research idea, data acquisition, data analysis and interpretation, and manuscript writing and reviewing; **Laila Ahmed Rashed**: performing and reviewing the laboratory workup; **Riham Hamdy Mostafa**: data acquisition, data analysis and interpretation; **Rania Shehata Ismail:** research idea, data acquisition and interpretation and manuscript writing and reviewing.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available due to current Cairo University regulations & Egyptian legislation but are available from the corresponding author on reasonable request and after institutional approval.

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