Abdelghaffar *et al.*
Egypt J Neurol Psychiatry Neurosurg (2022) 58:39
https://doi.org/10.1186/s41983-022-00473-x

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

RESEARCH Open Access

Sex hormones, CSF and serum leptin in patients with idiopathic intracranial hypertension

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Abstract

Background: Idiopathic intracranial hypertension (IIH) is typically seen in females of childbearing period; therefore, it is possible that female sex hormones have a pathogenic role in IIH. Obesity is considered as a strong risk factor for IIH, Leptin levels in the serum and CSF were found to be positively correlated with anthropological measures of obesity. The role of leptin and sex hormones in the pathogenesis of idiopathic intracranial hypertension is not fully understood. The aim of this work was to assess CSF leptin, serum leptin, estradiol, testosterone, Dehydroepiandrosterone sulfate (DHEAS) levels in idiopathic intracranial hypertension (IIH) patients.

Results: This is a case control study which was conducted on 38 IIH female patients and 38 females as controls. IIH patients had significantly higher levels of serum Leptin, CSF Leptin, serum estradiol and serum testosterone than controls (P value < 0.001, < 0.001, 0.005 and < 0.001, respectively), whereas there was no statistically significant difference between IIH patients and controls in serum DHEAS (P value $= 0.142$). IIH patients with body mass index (BMI) ≥ 30 kg/m^2 had significantly higher levels of serum Leptin, CSF Leptin, serum estradiol, serum testosterone, and serum DHEAS than IIH patients with BMI < 30 kg/m^2 (P value < 0.001, < 0.001, 0.009, < 0.001, and < 0.001, respectively).

Conclusions: Patients with IIH express a characteristic elevation in CSF leptin, serum leptin, estradiol and testosterone levels. These hormones are significantly elevated in patients with high BMI.

Keywords: IIH, Leptin, Sex hormones, BMI, Papilledema

Background

Idiopathic intracranial hypertension (IIH) is a syndrome characterized by increased intracranial pressure (ICP) with normal content of cerebrospinal fluid (CSF) and with no evidence of mass lesion or dilated ventricles by imaging [1]. The incidence of IIH around the world is 12–20/100,000/year, typically seen in obese women in childbearing period [2, 3]. The IIH patients mainly complain from headache (94%), blurring of vision (30%), transient visual obscurations (68%), double vision (38%), retrobulbar pain (44%) and tinnitus (58%). Papilledema, due to intracranial pressure elevation, is considered the fundamental sign of IIH. Papilledema is considered the main cause of loss of vision in IIH either directly or indirectly. High grade papilledema, is considered the most important risk of the visual loss. Visual field defects occur in almost all cases of IIH. The enlargement of the blind spot and loss of inferonasal portions of the visual field are the most common defects [4].

Obesity is considered a strong risk factor for IIH. This increased the interest of studying the association between elevated serum leptin level and IIH. Leptin levels in the serum and CSF were found to be positively correlated with anthropological measures of obesity [5].

IIH is typically seen in females of childbearing period; therefore, it is possible that female sex hormones have a pathogenic role in IIH. However, a characteristic

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hormonal profile has not yet been described in IIH [6]. Some case reports have suggested a relation between the development of IIH and oral contraceptives as well as pregnancy [7, 8]. These findings suggest an important role for female sex hormones in IIH [9, 10].

The aim of this study was to assess CSF leptin, serum leptin, estradiol, testosterone, Dehydroepiandrosterone sulfate (DHEAS) levels in patients with IIH.

Methods

This is a case control study that was conducted on 38 patients with idiopathic intracranial hypertension and 38 controls. All our participants were females more than 18 years, only patients who were newly diagnosed IIH and did not start any treatment were included, and ICP > 25 cmH_2O was required. Subjects in whom intracranial hypertension was negated with no neuro ophthalmological signs were included as controls. All our patients fulfilled the modified Dandy criteria for diagnosis of idiopathic intracranial hypertension (symptoms and signs of increased intracranial pressure, normal neurologic exam except 6th cranial nerve palsy, the patient is awake and alert, increased CSF opening pressure (> 25 cm H_2O) with normal biochemical and cytological composition of CSF, no evidence of hydrocephalus, structural or vascular lesion on imaging, and no other cause of increased ICP) [11]. We had excluded patients with intracranial hypertension which is secondary to cerebral sinus thrombosis, or secondary to systemic diseases (hepatic or renal failure, systemic lupus and malignancy) and patients with structural lesion in MRI brain. Females who were pregnant or on hormonal contraceptive methods were also excluded from both patients and controls.

The subjects were recruited from Neurology clinic, Cairo University hospitals during the period from January 2020 to January 2021. Written informed consent was obtained from all participants in the study. The study was approved by the local ethical committee of Faculty of medicine, Cairo University.

Clinical data were collected from the included patients with special emphasis on hypertension, diabetes, and body mass index (BMI), headache and visual symptoms. Headache severity was assessed using the visual analogue scale (VAS) [12]. Papilledema was graded using the Frisén Scale [13]. Grade 0 indicated the absence of halo of obscuration of the peripapillary nerve fiber layer. Grade 1 indicated a C-shaped halo of retinal nerve fiber layer edema obscuring the peripapillary retina. Grade 2 indicated that halo was circumferential with no vessel obscuration. Grade 3 indicated that major vessels were obscured by edema. Grade 4 indicated that major vessels were obscured by edema on the optic disc. Grade 5 indicated that all vessels were at least partially obscured by edema.

Diagnostic lumbar puncture was done under complete aseptic condition. The patient is placed in lateral decubitus position with extended legs, head and spine strictly horizontal, and as relaxed as possible. A 22-gauge needle was inserted at the space between L4 vertebra and L5 aiming to reach the spinal canal and drain the CSF. Opening pressure was measured by the height of the CSF column. CSF pressure between 6 and 20 cm H_2O was considered normal, although in overweight individuals with pressure 25 cm H_2O were considered normal. Enough time was allowed for the pressure to stabilize.

Laboratory assessment included the routine workup: Complete blood picture, erythrocyte sedimentation rate, and liver and kidney functions. Serum levels of leptin, estradiol, testosterone, Dehydroepiandrosterone sulfate (DHEAS) and cerebrospinal fluid (CSF) leptin level were measured to all subjects. CSF and serum leptin were measured with the Active Human Leptin ELISA Kit (Diagnostic System Laboratories Inc, Webster, TX, USA). CSF and blood samples were obtained between 8:00 am and 12:00 pm. Blood samples were collected at 37 °C by venipuncture from blood samples. The collected serum was separated, aliquoted, and stored at − 80 °C.

CSF samples were collected at the time of LP and transported on ice before being promptly centrifuged at 176 g for 10 min and aliquoted. All samples were stored at − 80 °C and analyzed after a maximum of one freeze–thaw cycle. Testosterone is measured by enzyme linked immunosorabant assay (ELISA) (GWB_462C5C). Estradiol and DEHAS are measured by immunosorabant assay (ELISA) assay kit manufactured in USA, respectively.

The required sample size was calculated using the IBM[a] SPSS[a] Sample Power[a] version 3.0.1 (IBM[a] Corp., Armonk, NY, USA). Based on intensive literature review, the median and IQR range of CSF leptin in the control group was found to be 0.83 ng/ml (0.67–1.32) versus 0.94 ng/ml (0.74–1.74) in the IIH group as reported by Behbehani and colleagues [13]. This difference between the groups was taken for calculating the sample size. At 95% level of significance and power of 80%, the minimal sample size calculated was 38 in each group.

Magnetic resonant imaging (MRI) of brain (T1, T2 and FLAIR) and Magnetic resonance venography (MRV) were performed at the Diagnostic Radiology Department, Cairo University hospitals. Scans were done on a 1.5 Tesla Philips intera scanner (Brand: Philips, Model: 1.5 Tesla Philips intera scanner, made in United States) to all patients to rule out both intracranial mass lesion and dural sinus thrombosis.

Statistical analysis

The collected data were coded and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative (categorical) data were represented as frequencies and relative percentages. Chi square test (χ^2) was used to compare two or more independent groups of qualitative data. Quantitative data were expressed as mean ± SD (Standard deviation) or median (range). Comparison between two independent groups of quantitative data was performed using the *t* test for parametric data and the Mann–Whitney *U* test for non-parametric data. Significance test results were quoted as two-tailed probabilities and $P \leq 0.05$ indicates a significant difference.

Table 1 Demographic data and comorbidities in IIH patients and control group

		IIH group ($n=38$)	Control group ($n=38$)	*P* value
Age (mean ± SD)		34 ± 8.6	33.7 ± 8	0.823
BMI (mean ± SD)		36.3 ± 6.2	34 ± 4.1	0.0603
DM	Yes [*n* (%)]	8 (21.1%)	6 (15.8%)	0.126
	No [*n* (%)]	30 (78.9%)	32 (84.2%)	
Hypertension	Yes [*n* (%)]	4 (10.5%)	5 (13.2%)	0.243
	No [*n* (%)]	34 (89.5%)	33 (86.8%)	

BMI body mass index, *DM* diabetes mellitus, *IIH* idiopathic intracranial hypertension

P value ≤ 0.05 was considered significant

Results

This is a case control study which was conducted on 38 female patients diagnosed with IIH and 38 age matched females as controls. There was no statistically significant difference between IIH patients and controls in either age, BMI, DM or HTN (*P* value > 0.05) (Table 1).

All IIH patients reported headache and visual symptoms. The median grade of papilledema among IIH patients was 3 (2–4), whereas the median value for VAS was 6 (3–10).

CSF opening pressure was significantly higher in IIH patients compared to controls ($P < 0.001$) (Table 2). Regarding the laboratory data, IIH patients had significantly higher levels of serum Leptin, CSF Leptin, serum estradiol and serum testosterone than controls (*P* value < 0.001, < 0.001, 0.005 and < 0.001, respectively). There was no statistically significant difference between IIH patients and controls in serum DHEAS (*P* value = 0.142) (Table 2).

IIH patients with BMI ≥ 30 kg/m^2 had significantly higher levels of serum Leptin, CSF Leptin, serum estradiol, serum testosterone, and serum DHEAS than IIH patients with BMI < 30 kg/m^2 (*P* value < 0.001, < 0.001, 0.009, < 0.001 and < 0.001, respectively) (Table 3).

Discussion

Hormonal profile in women of childbearing age was believed to have a role in the pathogenesis of IIH. However, to date, there is no established hormone profile in individuals with IIH [14]. The aim of our work was to assess CSF leptin, serum leptin, estradiol, testosterone, Dehydroepiandrosterone sulfate (DHEAS) levels in patients with IIH.

In our study, Only newly diagnosed IIH patients who did not start acetazolamide treatment were included,

Table 2 Laboratory data and CSF pressure in IIH and control groups

	IIH group ($n=38$)	Control group ($n=38$)	*P* value
Serum leptin (ng/ml) (mean ± SD)	68.2 ± 19.56	21.13 ± 14.5	< 0.001*
CSF leptin (ng/ml) (mean ± SD)	3.64 ± 1.88	1.08 ± 0.64	< 0.001*
Serum estradiol (Pg/ml) (mean ± SD)	196.15 ± 75.26	79.45 ± 45.15	0.005*
Serum testosterone (nmol/l) (mean ± SD)	1.78 ± 0.53	0.93 ± 0.27	< 0.001*
Serum DHEAS (µmol/L) (mean ± SD)	5.21 ± 1.84	4.97 ± 1.36	0.142
CSF pressure (cm H_2O) (mean ± SD)	36.4 ± 7.3	17.6 ± 5.7	< 0.001*

DHEAS dehydroepiandrosterone sulfate, *IIH* idiopathic intracranial hypertension, *CSF* cerebrospinal fluid, *: significant

P value ≤ 0.05 was considered significant

Table 3 Laboratory data in IIH patients in relation to BMI

	IIH patients with BMI < 30 kg/m^2 ($n=16$)	IIH patients with BMI ≥ 30 kg/m^2 ($n=22$)	*P* value
Serum leptin (ng/ml) (mean ± SD)	43.22 ± 14.2	93.19 ± 24.6	< 0.001*
CSF leptin (ng/ml) (mean ± SD)	2.63 ± 1.19	4.65 ± 2.59	< 0.001*
Serum estradiol (Pg/ml) (mean ± SD)	138.08 ± 43.19	254.17 ± 107.61	0.009*
Serum testosterone (nmol/l) (mean ± SD)	1.26 ± 0.41	2.3 ± 0.62	< 0.001*
Serum DHEAS (µmol/l) (mean ± SD)	4.99 ± 1.4	5.43 ± 2.28	< 0.001*

CSF: cerebrospinal fluid, *DHEAS*: dehydroepiandrosterone sulfate, *IIH* idiopathic intracranial hypertension, *: significant

P value ≤ 0.05 was considered significant

to avoid the effect of carbonic anhydrase inhibitors on decreasing the CSF pressure and to avoid its effect on reducing weight as discussed by Woodman and colleagues who assumed that acetazolamide, a strong inhibitor of carbonic anhydrase, would reduce chloride/bicarbonate co-transport and decrease food intake, stimulate locomotion, and reduce weight gain from emotional eating [15].

In the present study, our results revealed that IIH patients had significantly higher levels of serum and CSF Leptin than controls. In agreement with our findings, Behbehani et al. who reported a significant elevation of serum leptin in IIH cases compared to controls ($P<0.05$) [16]. Similarly, Ball et al., found that serum and CSF leptin levels were significantly higher in IIH patients compared to controls ($P<0.001$) [17]. Although leptin hormone induces satiety, its levels was found to be increased in overweight persons, who are at higher risk to have IIH. This supports the theory of increased leptin resistance in such population [18, 19].

The exact mechanism by which leptin could induce IIH remains unclear. However, some researchers believe that chronic CSF leptin elevation could increase Na/K ATPase activity in the choroid plexus, leading to increased CSF secretion [10].

On the other hand, other authors negated any significant difference between IIH cases and controls regarding serum leptin (*P* value < 0.05) [16]. Another small study confirmed the non-significant difference regarding CSF leptin levels in IIH cases and controls [20]. The disparity between different studies could be explained by different CSF leptin measurement assay, variation of CSF leptin level if measured over 24 h period, or exposure to some drugs affecting its levels [21, 22].

In the present study, IIH patients had significantly higher levels of serum estradiol than controls. Farukhi et al., stated that estradiol can induce increased permeability rates of aquaporin-1 when compared to estrone and estriol. As estradiol is the main circulating estrogen form during the child bearing period, the hormonal preference of AQP-1 may explain the increased prevalence of idiopathic intracranial hypertension in women of childbearing period [23].

In contrast to our findings, other authors negated the significant elevation of estradiol levels in IIH cases [24]. Surprisingly, another study reported that estrogen and progesterone could decrease CSF production by the choroid plexus, either individually or in combination [25].

In the current study, serum testosterone showed a significant elevation in IIH cases compared to controls ($P<0.001$). Likewise, O'Reilly et al., confirmed these findings regarding serum testosterone, as it had a median value of 1.7 (range 1–2.4) nmol/ml in IIH cases and 1 (0.5–1.4) nmol/ml in controls, with a high significant difference between the two groups ($P<0.001$) [26]. Moreover, it was reported that about 39–57% of IIH patients have polycystic ovary syndrome (PCOS) which is characterized by androgen overproduction [27–29].

Our results showed that serum DHEAS was not significantly different between IIH cases and controls ($P=0.142$). In line with our findings, O'Reilly et al., negated any significant difference between IIH and controls regarding serum DHEAS ($P>0.05$) [26].

In the present study, IIH patients with BMI ≥ 30 g/m^2 had significantly higher levels of serum Leptin, CSF Leptin, serum estradiol, serum testosterone, and serum DHEAS than IIH patients with BMI < 30 g/m^2.

In accordance to our findings, Behbehani et al. reported that serum leptin level was significantly elevated in patients with higher BMI ($P=0.017$) [16]. On the other hand, Ball and colleagues negated any significant correlation between leptin levels (serum or CSF) and BMI in patients with IIH. However, a significant positive correlation was noted regarding these variables when applied in controls [17]. Klein et al., reported insignificant impact of BMI in IIH cases on serum estradiol (*P* value = 840), testosterone (*P* value = 0.952) or DHEAS levels ($P=0.511$) [24].

Our study has some limitations, first of all, it is a single center study that included a relatively small sample size. Second, the effect of weight loss on the studied parameters was not investigated. We recommend that the upcoming research should focus on the molecular mechanisms by which these hormonal changes could induce this increase in intracranial pressure.

Conclusions

Patients with IIH express a characteristic elevation in CSF leptin, serum leptin, estradiol and testosterone levels. These hormones are significantly elevated in IIH patients with BMI ≥ 30 kg/m^2 in comparison to those with BMI < 30 kg/m^2.

Abbreviations

CSF: Cerebrospinal fluid; IIH: Idiopathic intracranial hypertension; DHEAS: Dehydroepiandrosterone sulfate; BMI: Body mass index; MRI: Magnetic resonance imaging; MRV: Magnetic resonance venography; VAS: Visual analogue scale; ELISA: Enzyme linked immunosorabant assay; LP: Lumbar puncture; PCOS: Polycystic ovary syndrome.

Acknowledgements

The authors acknowledge subjects for their participation and cooperation in this study.

Authors' contributions

MA participated in study design, collection of data and helped to draft manuscript. MH participated in study design, analysis of data and helped to draft manuscript. SA performed the laboratory work up and helped to draft manuscript. HE: participated in study design, and helped to draft manuscript. All authors have read and approved the final manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Availability of data and materials

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

Declarations

Ethics approval and consent to participate

An informed written consent was taken from each patient. All data obtained from every patient were confidential and were not used outside the study. The patients have rights to withdraw from the study at any time without giving any reason. All the cost of the investigations was afforded by the researcher. Our study was approved by ethical committee of the Department of Neurology, Faculty of Medicine, Fayoum University on 4/1/2020.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 25 November 2021 Accepted: 19 March 2022
Published online: 08 April 2022

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