Journal of the Neurological Sciences 399 (2019) 89–93

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Predictive role of presenting symptoms and clinical findings in idiopathic intracranial hypertension

Aleksandra Radojicic[a,*], Vlasta Vukovic-Cvetkovic[b], Tatjana Pekmezovic[c], Goran Trajkovic[d], Jasna Zidverc-Trajkovic[a], Rigmor Højland Jensen[b]

[a] Neurology Clinic, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
[b] Danish Headache Center, Department of Neurology, University of Copenhagen, Rigshospitalet-Glostrup, Denmark
[c] Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Serbia
[d] Department of Medical Statistics and Informatics, Faculty of Medicine, University of Belgrade, Serbia

ARTICLE INFO

Keywords:
Idiopathic intracranial hypertension
Headache
Papilledema
Obesity
Presenting symptoms

ABSTRACT

Background: The aim of the study was to evaluate the presenting symptoms and signs of idiopathic intracranial hypertension (IIH) in a large cohort of patients and to estimate their possible role in establishing the diagnosis of IIH.

Methods: This prospective cohort study in two tertiary centers, the Danish Headache Center in Rigshospitalet-Glostrup and the Neurology Clinic of the Clinical Center of Serbia, included 286 patients referred by attending specialists for possible IIH evaluation. Patients were divided into two groups: one with confirmed IIH diagnosis and one with rejected IIH diagnosis.

Results: The diagnosis of IIH was confirmed in 219 (76.6%) patients. It was more often confirmed if the patient was referred by an ophthalmologist than if the referral was from a neurologist (83.6% vs. 69.8%, $p = .029$) and in patients with higher body mass index (BMI) ($p = .032$). Transient visual obscurations ($p = .006$), double vision ($p = .033$), neck pain ($p = .025$), and tinnitus ($p = .013$) were presenting symptoms more frequently reported by patients with IIH diagnosis. In the same group of patients, papilledema ($p < .001$) and sixth nerve palsy ($p = .010$) were noted significantly more often. Papilledema was extracted by multivariate analysis as an independent predictor of IIH diagnosis ($p < .001$).

Conclusion: Although studies investigating IIH report an abundance of presenting symptoms, our results indicate that these symptoms are not diagnostic for IIH. Papilledema is the most reliable clinical sign predicting the correct IIH diagnosis in patients with suspected IIH.

1. Introduction

Idiopathic intracranial hypertension (IIH) is a disease characterized by raised intracranial pressure (ICP) in the absence of intracranial space-occupying lesions or any other detectable cause [1]. Epidemiological studies worldwide suggest that IIH is a rare disease with an estimated incidence in the general population of only 0.5–2 per 100,000 people per year, but in the group of obese women of childbearing age, the incidence is 10 to 20 times higher, reaching 12–20 per 100,000 people per year [2,3]. The clinical presentation of IIH varies, presenting most frequently with headache and a finding of papilledema [4]. Headache is present in > 90% of patients at the time of diagnosis, usually unremitting or occurring daily or nearly daily [5]. Swelling of the optic nerve head as a consequence of raised ICP is usually bilateral, although it may be asymmetric [6] or, rarely, absent [7] and if long-standing can result in secondary optic atrophy and permanent visual loss. Transient visual obscurations (TVO), described as monocular or binocular blurring lasting for several seconds, are often seen in patients with papilledema, most likely as a manifestation of transient ischemia of the optic nerve [8]. One characteristic of IIH is the presence of pulsatile tinnitus, rarely reported by patients unless they are specifically asked about it. Unilateral or bilateral sixth nerve palsy may also develop as a result of increased ICP, leading to double vision. Other symptoms include dizziness, nausea, neck and back pain, disturbed concentration, and memory impairment [9].

The diagnostic value of this variety of presenting symptoms and clinical findings has not been thoroughly investigated. Although they do not seem specific for IIH, these presenting symptoms and signs may

* Corresponding author at: Neurology Clinic, Clinical Center of Serbia, Dr Subotica 6, 11000 Belgrade, Serbia.
E-mail address: aleksandraradojicic@gmail.com (A. Radojicic).

https://doi.org/10.1016/j.jns.2019.02.006
Received 7 September 2018; Received in revised form 4 February 2019; Accepted 5 February 2019
Available online 06 February 2019
0022-510X/

suggest raised ICP and direct physicians toward further investigation to confirm or reject a diagnosis of intracranial hypertension (IH). The modified Dandy criteria require only the following neurological symptoms and signs: raised ICP above 25 cm H20, normal cerebrospinal fluid composition, normal imaging studies, and no other identified cause of IH [10]. However, neurological symptoms and signs of raised ICP are not specified by these criteria. Due to advances in neuroimaging, new diagnostic criteria for IIH have been proposed by Friedman [11]. Other than papilledema, they are not based on the clinical presentation of the disease.

The aims of our study were to evaluate the presenting symptoms and signs of IIH in a large cohort of patients and to estimate their possible role in establishing the diagnosis of IIH.

2. Patients and methods

We performed a prospective cohort study in two tertiary centers: the Danish Headache Center at Rigshospitalet-Glostrup and the Neurology Clinic of the Clinical Center of Serbia. Patients were referred by an attending specialist for the evaluation of possible IIH and were consecutively included from January 2007 to March 2016. The study was approved by the Ethics Committee of Rigshospitalet-Glostrup (H-3-2011-016) and the Institutional Review Board of the Neurology Clinic Clinical Center of Serbia. Written informed consent was obtained from all patients.

A clinical semi-structured interview with a questionnaire designed for the study was used to collect the following data: gender, body mass index (BMI), age at disease onset, presenting symptoms of the disease, medication use prior to disease onset, presence of primary headaches, and comorbid disorders.

We analyzed the following presenting symptoms: presence of headache, nausea, vomiting, photo- and phonophobia, visual disturbances, tinnitus, neck pain, dizziness, concentration, and memory difficulties. The analyzed visual disturbances were occurrence of TVO, blurred vision, and double vision. Comorbid disorders, including skin diseases, polycystic ovary syndrome, depression and anxiety, sleep apnea, some medications (tetracyclines, vitamin A preparations, corticosteroids, hormonal contraception), and weight gain were analyzed due to previous reports of their possible role in IH.

The criteria proposed by Friedman in 2002 and its revision from 2013 were applied for diagnostic purposes [11,12]. IH was demonstrated by increased values of opening ICP ≥ 25 cm H20 as measured by lumbar puncture with the patient in the lateral decubitus position with the legs extended and as relaxed as possible. ICP measurement was performed in all patients. In patients in whom acetazolamide treatment was initiated prior to referral, it was withheld 72 h prior to lumbar puncture. Diagnosis of IIH was established by exclusion of secondary causes of IH based on normal results of neuroimaging studies and cerebrospinal fluid examination. In patients with prior use of tetracyclines and vitamin A preparations, IH was considered to be secondary only if the medications were consumed orally; topical use (drops or ointments) was not an exclusion factor for diagnosing IIH in our study. Likewise, stable, long-term, and low-dose systemic corticosteroid therapy did not exclude IIH diagnosis. Neurological examination and head computed tomography (CT) procedures were routinely performed in all patients. In all patients with confirmed IH, brain magnetic resonance imaging (MRI) supplemented by venography was used to exclude cerebral venous sinus thrombosis and other secondary causes. Seven patients in whom MRI was contraindicated or could not be performed due to claustrophobia or body weight limitation were examined by contrast-enhanced CT with CT venography. Neuro-ophthalmological examinations, including eye motility, visual acuity, visual field testing, and ophthalmoscopy were also routinely performed in all patients together with optical coherence tomography (OCT) in some patients. The detailed outcome of the neuroimaging and neuro-ophthalmological findings, apart from papilledema and sixth nerve palsy, were not included in this study but were used to confirm the diagnosis. In order to define presenting symptoms and signs of IIH, patients were divided into two groups: one group with confirmed IIH diagnosis and one group in whom IIH diagnosis had been rejected.

2.1. Statistics

The collected data were compared between the two groups. Clinical symptoms and findings that predict the diagnosis of IIH were analyzed and independent predictors were estimated. ANOVA and chi-square tests were used to compare data between the two groups depending on data distribution. Multivariate logistic regression (enter method) was applied to determine the diagnostic predictors. The criterion for the inclusion of variables in the multivariate model was statistical significance at the level of 5% ($p < .05$) obtained by univariate analysis. Sensitivity, specificity, and likelihood ratios were calculated for all statistically significant predictors, while ROC curve and AUC were obtained for multivariate logistic model.

3. Results

The whole examined cohort consisted of 286 patients: 249 from Denmark and 37 from Serbia. The diagnosis of IIH was confirmed in 219 (76.6%) patients and rejected in 67 (23.4%) patients (non-IIH).

There were no differences between the two groups in terms of gender and age at disease onset. The diagnosis of IIH was more often confirmed if the patient was referred by an ophthalmologist than by a neurologist, and in patients with higher BMI (Table 1).

In the group of non-IIH patients referred by a neurologist (55 patients), the final diagnosis was chronic headache (tension-type headache, medication overuse headache, migraine, posttraumatic headache, hemicrania continua, or combinations hereof) in 46.4% and episodic primary headache (migraine and tension-type headache) in 14.3% of the patients. Elevated ICP was not confirmed in these patients. In the remaining 21.8% of non-IIH patients, values of ICP between 25 cm H20 and 41 cm H20 were recorded; however, secondary causes of IH were identified (renal failure in 2 patients, Addison's disease in 1 patient, oral tetracycline consumption in 1 patient, sleep apnea in 1 patient, viral meningitis in 3 patients, and sinus venous thrombosis in 3 patients). In the group of non-IIH patients who were referred by an ophthalmologist, pseudopapilledema was the most common misdiagnosis (36.4%), along with nonarteritic anterior ischemic optic neuropathy, papillitis, and optic atrophy.

TVO, double vision, tinnitus, and neck pain were the presenting symptoms more frequently reported by patients with established IIH diagnosis; concentration difficulties and memory impairment were significantly less reported in this patient group. Papilledema and sixth nerve palsy were noted significantly more often in patients with IIH (Table 2).

A positive medical history of skin diseases and sleep apnea was significantly less reported by patients with confirmed IIH diagnosis. There were no differences between the two groups in terms of a history of primary headaches, other comorbid disorders, weight gain within the

Table 1
Demographic data and referring provider of IIH and non-IIH patients.

Variable	IIH $N = 219$	Non-IIH $N = 67$	p-Value
Gender – female, n (%)	196 (89.5)	55 (82.1)	0.105
Age at onset (mean ± SD), y	31.0 ± 11.3	33.9 ± 13.3	0.081
BMI (mean ± SD), kg/m^2	34.8 ± 7.4	32.1 ± 7.0	**0.032**
Referrals by ophthalmologist, n (%) vs. neurologist, n (%)[a]	56 (83.6) vs. 127 (69.8)	11 (16.4) vs. 55 (30.2)	**0.029**

p values < 0.05 were considered as statistically significant.
[a] 36 IIH and 1 non-IIH patients were referred by other specialists.

Table 2
Presenting symptoms and signs in IIH and non-IIH patients.

Variable	IIH N = 219	Non-IIH *N* = 67	*p*-Value
Headache, n (%)	198 (90.8)	56 (83.6)	0.096
Blurred vision, n (%)	140 (64.2)	37 (55.2)	0.184
TVO, n (%)	124 (56.6)	25 (37.3)	**0.006**
Double vision, n (%)	87 (39.7)	17 (25,4)	**0.033**
Tinnitus, n (%)	134 (62.6)	30 (45.5)	**0.013**
Neck pain, n (%)	27 (12.5)	2 (3.0)	**0.025**
Dizziness, n (%)	49 (23.2)	8 (12.5)	0.064
Nausea, n (%)	122 (56.2)	36 (54.5)	0.191
Vomiting, n (%)	61 (28.1)	17 (25.8)	0.183
Photophobia, n (%)	114 (53.0)	37 (56.1)	0.792
Phonophobia, n (%)	89 (41.6)	34 (52.3)	0.280
Concentration difficulty, n (%)	103 (49.0)	44 (67.7)	**0.008**
Memory impairment, n (%)	106 (50.7)	43 (65.2)	**0.040**
Papilledema, n (%)	195 (93.3)	13 (19.4)	< **0.001**
VI nerve palsy, n (%)	30 (14.9)	2 (3.0)	**0.010**

p values < 0.05 were considered as statistically significant.

Table 3
Comorbid disorders, weight gain and medication use prior to the disease onset in IIH and non-IIH patients.

Variable	IIH N = 219	Non-IIH N = 67	p-Value
Migraine without aura, n (%)	26 (12.2)	11 (16.7)	0.351
Migraine with aura, n (%)	13 (6.1)	7 (10.8)	0.206
Tension type headache, n (%)	60 (28.3)	20 (30.3)	0.754
Skin disease[a], n (%)	25 (11.7)	15 (22.4)	**0.030**
Polycystic ovary syndrome, n (%)	13 (6.8)	3 (5.5)	0.714
Depression, n (%)	47 (22.0)	19 (28.4)	0.281
Anxiety, n (%)	33 (15,4)	10 (14.9)	0.922
Sleep apnea, n (%)	5 (2.3)	7 (10.4)	**0.004**
Tetracyclines, n (%)	8 (5.0)	1 (1.7)	0.269
Vitamin A preparations, n (%)	2 (1.2)	1 (1.7)	0.808
Corticosteroids, n (%)	19 (11.8)	7 (11.7)	0.978
Hormonal contraception, n (%)	63 (37.7)	15 (28.8)	0.510
Weight gain, n (%)	53 (36.3)	13 (23.6)	0.088

p values < 0.05 were considered as statistically significant.
[a] Skin diseases: atopic dermatitis, acne, psoriasis, keratosis, lichen.

last 12 months, and usage of medications prior to disease onset (Table 3).

Sensitivity and specificity for all statistically significant predictors were low, with the exception of papilledema (Table 4).

Among patients diagnosed with IIH, the prevalence of those without papilledema was 6.7% (n = 13). They were all referred by a neurologist and did not differ from IH patients in whom papilledema was detected in terms of demographic features, past medical history, or comorbid

Table 4
Diagnostic accuracy of predictor variables.

Variable	Sensitivity	Specificity	LR+	LR−
BMI (cut-off > 34.1)	0.50	0.69	1.60	0.73
Referrals by ophthalmologist vs. neurologist	0.69	0.17	0.83	1.84
TVO	0.57	0.63	1.52	0.69
Double vision	0.40	0.75	1.57	0.81
Tinnitus	0.63	0.55	1.38	0.69
Neck pain	0.13	0.97	4.19	0.90
Concentration difficulty	0.49	0.32	0.72	1.58
Memory impairment	0.51	0.35	0.78	1.41
Papilledema	0.93	0.81	4.81	0.08
VI nerve palsy	0.15	0.97	4.95	0.88
Skin disease	0.12	0.78	0.52	1.14
Sleep apnea	0.02	0.90	0.22	1.09

LR+ Likelihood ratio positive, LR− Likelihood ratio negative.

Table 5
Variables extracted by multivariate logistic analysis as predictors of IIH diagnosis.

Variable	B	SE	p-Value
BMI	0.06	0.04	0.105
Referrals by ophthalmologist vs. neurologist	0.51	0.83	0.536
TVO	0.37	0.60	0.543
Double vision	−0.19	0.72	0.791
Tinnitus	−0.28	0.64	0.659
Neck pain	0.60	1.14	0.600
Concentration difficulty	0.33	0.77	0.664
Memory impairment	0.06	0.77	0.943
Papilledema	4.61	0.77	< **0.001**
VI nerve palsy	19.28	7906.44	0.998
Skin disease	−0.86	0.69	0.217
Sleep apnea	−0.94	1.11	0.395

p values < 0.05 were considered as statistically significant.

disorders. They less frequently reported TVO (21.4% vs. 58.5%, p = .007) and tinnitus (35.7% vs.63.4%, p = .040). Headache was by far the most common presenting symptom occurring in all IIH patients without papilledema.

Papilledema was extracted as a single independent positive predictor of IIH diagnosis (Table 5).

A multivariate logistic predictive model shows a high capacity for identifying the patients with IIH mostly due to the high sensitivity and specificity of papilledema (AUC 0.93, 95% CI 0.88–0.98) (Fig. 1).

4. Discussion

Our study investigated presenting symptoms and clinical findings in a large cohort of probable IIH patients. Of the 286 participants that were enrolled in the study, the diagnosis of IIH was confirmed in 3 out of 4 of them. Our findings are in accordance with the recent prospective study analyzing the baseline clinical characteristics of IIH; that study included 165 participants with IIH from North America [9] and showed that IIH is primarily a disorder of young women who are at the beginning of their fourth decade of life and who are suffering from obesity.

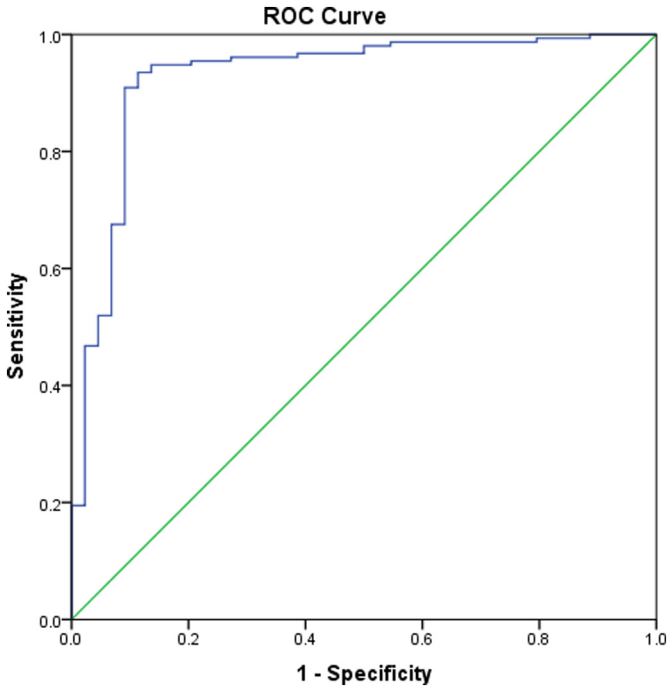

Fig. 1. ROC for multivariate logistic predictive model.

The most common presenting symptom in our IIH patients was headache, reported by > 90% of the patients, followed by blurred vision, tinnitus, TVO, and nausea. Headache was by far the most common presenting symptom in both patient groups; neck pain was significantly more frequent in the IIH group. Neck and shoulder pain, sometimes with radicular distribution, have been noted in other large IIH series [9,13], suggesting early spinal nerve root irritation related to raised CSF pressure.

Visual disturbances were also frequent complaints in the cohort. In the literature, TVO typically occur with postural provocation; their frequency does not correlate with the severity of papilledema or the degree of increased ICP, and it does not predict future permanent visual loss [14]. Even though not unique to IIH, TVO are an important symptom, reported by 56.6% of our IIH patients. TVO and double vision due to sixth nerve palsy should raise concerns about IH, since these are not symptoms of primary headaches. Our results support previous findings [4] indicating that blurred vision is a less specific symptom than TVO and that it is not more frequent in IIH, as was noted in more than half of our non-IIH patients.

Tinnitus is generally explained by the flow turbulence within the transverse venous sinus; in our cohort, it occurred in 62.6% of IIH patients. Wall et al. reported the presence of tinnitus in more than half of the patients in two different cohorts of IIH patients examined within a 20-year interval [9,15]. The prevalence of tinnitus in the general adult population has shown rates between 10% and 15% and it increases with aging [16]. < 10% of tinnitus patients experience pulsatile tinnitus, so if it is present and especially if it is bilateral, it may suggest IH [17].

A history of skin diseases and medications that are applied in the treatment of these diseases, such as tetracycline, vitamin A, and corticosteroids often indicate the possibility of IH due to secondary causes. Over the years, systemic administration of tetracyclines or vitamin A has been associated with the increase of ICP in several reports [18,19]; similar evidence for topical application of the same medicines is lacking. Interestingly, there were more patients in IIH group using a topical form of tetracycline than in the non-IIH group, although without statistical significance. Further research focused on the possible effect of these medications on ICP is needed to resolve this question. Similarly, the problem with corticosteroids is even more complex. Corticosteroid therapy withdrawal after long-term systemic administration has been implicated in the development of IH [20]; corticosteroids have also been proposed as one of the treatment options for severe papilledema in IIH [21]. In our study, 11.8% of the IIH patients used topical steroids and inhalers, with only one patient taking prednisone orally for inflammatory bowel disease up to 3 months prior to diagnosis. In this patient, the symptoms started prior to the initiation of prednisone and did not change during prednisone treatment or during withdrawal. Equivalently, 11.7% of patients in the non-IIH group were treated with corticosteroids, but IH could not be attributed solely to corticosteroid usage in any of them. Chronic skin diseases were evaluated in a population-based prospective and case-control study on IIH, and no significant differences between cases and controls were observed [22]. The prevalence of skin diseases in our IIH cohort is two times lower than a recently reported 22.4% in the general population in the same age group (18–44 years) [23] and in our non-IIH patients, as well. Even though our data are self-reported, this result deserves additional investigation.

Correlations between elevated BMI and risk of IIH have been firmly demonstrated [24,25]. There are several proposed underlying mechanisms, from increased intrathoracic pressure causing the increase of venous pressure and consequently ICP [26], to the dysregulation of adipokines and cytokines and even possibly hypothalamic leptin resistance resulting in obesity in IIH patients [27]. Weight loss is recognized as an effective treatment for IIH with sustained improvement in symptoms, signs, and ICP [28], as are associations between increased weight and disease recurrence [29]. In agreement with the literature, 75.6% of the patients in our IIH cohort were obese, though the mean BMI was lower than reported in a North American study [9].

The main result of our study is that not a single symptom of the disease can predict the correct IIH diagnosis in patients with suspected IIH. The most important predictor in our patient group was a clinical sign: the presence of papilledema.

Papilledema was the most common clinical finding, occurring more frequently than headache in our IIH cohort, which is likely the reason the diagnosis of IIH was confirmed more often if the patient was referred by an ophthalmologist than if the patient was referred by a neurologist. Still, papilledema is not pathognomonic for IIH and was also observed in our non-IIH patients with IH due to sinus venous thrombosis, tetracycline consumption, renal failure and viral meningitis. Furthermore, bilateral optic disc swelling was identified in one patient with lymphomatous infiltration of the optic nerve and in a patient with bilateral anterior ischemic optic neuropathy in whom ICP measurement values were within normal range. The significance of this clinical sign has not been specifically emphasized in the modified Dandy criteria; however, the presence of papilledema is essential for IIH diagnosis according to the new criteria from 2013 [11]. The absence of papilledema despite elevated ICP is an intriguing question in current research, especially since it has been noticed in treatment-resistant chronic migraine patients, suggesting a diagnosis of IIH without papilledema [30]. Our study showed the strongest association between papilledema and IIH diagnosis in a large cohort of patients with suspected IIH that included a distinct number of chronic headache patients. This finding supports the current recommendation for additional clinical and neuroradiological confirmation of IIH diagnosis in all patients without papilledema [11].

The strength of this study is the prospective design and the large number of included patients. The assessment of patient symptoms was standardized and primarily performed prior to neurological examination and further investigations, and it was thus blinded to final diagnosis. However, a reporting bias cannot be excluded and may represent a limiting factor of the present study although it is likely to be similar in both groups. Failure to perform brain MRI for all IIH patients could be considered a limiting factor, but it also reflects normal clinical practice in a complex patient group.

Our study was intended to estimate the reliability of clinician suspicion for IIH. It was therefore designed to separate the patients with IIH from non-IIH patients and thus create a situation similar to real clinical practice. As a result, the non-IIH group consisted of patients with increased ICP together with patients with normal ICP values in whom some of the demographic features, symptoms, signs, or comorbidities were suggestive of IIH. The lack of predictive significance of any presenting symptom for the diagnosis of IIH could be the consequence of our applied design, since analyzed symptoms may reflect ICP regardless of etiology. The search for a specific diagnostic IIH-marker must continue.

In conclusion, although studies investigating IIH report an abundance of presenting symptoms, our results indicate that these symptoms are not diagnostic for IIH. Papilledema is the most reliable clinical sign predicting IIH diagnosis.

Disclosure of conflicts of interest

RHJ has received honoraria for lectures and patient leaflets from MSD, Berlin-Chemie Menarini, ATI, and Pfizer; has served on medical advisory boards for ATI and Electrocore; and is conducting clinical trials for Eli-Lilly. The remaining authors have no conflicts to report.

Funding

The study was supported by grants from “Professor Dr. Risto Bokonjic Stiftung” and Region Hovedstadens Forskningsfond. The funding sources had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in

the decision to submit the paper for publication.

References

[1] B.R. Wakerley, M.H. Tan, E.Y. Ting, Idiopathic intracranial hypertension, *Cephalalgia* 35 (2015) 248–261.
[2] A. Kesler, N. Stolovic, Y. Bluednikov, T. Shohat, The incidence of idiopathic intracranial hypertension in Israel from 2005 to 2007: results of a nationwide survey, Eur. J. Neurol. 21 (2014) 1055–1059.
[3] K. Radhakrishnan, J.E. Ahlskog, S.A. Cross, L.T. Kurland, W.M. O'Fallon, Idiopathic intracranial hypertension (pseudotumor cerebri). Descriptive epidemiology in Rochester, Minn, 1976 to 1990, Arch. Neurol. 50 (1993) 78–80.
[4] H.M. Yri, R.H. Jensen, Idiopathic intracranial hypertension: clinical nosography and field-testing of the ICHD diagnostic criteria. A case-control study, Cephalalgia 35 (2015) 553–562.
[5] H. Yri, C. Ronnback, M. Wegener, S. Hamann, R. Jensen, The course of headache in idiopathic intracranial hypertension: a 12-month prospective follow-up study, Eur. J. Neurol. 21 (2014) 1458–1464.
[6] S. Bidot, B.B. Bruce, A.M. Saindane, N.J. Newman, V. Biousse, Asymmetric papilledema in idiopathic intracranial hypertension, J. Neuroophthalmol. 35 (2015) 31–36.
[7] K.B. Digre, B.K. Nakamoto, J.E. Warner, et al., A comparison of idiopathic intracranial hypertension with and without papilledema, Headache 49 (2009) 185–193.
[8] R.H. Jensen, A. Radojicic, H. Yri, The diagnosis and management of idiopathic intracranial hypertension and the associated headache, Ther. Adv. Neurol. Disord. 9 (2016) 317–326.
[9] M. Wall, M.J. Kupersmith, K.D. Kieburtz, et al., The idiopathic intracranial hypertension treatment trial: clinical profile at baseline, JAMA Neurol. 71 (2014) 693–701.
[10] J.L. Smith, Whence pseudotumor cerebri? J. Clin. Neuroopthalmol. 5 (1985) 55–56.
[11] D.I. Friedman, G.T. Liu, K.B. Digre, Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children, Neurology 81 (2013) 1159–1165.
[12] D.I. Friedman, D.M. Jacobson, Diagnostic criteria for idiopathic intracranial hypertension, Neurology 59 (2002) 1492–1495.
[13] R. Round, J.R. Keane, The minor symptoms of increased intracranial pressure: 101 patients with benign intracranial hypertension, Neurology 38 (1988) 1461–1464.
[14] J.J. Corbett, P.J. Savino, H.S. Thompson, et al., Visual loss in pseudotumor cerebri. Follow-up of 57 patients from five to 41 years and a profile of 14 patients with permanent severe visual loss, Arch. Neurol. 39 (1982) 461–474.
[15] M. Wall, D. George, Idiopathic intracranial hypertension: a prospective study of 50 patients, Brain 114 (1991) 155–180.
[16] D. Baguley, D. McFerran, Hall D. Tinnitus, Lancet 382 (2013) 1600–1607.
[17] E. Hofmann, R. Behr, T. Neumann-Haefelin, K. Schwager, Pulsatile tinnitus: imaging and differential diagnosis, Dtsch. Arztebl. Int. 110 (2013) 451–458.
[18] B.N. Walters, S.S. Gubbay, Tetracycline and benign intracranial hypertension: report of five cases, *Br. Med. J. (Clin. Res. Ed.)* 282 (1981) 19–20.
[19] A.G. Lee, Pseudotumor cerebri after treatment with tetracycline and isotretinoin for acne, Cutis 55 (1995) 165–168.
[20] G.T. Liu, M.D. Kay, D.C. Bienfang, et al., Pseudotumor cerebri associated with corticosteroid withdrawal in inflammatory bowel disease, Am J. Ophthalmol. 117 (1994) 352–357.
[21] G.T. Liu, J.S. Glaser, N.J. Schatz, High-dose methylprednisolone and acetazolamide for visual loss in pseudotumor cerebri, Am J. Ophthalmol. 118 (1994) 88–96.
[22] K. Radhakrishnan, A.K. Thacker, N.H. Bohlaga, J.C. Maloo, S.E. Gerryo, Epidemiology of idiopathic intracranial hypertension: a prospective and case-control study, J. Neurol. Sci. 116 (1993) 18–28.
[23] H.W. Lim, S.A.B. Collins, J.S. Resneck Jr.et al., The burden of skin disease in the United States, J. Am. Acad. Dermatol. 76 (2017) 958–972.
[24] A.B. Daniels, G.T. Liu, N.J. Volpe, et al., Profiles of obesity, weight gain, and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri), Am J. Ophthalmol. 143 (2007) 635–641.
[25] A. Kesler, A. Hadayer, Y. Goldhammer, Y. Almog, A.D. Korczyn, Idiopathic intracranial hypertension: risk of recurrences, Neurology 63 (2004) 1737–1739.
[26] H.J. Sugerman, E.J. DeMaria, W.L. Felton 3rd, M. Nakatsuka, A. Sismanis, Increased intra-abdominal pressure and cardiac filling pressures in obesity-associated pseudotumor cerebri, Neurology 49 (1997) 507–511.
[27] A.K. Ball, A.J. Sinclair, S.J. Curnow, et al., Elevated cerebrospinal fluid (CSF) leptin in idiopathic intracranial hypertension (IIH): evidence for hypothalamic leptin resistance? Clin. Endocrinol. 70 (2009) 863–869.
[28] A.J. Sinclair, M.A. Burdon, P.G. Nightingale, et al., Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study, BMJ 341 (2010) c2701.
[29] M.W. Ko, S.C. Chang, M.A. Ridha, et al., Weight gain and recurrence in idiopathic intracranial hypertension: a case-control study, Neurology 76 (2011) 1564–1567.
[30] R. De Simone, A. Ranieri, S. Montella, et al., Intracranial pressure in unresponsive chronic migraine, J. Neurol. 261 (2014) 1365–1373.