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ESTIMATION OF THE PREDICTIVE ROLE OF PRESENTING SYMPTOMS IN ESTABLISHING THE DIAGNOSIS OF IDIOPATHIC INTRACRANIAL HYPERTENSION, COURSE AND OUTCOME OF THE DISEASE

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PROCENA PREDIKTIVNE ULOGE PREZENTUJUĆIH SIMPTOMA ZA POSTAVLJANJE DIJAGNOZE IDIOPATSKE INTRAKRANIJALNE HIPERTENZIJE, TOK I ISHOD BOLESTI

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ESTIMATION OF THE PREDICTIVE ROLE OF PRESENTING SYMPTOMS IN ESTABLISHING THE DIAGNOSIS OF IDIOPATHIC INTRACRANIAL HYPERTENSION, COURSE AND OUTCOME OF THE DISEASE

ABSTRACT

Background: Idiopathic intracranial hypertension (IIH) is a rare disease characterized by increased intracranial pressure (ICP) in the absence of any other detectable cause. Clinical presentation of IIH is variable, with the most frequent finding of papilledema and headache. Other symptoms include transient visual obscurations (TVO), blurred vision, double vision due to sixth nerve palsy, tinnitus, dizziness, nausea, neck pain, disturbed concentration and memory impairment. The diagnostic value of this variety of presenting symptoms and clinical findings has been scarcely investigated. Current diagnostic criteria for IIH are not based on clinical presentation of the disease, and unlike former criteria do not include specific symptoms of raised ICP. Low prevalence of IIH results in insufficient data regarding the course and long-term outcome of the disease.

Objectives: The main aims of the study are to a) characterize the presenting symptoms and signs of IIH defined according to the existing diagnostic criteria, b) analyze the correlation of presenting symptoms and signs with the results of diagnostic procedures: ICP measurement, presence of papilledema, and neuroimaging markers of raised intracranial pressure c) investigate the correlation of presenting symptoms and signs with the course and disease outcome.

Methods: This cohort study was conducted in two tertiary centers: Neurology Clinic of the Clinical Center of Serbia and the Danish Headache Center-Rigshospitalet, Glostrup. The study included 286 patients that were consecutively referred by attending neurologist and ophthalmologist for the evaluation of possible IIH from January 2007 to March 2016. The study was conducted in two phases. At first, clinical data were prospectively collected from all study participants in order to evaluate the presenting symptoms and signs of IIH. Clinical interview and a comprehensive semi-structured

questionnaire designed for the study was used to collect the demographic data, characteristics of presenting symptoms, medication use prior to disease onset and the presence of comorbid disorders. Neurological and neuro-ophthalmological examination, ICP measurement and neuroimaging were performed in all participants. In the second phase of the study were included 182 patients with IIH who were followed by neurologist and ophthalmologists at least one year after the confirmation of diagnosis. The duration of follow-up ranged from 12 to 144 months. A retrospective chart review was performed in order to identify the course and outcome of the disease. Clinical symptoms and findings that predict the diagnosis and outcome of IIH were analyzed and independent predictors were estimated.

Results: The diagnosis of IIH was confirmed in 219 (76.6%) patients. It was more often confirmed in patients with higher body mass index (BMI) ($p=0.032$) and if the patient was referred by an ophthalmologist than if the referral was from a neurologist (83.6% vs. 69.8%, $p=0.029$). Double vision ($p=0.033$), TVO ($p=0.006$), tinnitus ($p=0.013$), and neck pain ($p=0.025$) were presenting symptoms more frequently reported by patients with IIH diagnosis; papilledema ($p<0.001$) and sixth nerve palsy ($p=0.010$) were also noted significantly more often in this patients. Papilledema was extracted by multivariate analysis as an independent predictor of IIH diagnosis ($p<0.001$). Headache was the most common symptom of IIH reported by 90.8% of patients at presentation. Visual field defects resulting from IIH were found in 75% of patients at baseline, while papilledema was noted in 93.3% of IIH patients. There was a significant correlation between the presence of papilledema, sixth nerve palsy, TVO and double vision, with the ICP values. A positive relationship was found between the presence of MRI markers of raised ICP and papilledema in IIH. Younger age at disease onset has been associated with the higher values of ICP and the presence of headache, tinnitus, double vision due to sixth nerve palsy, nausea and vomiting at presentation. A significant positive correlation of visual impairment (decreased visual acuity, double vision, and visual field defect at least on one eye) at the time of diagnosis was found with BMI. Full remission of symptoms and signs of IIH was documented in 72 (39.6%) patients at the final follow-up visit. Higher ICP and headache reaching maximum intensity within one day were extracted as positive predictors of remission by univariate analysis, while the

presence of neck pain at the disease onset (HR=4.959, CI 2.438-10.087, p<0.001) and the absence of phonophobia (HR=0.230, CI 0.106-0.501, p<0.001) and concentration difficulties (HR=0.360, CI 0.186-0.697, p=0.002) at baseline were identified by multivariate analysis. Relapsing course of the disease was identified in 34 (18.7%) patients. Headache announcing IIH, the occurrence of photophobia, concentration and memory problems, preserved visual acuity bilaterally at the time of diagnosis as well as ICP value derived from univariate analysis were associated with relapsing IIH course, but none of the predictors reached statistical significance in multivariate Cox regression analysis. Refractory IIH was identified in 76 (41.7%) patients at the end follow-up. Higher BMI, comorbid depression, and empty sella sign on MRI scanning were positively associated with refractory disease in univariate analysis, while constant headache of frontal localization and dizziness showed a negative correlation. Older age at onset (HR=1.066, CI 1.025-1.110, p=0.002), aggravation of headache by physical activity (HR=7.525, CI 2.505-22.604 p<0.001), visual field defect beyond enlarged blind spot at baseline (HR=2.550, CI 1.166-5.581, p=0.019) were extracted as positive independent predictors of refractory IIH, while pressing headache (HR=0.179, CI 0.073-0.437, p<0.001) is identified as a negative predictor.

Conclusions: 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. The predictors of favorable IIH outcome are neck pain at the disease onset and the absence of phonophobia and concentration difficulties, while the refractory disease is more likely to occur in older patients in whom headache aggravates by physical activity, and visual field defect exceeds an enlarged blind spot at the baseline eye examination.

Key words: idiopathic intracranial hypertension, intracranial pressure, papilledema, headache, diagnostic criteria, outcome

Scientific field: Medicine

Narrow scientific field: Neurology

UDK number:

PROCENA PREDIKTIVNE ULOGE PREZENTUJUĆIH SIMPTOMA ZA POSTAVLJANJE DIJAGNOZE IDIOPATSKE INTRAKRANIJALNE HIPERTENZIJE, TOK I ISHOD BOLESTI

SAŽETAK

Uvod: Idiopatska intrakranijalna hiprtenzija (IIH) je retko oboljenje koje karakteriše povišen intrakranijalni pritisak (IKP) bez jasno detektabilnog uzroka. Kliničko ispoljavanje IIH je varijabilno a bolest se najčešće manifestuje glavoboljom i edemom papile optičkog živca. Ostale simptome čine tranzitorne vizuelne opskuracije (TVO), zamagljen vid, duple slike usled lezije VI kranijalnog živca, zujanje u ušima, vrtoglavica, mučnina, bol u vratu, teškoće sa pamćenjem i koncentracijom. Dijagnostički značaj različitih prezentujućih simptoma i znakova bolesti nije dovoljno ispitan. Aktuelni dijagnostički kriterijumi za IIH nisu bazirani na kliničkoj prezentaciji bolesti, i za razliku od prethodnih ne zahtevaju postojanje simptomatologije povišenog IKP. Imajući u vidu nisku prevalenciju IIH, u literaturi nema dovoljno podataka o toku i dugoročnom ishodu bolesti.

Ciljevi: Ciljevi istraživanja su a) utvrđivanje prezentujućih simptoma i znakova bolesti kod osoba kod kojih je dijagnoza IIH postavljena prema aktuelnim dijagnostičkim kriterijumima, b) uvrđivanje korelacije prezentujućih simptoma i znakova IIH sa rezultatima dijagnostičkih procedura: vrednostima IKP, prisustvom edema papile optičkog živca i neuroradiološkim znacima intrakranijalne hipertenzije, c) utvrđivanje korelacije prezentujućih simptoma i znakova IIH sa kliničkim tokom i ishodom bolesti.

Metodologija: Ova kohortna studija je sprovedena u dva tercijarna centra: Klinici za neurologiju Kliničkog centra Srbije u Beogradu i Danskom centru za glavobolje bolnice Rigshospitalet, u Glostrupu. U istraživanje je uključeno 286 bolesnika koji su konsekutivno upućivani od strane neurologa ili oftalmologa pod sumnjom na IIH u periodu od januara 2007. do marta 2016. godine. Istraživanje je sprovedeno u dve faze. U prvoj fazi su klinički podaci prospektivno prikupljani od svih ispitanika sa ciljem da se ustanove prezentujući simptomi i znaci IIH. Klinički intervju i detaljan semi-

strukturisani uputnik sastavljen za potrebe ovog istraživanja je korišćen za prikupljanje demografskih podataka, karakteristika prezentujućih simptoma, podataka o korišćenju lekova pre pojave bolesti i komorbiditetima. Svim ispitanicima je urađen neurološki i neurooftalmološki pregled, merenje IKP i neuroimidžing. U drugi deo istraživanja uključeno je 182 bolesnika sa IIH koji su praćeni od strane neurologa i oftalmologa bar godinu dana nakon postavljanja dijagnoze. Period praćenja je bio između 12 i 144 meseci. Tok i ishod bolesti su procenjeni retrospektivnom analizom specijalističkih izveštaja sa kontrolnih pregleda. Analiziran je prediktivni značaj simptoma i znakova bolesti za postavljanje dijagnoze i ishod IIH i utvrđeni su nezavisni prediktori.

Rezultati: Dijagnoza IIH je potvrđena kod 219 (76.6%) bolesnika. Češće je potvrđena kod bolesnika sa većim indeksom telesne mase (BMI) ($p=0.032$) i kod onih koji su upućeni od strane oftalmologa a ne neurologa (83.6% vs. 69.8%, $p=0.029$). Duple slike ($p=0.033$), TVO ($p=0.006$), zujanje u ušima ($p=0.013$) i bol u vratu ($p=0.025$) su čeće prijavljivali ispitanici sa IIH, a kod njih je takođe pregledom češće uočen edem papile vidnog živca i lezija VI kranijalnog živca. Multivarijantnom analizom je edem papile izdvojen kao samostalan prediktor IIH ($p<0.001$). Glavobolja je bila najčešči simptom IIH, prisutna kod 90.8% pacijenata na početku bolesti. Defekti vidnog polja koji su nastali kao posledica IIH nađeni su kod 75% pacijenata, a edem papile kod 93.3%. Postojala je značajna korelacija između vrednosti IKP i prisustva edema papile vidnog živca, lezije VI kranijalnog živca, TVO i duplih slika. Ustanovljena je povezanost između prisustva edema papile vidnog živca i znakova povišenog IKP na MR mozga. Mlađi uzrast na početku bolesti bio je povezan sa višim vrednostima IKP, kao i kliničkom prezentacijom u vidu glavobolje, zujanja u ušima, duplih slika usled lezije VI kranijalnog živca, mučnine i povraćanja. Nađena je značajna korelacija oštećenja vida (snižena oštrina vida, duple slike i defekt vidog polja bar na jednom oku) u vreme postavljanja dijagnoze sa BMI. Kompletna remisija simptoma i znakova IIH je potvrđena kod 72 (39.6%) bolesnika na poslednjoj kontroli. Više vrednosti IKP i glavobolja koja je dostigla maksimalnu jačinu unutar jednog dana su univarijantnom analizom izdvojeni kao pozitivni prediktori remisije, dok su bol u vratu na početku bolesti (HR=4.959, CI 2.438-10.087, $p<0.001$), kao i odsustvo fonofobije (HR=0.230, CI 0.106-0.501, $p<0.001$) i teškoća sa koncentracijom (HR=0.360, CI 0.186-0.697,

p=0.002) potvrđeni kao nezavisni prediktori remisije multivarijantnom analizom. Relapsni tok bolesti je imalo 34 (18.7%) pacijenata. Glavobolja kao prvi simptom bolesti, pojava fotofobije, teškoće sa koncentracijom i pamćenjem, obostrano očuvana oštrina vida u vreme postavljanja dijagnoze kao i vrednost IKP izdvojeni univarijantnom analizom su bili povezani sa relapsnim tokom bolesti, ali ni jedan od ovih prediktora nije dostigao značajnost u multivarijantnoj Cox regresionoj analizi. Refraktorna IIH ustanovljena je kod 76 (41.7%) pacijenata na kraju praćenja. Viši BMI, komorbidna depresija i empty sella znak na MR pregledu glave su pozitivno korelirali sa refraktornom bolešću, dok je negativna povezanost uočena sa konstantnom glavoboljom čeone lokalizacije i vrtoglavicom. Stariji uzrast na početku bolesti (HR=1.066, CI 1.025-1.110, p=0.002), glavobolja koja se pogoršava na fizičku aktivnost (HR=7.525, CI 2.505-22.604, p<0.001) i oštećenje vidnog polja koje prevazilazi proširenu slepu mrlju (HR=2.550, CI 1.166-5.581, p=0.019) čine nezavisne pozitivne prediktore refraktorne IIH, dok je stežuća glavobolja (HR=0.179, CI 0.073-0.437, p<0.001) identifikovana kao negativan prediktor.

Zaključci: Iako studije koje su istraživale IIH opisuju obilje prezentujućih simptoma, naši rezultati ukazuju na to da simptomi nemaju dijagnostičku vrednost. Edem papile optičkog živca je najpouzdaniji klinički znak za predikciju tačne dijagnoze IIH kod osoba kod kojih se sumnja na ovu bolest. Prediktori povoljnog ishoda IIH su bol u vratu na početku bolesti, odsustvo fonofobije i teškoća sa koncentracijom, dok kasniji početak bolesti, pojačanje glavobolje na napor i oštećenje vidnog polja koje prevazilazi proširenu slepu mrlju na inicijalnom oftalmološkom pregledu predviđaju refraktornu bolest.

Ključne reči: idiopatska intrakranijalna hipertenzija, intrakranijalni pritisak, edem papile, glavobolja, dijagnostički kriterijumi, ishod

Naučna oblast: Medicina
Uža naučna oblast: Neurologija
UDK broj:

CONTENT

1. INTRODUCTION

1.1 The history of idiopathic intracranial hypertension, definition and terminology considerations in the literature

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].

The nomenclature together with diagnostic criteria used to define this condition has significantly changed and evolved over time which reflects the unclear etiology of this condition. German physician Henrich Quincke was the first who reported the case of IIH in 1893 and termed it serous meningitis[2]. From a historical perspective, the initial acknowledgment of the disease depended on the invention of ophthalmoscope in 1851 and introduction of a lumbar puncture (LP) by Quincke, a technique that first provided the accurate measurement of the cerebrospinal fluid (CSF) pressure[3]. Quincke ascribed the clinical manifestations of headache and visual disturbance to the elevation of ICP and proposed that increased CSF production was the possible cause, thus initiated the concept of IIH as a specific disease entity. Overall, he reported 10 cases suggestive of IIH (seven females, three males) and brought attention to the female preponderance[4]. Several years later, Max Noone, a neurologist from Hamburg described a series of 18 cases of raised ICP without intracranial tumor and introduced the term pseudotumor cerebri, which remained the most commonly used term in the literature until today[5].

In subsequent years, the development of radiological techniques such as ventriculography demonstrated the lack of any ventricular dilatation in these patients which resulted in several new hypotheses of underlying pathology and first diagnostic criteria for the condition proposed by Dandy in 1937[6]. Dandy also indicated that cerebral circulation changes were responsible for the raised ICP, rather than an increase of CSF volume as previously postulated. Accumulation of new evidence on pathophysiological mechanisms brought also a new term for the same disease -benign intracranial hypertension (BIH)[7]. It was introduced by Foley in 1955 and was widely

accepted in the literature in the next several decades. However, it was later abandoned, since the natural history of the disease proved not to be always benign considering that some patients with "BIH" developed permanent blindness and substantial reduction in quality of life[8]. Finally, the term IIH was found to be the most appropriate to describe this challenging disease[9].

In recent years, terms pseudotumor cerebri syndrome (PTCS) and IIH are equally present in the literature but do not have identical meanings. The current literature marks a clear terminological distinction between them; as PTCS encompasses a wide range of diseases and conditions with elevated ICP, not only idiopathic like IIH but also secondary, i.e. intracranial hypertension of detectable cause[10]. Therefore, IIH, the syndrome of increased ICP of unknown etiology, is always a diagnosis of exclusion.

1.2 Epidemiology of IIH

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 [11–13], but due to the nomenclature and diagnostic inconsistency the precise incidence and prevalence in a different geographical area are still to be determined. IIH is seen in all ages but more frequently in obese women in childbearing age in whom the incidence is as much as 10-20 times higher and reaches 12-20 per 100 000 people per year[11,12].

IIH has a strong predilection for women, with an estimated female: male ratio 4.3: 1 to 15: 1[11–13]. Several large IIH series report more than 90% of patients with IIH being women[14,15]. The disease is generally diagnosed in people aged 25-36 years, although it may affect individuals of any age[11–13]. In children with IIH, no female predominance exists before puberty, and younger patients are often not obese[16,17]. Familial occurrence has been recorded in several cases[18–20] but has never been further evaluated.

Obesity is hypothesized to be probably the most important risk factor for IIH[21]. Approximately 70%–80% of IIH patients are obese with a body mass index (BMI) ≥30 kg/m^2 and over 90% are overweight (BMI ≥25 kg/m^2)[13,22]. The risk of developing IIH in women increases with increasing BMI as odds ratio increases from 19.5 with a BMI of

30–35 kg/m^2 to 26 with a BMI >35 kg/m^2 [23]. Likewise, it increases from 3.6 with the annual weight gain of 5%–10% to 15.2 with an annual weight gain of 11%–15%[23]. Still, the role of obesity in IIH development in males has not been firmly proven. Kesler and colleagues reported that only 25% of men in their IIH cohort were overweight compared with 78% of women[24]. Other authors also found that men with IIH were less obese, but were more prone to visual loss than women[25].

So far, no evidence suggests that IIH has a predilection for any particular racial or ethnic group above any expected variations in the prevalence of obesity that are noted in the different groups. Owing to its close relationship with obesity, which has increased three-fold over just 15 years in Western countries[26], the incidence of IIH is expected to increase in line with the worldwide obesity epidemic[27].

1.3 Pathogenesis of IIH

The exact pathogenesis of IIH remains unknown; however, pathological mechanisms of changes in CSF pressure have been thoroughly investigated over the years, and several hypotheses have been proposed based on current knowledge on CSF circulation.

1.3.1 Physiology of ICP and CSF circulation

ICP represents a pressure inside the skull and is strongly dependent on 3 main components of intracranial space-brain parenchyma, CSF and blood volume. The concept of ICP (normal or abnormal) being a function of the volume and compliance of each component of the intracranial compartment was first proposed during the late 18th century by the Scottish anatomist and surgeon Alexander Monro and his student George Kellie and is known as the Monro-Kellie hypothesis[28,29]. Any changes in ICP are attributed to volume changes in one or more of the constituents contained in the cranium, since the cranium is a rigid structure and volume inside it is fixed. A pressure within the brain parenchyma is equal to the pressure in subarachnoid and ventricular spaces containing CSF. Normal CSF pressure is equal to ICP and varies from 60 to 250

mm H_2O in healthy adults with many diurnal variations[30]. For instance, abrupt changes of intrathoracic or intraabdominal pressure during coughing or Valsalva maneuver may strongly affect ICP.

CSF is a clear fluid circulating through the subarachnoid spaces (75%) and ventricles (25%) produced by the choroid plexus epithelium and ependymal lining of the cerebral ventricles[31]. CSF production of approximately 600 mL per day is relatively constant and up to some point independent of CSF pressure; yet, CSF synthesis decreases by aging[32], possibly contributing to why IIH is mainly a disorder of younger people[33]. CSF flows out of the ventricular system and into the subarachnoid space where it is resorbed for the most part through arachnoid granulations into the venous sinuses. The partial CSF outflow through the cribriform plate and cranial nerves into the lymphatic system has been demonstrated in various mammals including humans[34]. The flow of CSF across the arachnoid villi is thought to be proportional to the pressure difference between CSF space and venous sinuses, and inversely proportional to resistance to flow across the arachnoid villi[33]. A common assumption is that the total CSF volume of 160 mL is replaced approximately four times a day.

1.3.2 CSF dynamic changes in IIH

Increased ICP in IIH has been associated with increased production of CSF[35] but there is no evidence to support this theory. CSF hypersecretion typically leads to an increase in the size of the cerebral ventricles, which is not the case with IIH where the size of the ventricles is normal. Furthermore, structural changes such as hypertrophy of the choroid plexus have not been identified in IIH patients[33].

Compromised CSF resorption and venous drainage with venous hypertension have so far been the most investigated potential underlying mechanisms of intracranial hypertension in IIH, but the results of the previous studies are inconclusive or controversial. It has been speculated that insufficient CSF resorption would result in intracranial hypertension with a normal or decreased size of the ventricular system that is seen in IIH[36]. An abnormally increased outflow resistance has been demonstrated in

75–100% of IIH patients in several studies[36–38]. Impaired CSF resorption resulting in raised ICP is typically found in meningitis or subarachnoid hemorrhage; however, in these syndromes may be associated with the development of hydrocephalus[39,40]. More recent magnetic resonance imaging (MRI) study using dynamic phase contrast techniques demonstrated the increased extraventricular CSF volume and decreased jugular venous outflow in IIH patients compared to healthy overweight control subjects[41]. Increased intracranial elastance, a measure of volume-buffering capacity has also been observed in IIH; possibly contributing to the pathophysiology of IIH[42].

The association of venous sinus hypertension with some reported IIH cases has long been recognized. King was the first who proposed in 1995 venous stenosis as the key underlying mechanism in IIH[43] but then denied his claim in a follow-up publication when he demonstrated resolution of a venous pressure gradient in the transverse sinus after lowering ICP by CSF drainage[44]. He suggested that some parts of the venous system are collapsible under high pressure, and that they resolve with pressure normalization. His main conclusion was that the venous hypertension was due to compression of the transverse sinuses by raised ICP and not due to a primary obstructive process in the cerebral venous sinuses. Modern MRI techniques later showed a high prevalence of venous abnormalities in IIH patients. Bilateral transverse sinus stenosis was observed in nearly 90% of patients with IIH[45,46] and in only 1.8% of patients with normal ICP[47]. However, the degree of stenosis was not related to CSF pressure in the study that included 51 IIH patients with venous sinus stenosis[45]. Whether venous abnormalities are a primary or secondary phenomenon in IIH is still an unresolved question, but most authors agree that the consequent flow restriction may further increase CSF pressure and perpetuate this complex situation[1,33]. The term 'self-sustained venous collapse' is used in the literature to describe the circular mechanism which links several physiological processes and may explain the occurrence of chronically raised ICP in patients with IIH[1] (Figure 1). Raised ICP is postulated to induce transverse sinus stenosis (collapse) which results in outflow obstruction leading to venous hypertension and reduced absorption of CSF at arachnoid granulation, setting up finally a vicious "feed forward" cycle. It has been proposed that long-lasting

remission may be achieved in some patients by breaking this cycle[48] which led to the rational for transverse sinus stenting being one of the treatment options for IIH.

Venous sinus theory does not explain the female predominance of IIH in adults and adolescents neither the role of obesity.

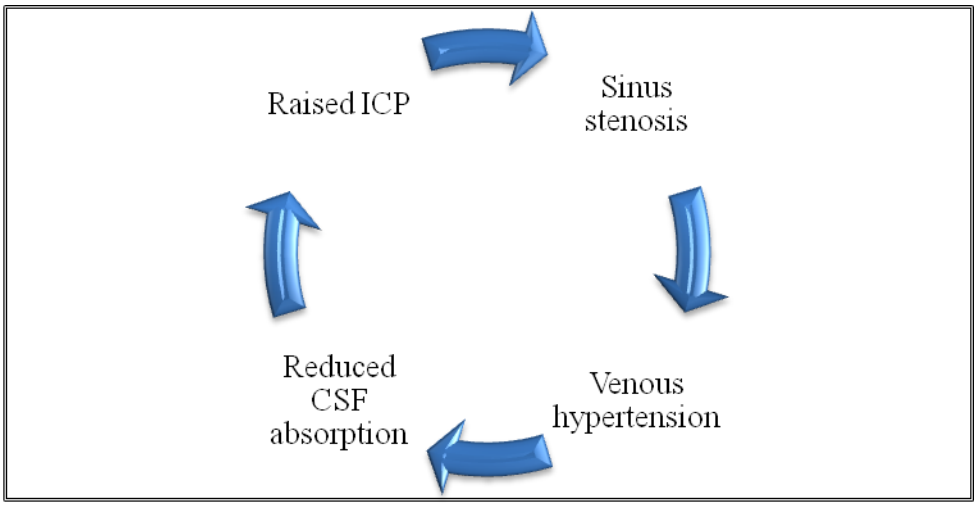

Figure1. The mechanism of self-sustained intracranial and venous hypertension modified from Warkley et al[1].

1.3.3 Role of hormones in IIH

Raised ICP has been intermittently recorded in patients with endocrine disorders as well as in women using hormonal contraception or during pregnancy, but only few studies have systematically evaluated the hormone profiles in IIH. One study investigated multiple hormones (cortisol, testosterone, bioavailable testosterone, prolactin, dehydroepiandrosterone sulfate, androstenedione, insulin, aldosterone, estradiol, follicle stimulating hormone and luteinizing hormone) using radioimmune assays and demonstrated that younger women with IIH had elevated testosterone and androstenedione; control cohort was not evaluated in this study[49]. In another small study, CSF concentrations of oestrone were higher in IIH patients than in controls; unfortunately, the control group was not matched by age or weight[50]. Multiple case reports suggested that iatrogenic use of glucocorticoids could be associated with the increase ICP for the most part after drug withdrawal[51,52]. The research has recently been

focused of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), an enzyme that regulates tissue specific glucocorticoid availability by converting cortisone to active cortisol and which activity is especially high in adipose tissue. Urinary metabolites of 11β-HSD1 in IIH patients significantly decrease with weight loss and correlate with the reduction of ICP[53]. Based on this finding it has been proposed that elevated 11β-HSD1 may represent a pathogenic mechanism in IIH, although further clarification of the functional role of 11β-HSD1 in IIH is needed.

1.3.4 Role of obesity in IIH

Despite the evident association between IIH and obesity, the pathophysiological mechanisms tying the two together are not sufficiently clear; IIH is a rare disorder, while obesity presents a major global health problem.

Obesity elevates intra-abdominal pressure[35,36], which increases pleural and cardiac filling pressures and impedes venous return from the brain. The resulting increase in intracranial venous pressure may reduce CSF absorption. This concept was supported by clinical observations of weight loss improving the condition. However, several studies failed to confirm that exact mechanism of causality, and showed that obesity contributes very little if anything to intracranial hypertension under normal circumstances. Bono at al. studied lumbar CSF opening pressure in 51 obese and overweight individuals with normal brain MRI and magnetic resonance venography (MRV), and found that no subject had a CSF pressure above 200 mm H_2O[47].

Adipose tissue serves as an active endocrine organ secreting a variety of different substances, and this may represent the link between obesity and IIH. Among these agents are proinflammatory cytokines and adipokines which have become a popular research focus. Markers of inflammation in the CSF of patients with IIH were found to be significantly higher than in controls, especially the concentration of chemokine ligand 2 and leptin which is a product of the obese gene Ob and is involved in appetite regulation and weight homoeostasis[54,55]. Concentrations of other inflammatory markers, such as interleukin 1, interleukin 1β, interleukin 8, tumor necrosis factor α, did not

differ significantly between the groups[54]. It has been suggested that CSF leptin could play an important role in the pathophysiology of IIH and that obesity in IIH may occur as a result of hypothalamic leptin resistance[54].

1.3.5 Role of Vitamin A in IIH

There are several reports in the literature linking hypervitaminosis A and development of symptoms and signs of increased ICP. Toxic ingestion of vitamin A rich liver and daily intake of 90 000-200 000 units of Vitamin A were identified as causative factors in PTCS almost 60 years ago[56,57]. It was later suggested that Vitamin A derivates such as etretinate, isotretinoin, and the all-trans-retinoic acid used to treat leukemia could all cause PTCS[58].

Vitamin A and retinoids are thought to interfere with CSF absorption. It has been observed that retinoic acid enhances expression of aquaporin 1, a water channel located in the luminal membrane of the choroid plexus[59]. Concentrations of CSF retinol were found to be higher in patients with IIH as compared with concentrations in serum and CSF of controls[60,61]. However, there is conflicting evidence as to whether these abnormalities of vitamin A metabolism cause IIH, since it is still not clear whether elevated CSF retinol is noxious to the arachnoid granulation reabsorption process or simply represent a marker of CSF overproduction by the choroid plexus[1]. The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), a recent study that prospectively analyzed large cohort of untreated patients with IIH comprehensively evaluated vitamin A and its metabolites in 96 IIH patients and 25 controls matched by gender, age and BMI[62]. Retinol, retinol binding protein, all-trans retinoic acid, alpha- and beta-carotenes, and beta-cryptoxanthin were all measured using accurate quantitative methods in both serum and CSF but failed to demonstrate a contributory role of Vitamin A toxicity in the causation of IIH.

1.3.6 Other potential underlying mechanisms in IIH

Obstructive sleep apnea, often affiliated with obesity, has been associated with IIH, particularly in men, and implicated in its pathogenesis[63,64]. It has been speculated that nocturnal hypoxia and hypercapnia could result in cerebral vasodilation causing the increased blood flow and consequently the raise of ICP[65]. However, papilledema, a hallmark of elevated ICP is not a frequent finding in patients with obstructive sleep apnea[66].

Iron deficiency anemia and IIH are conditions that are both present in young women. There are some suggestions that this association is not merely incidental, since it has been reported that the resolution of anemia led to reversal of intracranial hypertension in some patients[67]. The significance of this finding should be estimated in controlled studies.

Finally, familial occurrence of IIH has also been reported in the literature, indicating a possible genetic predisposition to the disorder[68]. A recent genetic survey of adult-onset IIH exposed highly significant association on a genome-wide scale for common alleles on chromosomes 2, 6 and12[69]. The research is still insufficient and further insight into genetics and the patterns of inheritance is required.

1.4 Clinical presentation of IIH

The clinical presentation of IIH is variable. Classical symptoms and signs which can be attributed to intracranial hypertension are headache and a finding of papilledema[70]. Transient visual obscurations (TVO) are characterized by monocular or binocular blurring lasting for several seconds most likely as a result of transient ischemia of the optic nerve in patients with papilledema[27]. Pulsatile tinnitus is another typical feature, but rarely reported by patients unless they are specifically asked about it. Double vision is usually associated with a finding of unilateral or bilateral sixth nerve palsy, which represents a false localizing sign, and reflects CSF pressure changes. Other symptoms include neck and back pain, dizziness, nausea, concentration difficulties, and memory impairment[15,71]. The symptoms are clearly summarized by a recent study IIHTT that included a large cohort of newly diagnosed IIH patients[15]. The study

revealed that in almost 40% of patients headache was the first symptom of the disease, followed by visual loss in 18%. The disease debuted with pulsatile tinnitus in approximately 12% of IIH patients. Simultaneous occurrence of headache and visual loss was noted in 17% of patients in their cohort[15].

1.4.1 Papilledema

Papilledema is the hallmark finding in IIH, while visual loss is its most important consequence.

The term papilledema is typically reserved for optic nerve swelling caused by increased ICP[72]. The evolution of papilledema is largely dependent on the conjunction of three pressure factors: intraocular pressure, CSF pressure, and systemic blood pressure[73]. Elevated CSF pressure compromise optic disc perfusion leading to axoplasmic flow stasis, optic disc swelling and subsequent intraneuronal ischemia[25].

Still, optic disc swelling may appear as s result of two entirely different situations. Local optic neuropathy and intracranial hypertension may both result in a quite similar disc appearance, however, underlying disorders producing papilledema usually present differently. The term optic disc edema suggests other causes of optic disc swelling than raised ICP, or dilemma regarding the cause[72]. Papilledema in intracranial hypertension and IIH is usually bilateral, although may be asymmetric in 4% of caes[74] or rarely absent[75]. Unilateral or absent papilledema in raised ICP is uncommon finding which is explained by the differences in morphology of arachnoid trabeculations and their meshwork within the nerve sheet[74]. Opposite to papilledema, optic disc edema is typically unilateral. There are some other features that can help a clinician to make a distinction between these two entities presented in Table 2.

Table 1. Differences between Optic Disc Edema and Papilledema adapted from Friedman et al.[72]

Clinical Features	Optic Disc Edema	Papilledema
Early impairment of visual acuity (loss of central vision)	Common	Uncommon[a]
Typical visual field defect	Central or paracentral scotoma, arcuate or altitudinal defect	Enlarged blind spot, arcuate defect, nasal step, inferotemporal loss, concentric constriction[b]
Spontaneous venous pulsations	May be present	Absent
Afferent pupillary defect	Present if unilateral or asymmetric visual loss	Usually absent unless asymmetric visual loss
Disc leakage on fluorescein angiogram	May be present	Yes
Associated symptoms	Pain on eye movement, other symptoms specific to etiology (eg, giant cell arteritis)	Symptoms of raised ICP, focal signs if space occupying lesion is present; rarely asymptomatic

[a] Early papilledema is usually associated with normal Snellen visual acuity, while the risk of visual decline increases with the duration of papilledema[76] ; loss of visual acuity is typically a late sign of papilledema. [b]Visual field defect from papilledema is related to the damage of the nerve fibers at the level of the optic disc, which can also be found in glaucoma or anterior ischemic optic neuropathy[77]. The extent of visual loss usually correlates with the severity of papiledema[74]. If left untreated, prolonged ischemia of the optic nerve head will lead to optic atrophy and finally irreversible sight loss in IIH patients.

Another challenge is to separate true papilledema from pseudopapilledema. Differentiating pseudopapilledema from papilledema is a crucial step to preclude overdiagnosis of IIH, further unnecessary invasive tests, medication use, and surgical procedures. Pseudopapilledema is a term that generally refers to the optic disc drusen and elevated disc in the small hyperopic eye; evaluation by a trained neuro-

ophthalmologist is often needed. Optic disc drusen are deposits of calcium that can be a frequent finding in a young person in the second and third decade of life, and are not related to any other systemic or ophthalmic disease; in most cases, they are incidentally discovered during a routine fundoscopy[78]. In some patients they may coexist with papilledema, which makes the differential diagnosis even more difficult. However, papilledema is more likely associated with disc elevation, blurred edges, lack of a physiologic cup, altered contour, and hemorrhages[72]. B-scan ultrasonography and CT scan of the orbits are common methods to confirm drusens, but in some cases, the auxiliary investigations may be required like fluorescein angiography[72] or optical coherence tomography (OCT) which provides noninvasive and accurate differentiation of optic disc edema and optic nerve head drusen[79]. Infiltration of the optic nerves that can be seen in malignancy, infection, or inflammation may resemble true papilledema, while bilateral optic disc edema may be found in patients with malignant hypertension accompanied by vascular narrowing, macular edema or retinal hemorrhages; in these patients a blood pressure should always be measured[72].

1.4.2 Headache

Headache is present in around 90% of IIH patients at the time of diagnosis and represents the leading reason for IIH patients to seek medical advice[80]. A change in a previously stable headache pattern or the occurrence of a new-onset constant or progressing headache should raise suspicion on disorders of ICP. Headache is well defined common symptom of both conditions- intracranial hypotension and hypertension. Furthermore, they may both present with isolated headaches, normal neurological examination and normal brain imaging, which makes a diagnosis challenging[30]. The underlying mechanism of headache arising from uncompensated changes of ICP is the same for hyper- and hypotension; headache is largely caused by traction on pain-sensitive structures, including intracranial large blood vessels and intracranial portions of the trigeminal, glossopharyngeal, vagus and upper cervical nerves[30].

The features of headache related to IIH vary substantially and the current criteria of the International Headache Society (IHS)[81] remain relatively unspecific in their

description (Table 2). All descriptive characteristics of headache related to IIH that were given in previous, second edition of the International Classification of Headache Disorders[82] are removed in the last revision.

Table 2.International Classification of Headache Disorders, third edition (ICHD-3) criteria for headache attributed to IIH[81]

A. New headache, or a significant worsening[a] of a pre-existing headache, fulfilling criterion C B. Both of the following: • idiopathic intracranial hypertension has been diagnosed[b] • CSF pressure exceeds 250 mm CSF (or 280 mm CSF in obese children)[c] C. Either or both of the following: • headache has developed or significantly worsened in temporal relation to the IIH, or led to its discovery • headache is accompanied by either or both of the following: a) pulsatile tinnitus b) papilledema[d] D. Not better accounted for by another ICHD-3 diagnosis[e,f].

[a] "Significant worsening" indicates a two-fold or greater increase in frequency and/or severity. [b]IIH should be diagnosed with caution in patients with altered mental status. [c]For diagnostic purposes, CSF pressure may be measured by LP performed in the lateral decubitus position without sedative medications or by epidural or intraventricular monitoring. It should be measured in the absence of medications to lower intracranial pressure. Because of diurnal variation of CSF pressure a single measurement may not be able to demonstrate the average CSF pressure and prolonged pressure monitoring may be required in cases of diagnostic uncertainty. [d]Papilledema must be distinguished from optic disc edema and pseudopapilledema. In patients without papilledema IIH should be diagnosed with caution. [e]Headache attributed to IIH may mimic the primary headaches, especially Chronic migraine and Chronic tension-type headache; otherwise, these disorders commonly coexist with IIH. [f]Medication-overuse headache should be excluded in patients lacking papilledema, VI nerve palsy or the characteristic neuroimaging signs of IIH[81].

There is limited data on headache characteristics in IIH since there were few clinical studies aimed to define and describe specific headache phenotype[70,83,84].

Headache attributed to IIH may mimic both migraine and TTH, or even fulfill diagnostic criteria for these conditions given by IHS. However, IIH-associated headaches are usually described by patients as being different from their pre-existing primary headaches in respect to intensity, pain quality and duration[84]. In a study that prospectively investigated headache phenotype in 139 newly-diagnosed IIH patients with mild visual loss and headache, the authors found that in 52% of patients it fulfilled criteria for migraine, in 16% for probable migraine, in 22% for TTH and in another 5,4% for probable TTH[83]. Frontal or frontotemporal localization has been most commonly described by 50-68% of patients[70,83]. About 30% of patients experience strictly unilateral headache[70,83]. It is more likely to be pulsating than pressing, as this quality has been reported by 52-83% of patients from several different studies[14,70]. Daily occurrence has been reported by 67-93% of patients[70,85,86], and overuse of analgesics in up to 11%[83]. The relationship between headache severity or frequency and values of ICP has not been proven[87]. Worsening of headache by coughing and straining, Valsalva-type maneuvers has also been demonstrated[70].

The headaches in IIH are the most important factor driving reduced quality of life[88] and may have substantial to severe impact on social functioning, vitality, cognitive functioning and psychological distress measured by standard indicator of headache burden -Headache Impact Test (HIT-6)[83]. The second edition of ICHD from 2004 emphasized the causality between headache and raised ICP by requiring for diagnosis a headache improvement after CSF withdrawal and complete resolution within 3 days after normalization of ICP[82]. Later research revealed that in every other patient headache persist despite ICP regulation[84]. Moreover, the relief of headache after CSF removal is not exclusively seen in IIH, but has been described in nearly a quarter (20%) of patients with other headache types[70].

1.4.3 Visual symptoms

Varies forms of visual disturbances were noted in IIH patients. Impairment of visual acuity, blurred vision, visual fields deficits, and even tunnel vision have been commonly reported, but none of them are specific for IIH.

Transient obscuration of vision, usually lasting seconds, occurs with postural provocation in 68–72% of patients with IIH in one or both eyes, usually many times daily[15,89]. TVO can be typically provoked by arising after bending over or from eye movement. Their presence is not specific to papilledema but may also occur with other optic nerve disorders without optic disc swelling. The pathogenesis of TVO is not quite clear. TVO is thought to be the consequence of the transient ischemia of the optic nerve head due to increased tissue pressure and may not be always related to intracranial hypertension[90]. Binocular and horizontal diplopia arises as a result of sixth nerve palsy and usually resolves with normalization of CSF pressure. In the presence of severe papilledema, monocular diplopia may appear as a consequence of macular edema and subsequent formation of epiretinal membrane[91]. IIH patients sometimes become conscious of their physiologic blind spot as it enlarges, reporting to see something moving in their peripheral vision; blurred, hazy or dim vision experience patients with substantial visual loss, secondary to chronic optic nerve ischemia or early in the disease in fulminant forms of IIH[72]. In others, ophthalmological examination reveals normal or near-normal visual acuity.

1.4.4 Other symptoms

Unlike idiopathic tinnitus, pulsatile tinnitus more frequently has a specific, traceable cause. The origin of pulsatile tinnitus may be arterial, arteriovenous or venous. Dissections of arterial wall, fibromuscular dysplasia and arteriosclerosis are common arterial causes, while arteriovenous fistula and tumors localized at the base of the skull may cause tinnitus at arteriovenous junction[92]. Pulsatile tinnitus in IIH is explained by flow turbulence within the transverse venous sinus, due to venous sinus stenosis, and in 2/3 of patients is bilateral[15,89]. It can be alleviated by compression of the internal jugular vein[92]. Low-frequency hearing loss and dizziness have also been noted in IIH patients. Auditory brainstem-evoked response revealed prolonged interpeak latencies in 1/3 of patients with IIH that became normal after treatment; compression or stretching of cochlear nerve and brainstem from raised ICP were proposed underlying mechanism[93].

IIH patients frequently complain about impaired memory and loss of concentration, which is also seen in other chronic headache disorders. However, cognitive screening revealed deficits in multiple domains of cognition, including executive function, working memory, processing speed, motor skills, visuospatial processing, attention, and memory[94,95]. A prospective case-control study from Yri at al. showed that reaction time and processing speed were the most affected domains, and that in half of the patients cognitive dysfunction persisted 3 months after the introduction of treatment despite substantial improvement of headache and normalization of ICP[94].

Besides headache, the other pain conditions have been frequently described in IIH, among them are back and neck pain with or without radicular distribution[15,96,97]. Less frequently, spontaneous CSF leaks may occur as a consequence of raised ICP, and except for rhinorrhea, these patients may otherwise be asymptomatic[98,99]. An impaired olfactory function has also been noted in several recent studies[100,101], while structural changes of olfactory bulb are detected by MRI techniques in IIH patients at an early stage of the disease[102].

Finally, asymptomatic cases of possible IIH have been reported, in whom papilledema was discovered during the routine ophthalmological examination, but the incidence and their clinical course are uncertain[103].

1.5 Diagnostic procedures in IIH

The first diagnostic step in case of suspected IIH patient is neurological examination supplemented by fundoscopy. With the exception of sixth cranial nerve palsy and papilledema neurological examination in IIH patients is completely normal. Fundoscopy is a simple, quick and accessible bedside tool, but in case of any diagnostic uncertainty it requires the expertise of experienced clinician in order to prevent further unnecessary investigations. Misdiagnosis of IIH occurs in up to 40% of patients, mostly due to incorrect assessment of papilledema[104]. Recent guidelines[105] suggest that in all patients with confirmed papilledema additional examination should be done, that include visual acuity and visual field testing by perimetry, pupil examination, and

intraocular pressure measurement. OCT has already been demonstrated in IIH patients to be a valuable additional tool for quantification and monitoring of papilledema over time[106,107].

The next step is neuroimaging, preferably a brain MRI supplemented by venography, or brain computed tomography (CT) if MRI is unavailable[27,105]. These procedures are mandatory to exclude any structural or space-occupying lesions, hydrocephalus, or abnormal meningeal enhancement, while venography is essential to rule out sinus venous occlusions[10]. Symptoms and signs of raised CSF pressure may be the only manifestation in up to 60% of patients with cerebral venous thrombosis[108]. Bilateral transverse sinus stenoses, but not occlusions, are frequently described in IIH patients[46,109,110] as a radiological marker of raised ICP. Other typical neurimaging features of raised ICP are findings of empty sella, flattening of the posterior aspect of the globe, increased tortuosity of the optic nerve, and perioptic subarachnoid space enlargement[10].

In the clinical setting intracranial hypertension is recorded by LP with manometry. In the absence of any obstruction, LP opening pressure corresponds closely with the ventricular pressure and serves as an indirect marker of ICP. A standardized procedure is essential and opening pressure should be measured in the lateral decubitus position. After the needle is inserted into the CSF space, the pressure should be measured with the patient relaxed as much as possible without sedative medications and with the extended legs. In order to minimize false positive result, the CSF pressure should be allowed to settle before taking the reading[105]. Opening pressure values above 25 cm H2O in adults and above 28 cm H2O in children are considered abnormal[10,81], however, it is recommended not to be interpreted in isolation when diagnosing IIH[105]. The LP opening pressure is only a point measurement, while there is a wide diurnal variation in CSF pressure. In cases with atypical presentation or in those with marginally elevated opening pressure repeated LPs or even intracranial ICP monitoring have been suggested[80,105]

In order to diagnose IIH in patients with demonstrated intracranial hypertension, secondary causes of raised ICP should be excluded. A comprehensive patient history is needed with a special consideration of the medications and diseases that were

previously linked to intracranial hypertension (Table 3), although the causality in some of them remains unclear.

Table 3. Medical conditions that may induce a secondary elevation of ICP or produce symptoms that mimic IIH (adapted from Hoffmann et al.)[80]

A. Disorders that may induce a venous outflow obstruction:	B. Medications	C. Other disorders
•Thrombophilia and other hypercoagulable disorders	• Tetracycline	• HIV
• Systemic lupus erythematodes	• Fluoroquinolones	•Syphilis
• Infections of the middle ear or mastoid	• Vitamin A and retinoids	•Borreliosis
• Infections of the central nervous system	• Anabolic steroids	•Varicella
• Increased right heart pressure with pulmonary hypertension	• Withdrawal of corticosteroids after prolonged administration	• Addison's disease
• Chronic obstructive pulmonary disease	• Administration of growth hormone	• Hypoparathyroidism
• Superior vena cava syndrome	• Lithium	• Obstructive sleep apnea
• Arteriovenous fistulas	• Nalidixic acid	• Obesity hypoventilation (Pickwickian) syndrome
• Glomus tumour	• Indomethacin	• Uremia
• Tumour process that may compress parts of the venous outflow system	• Oral contraceptives	• Severe iron deficiency anemia
	• Levonorgestrel implant system	• Renal failure
	• Amiodarone	• Turner syndrome
	• Cyclosporine	• Down syndrome
	• Cytarabine	

1.6 Diagnostic criteria for IIH

Evolving knowledge of the CSF physiology, etiology and underlying pathophysiological mechanisms of raised ICP, led to several revisions of the IIH definition over the years. A guide for diagnosis of IIH has been the criteria originally developed by Dandy in 1937[6], which were further modified by Smith in 1985[111]. These modified Dandy criteria required no other neurological symptoms and signs but those of raised ICP above 25 cm H20, normal cerebrospinal fluid composition, normal imaging studies and no other identified cause of intracranial hypertension. Neurological symptoms and signs of raised ICP were not specified by these criteria. Due to advances in neuroimaging, new diagnostic criteria for IIH have been proposed by Friedman et al. in 2002[112] and 2013[10]. They provoked substantial controversy by reintroducing the old term of "pseudotumor cerebri", the umbrella concept that characterize both primary (IIH) and secondary forms of intracranial hypertension. Papilledema is the major criteria for definite IIH in the latest diagnostic criteria[10], but other than papilledema, these criteria are not based on the clinical presentation of the disease (Table 4). In the absence of papilledema, a definitive diagnosis of IIH can be made only in patients with a sixth nerve palsy, or suggested according to the neuroimaging findings associated with increased ICP in those without sixth nerve palsy.

Table 4. Diagnostic criteria for pseudotumor cerebri syndrome, adapted from Friedman et al.[10]

1. Required for diagnosis of PTCS[a]
A. Papilledema
B. Normal neurologic examination except for cranial nerve abnormalities
C. Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI for typical patients (female and obese), and MRI, with and without gadolinium, and MRV for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used
D. Normal CSF composition
E. Elevated lumbar puncture opening pressure (≥250 mm CSF in adults and ≥280 mm CSF in children (250 mmCSF if the child is not sedated and not obese)) in a properly performed lumbar puncture

2. Required for diagnosis of PTCS without papilledema

-In the absence of papilledema, a diagnosis of PTCS can be made if B–E from above are satisfied, and in addition the patient has a unilateral or bilateral abducens nerve palsy.

-In the absence of papilledema or sixth nerve palsy, a diagnosis of PTCS can be suggested but not made if B–E from above are satisfied, and in addition at least three of the following neuroimaging criteria are satisfied:

i. Empty sella

ii. Flattening of the posterior aspect of the globe

iii. Distention of the perioptic subarachnoid space with or without a tortuous optic nerve

iv. Transverse venous sinus stenosis

[a]A diagnosis of PTCS is definite if the patient fulfills criteria A–E. The diagnosis is considered probable if criteria A–D are met but the measured CSF pressure is lower than specified for a definite diagnosis.

1.7 IIH management

The goal of IIH management is to preserve the vision and achieve headache relief by reducing raised ICP. Over the years the treatment strategies for IIH were based on clinical experience, but recently guidelines have been published based on the evidence from well-designed clinical trials assessing acetazolamide and weight loss, and expert consensus[80,105]. Therapeutic approach is largely determined by the degree of visual loss and disease progression and includes various interventions: diet with lifestyle modification, drug treatment, repeated LPs, surgical and endovascular procedures.

1.7.1 Weight reduction

Weight reduction plays an important role in IIH management. It is considered as the only disease-modifying therapy of IIH[80]. Originally, the beneficial effect of weight loss was observed from case reports, retrospective studies, and uncontrolled trials, but was recently confirmed in a prospective cohort trial from Birmingham group[113]. Sinclair et al. prospectively treated twenty-five women with IIH with a very low-calorie diet for three months following a three-month observational period. They included patients with a stable IIH disease, with mean disease duration over 3 years. Upon diet, patients lost an

average of 15.7 kg (15% of body weight) which resulted in a significant reduction in ICP, and improvement of headaches and papilledema. Yet, no correlation was found between the amount of weight loss and change in ICP[113]. Another open-labeled design study of newly diagnosed IIH, demonstrated a significant reduction of CSF pressure in patients with ⩽3.5% reduction of BMI on diet, in contrast to patients who did not achieve weight loss[114]. Still, the exact amount of weight loss required for disease remission is not known. Additionally, the optimal method of long-term weight reduction is uncertain too, as dietary strategies are difficult to maintain.

There has been substantial interest in bariatric surgery, one of the promising options for faster and sustained weight loss in obese patients with severe IIH features. Several studies suggested that bariatric surgery in obese individuals resulted in greater weight loss compared to diet, with a mean reduction in BMI of 7.05–15.34 m/kg2 at 1 year after intervention and led to sustained long term weight reduction[115,116]. The review of the literature by Fridley and colleagues revealed the resolution of IIH symptoms in 92% of IIH patients post-surgery, and regression of papilledema in 34 of 35 patients[117], while more recent data indicate 100% resolution of papilledema and headache improvement in 90% of IIH patients[118]. The more prospective controlled evidence considering the role of this intervention in IIH treatment is required.

1.7.2 Drug treatments

Acetazolamide is considered to be the first drug of choice in IIH management since it is the only therapeutic that has been evaluated in randomized controlled trials. It has a significant sulfonamide carbonic anhydrase inhibitor effect and most efficaciously lower ICP at doses of 3-4 g daily[119]. Side effects during IIH treatment are common and include acroparesthesias, fatigue, dysgeusia, nephrolithiasis, gastrointestinal symptoms such as nausea, vomiting and diarrhea, while Stevens–Johnson syndrome or other severe adverse effects are rare[120,121]. Acetazolamide treatment is also frequently associated with laboratory abnormalities such as hypokalemia or development of metabolic acidosis. In a randomized, open-label pilot study of acetazolamide versus no acetazolamide in IIH, acetazolamide failed to show treatment effect[120]. Moreover,

adverse effects were the reason why 48% of IIH patients in the active group stopped or reduced the planned dose up to a maximum of 1500 mg. It was traditionally thought that tolerability of acetazolamide was dose-dependent until the data from IIHTT showed that adverse effects did not increase with dosage, suggesting that if a patient tolerates acetazolamide at a low dose, they are likely to tolerate a higher dose. However, side effects often limit upward titration of the dose, despite that an acceptable safety profile at dosages up to 4g per day has been observed[121].

The efficacy of acetazolamide in IIH has been recently investigated in IIHTT, a large, multicenter, randomized, double-blind, placebo-controlled study which included 165 participants with mild visual loss[122]. Use of acetazolamide with a low-sodium diet compared with diet alone resulted in a small but beneficial effect in visual field function. The improvement of headache and TVO has not been demonstrated with acetazolamide therapy in the same trial. However, positive effects of acetazolamide on neck pain and pulsatile tinnitus were observed, but did not reach statistical significance; still, they outweighed a negative effect of acetazolamide due to its side effects, on quality of life of IIH patients treated with that medication. Weight loss and dietary restrictions were treatment strategies that were associated with headache relief and reduced TVOs in IIHTT[123]. A very limited effect of acetazolamide in that trial could be explained by the methodological approach, and the decision to include due to ethical reasons, only patients who had a mild visual loss.

Based on the results of two randomized controlled trials[120,122], the current Cochrane review on IIH management and use of acetazolamide concluded that "there is insufficient evidence to recommend or reject the efficacy of this intervention, or any other treatments currently available, for treating people with IIH"[124].

The common alternative therapeutic agents used in IIH are furosemide and topiramate. Intravenous of intraventricular application of furosemide has been shown to reduce CSF secretion by 20–50% in animal studies[125–127]. There is little evidence to support the routine use of furosemide alone in IIH. A small pediatric case series

demonstrated the efficacy of a combination of acetazolamide and furosemide in the reduction of ICP in children with IIH over 6 weeks[128].

Topiramate, an antiepileptic drug, has also been reported to be effective in IIH treatment[129,130]. Like acetazolamide, it inhibits carbonic anhydrase enzyme in the choroid plexus which results in decreased CSF production and pressure, although its effect on carbonic anhydrase inhibition is weaker than acetazolamide. However, topiramate is a strong prophylactic medication for migraine and has a positive side effect of appetite suppression and weight loss. These characteristics make topiramate an appealing treatment option in IIH. As headache is such a prevailing and disabling symptom in IIH, topiramate is often prescribed in a combination with acetazolamide or even as a monotherapy. Marked side effects frequently prevent the long -term treatment with this drug; most of them are very similar to acetazolamide with paresthesia, gastrointestinal symptoms, and fatigue in addition to cognitive, coordination, and gait problems[27]. Cognitive side effects of topiramate are highly undesirable in IIH patients since they are already affected by a various degree of cognitive impairment.

Novel therapeutics targeted to control ICP by enhancing weight reduction have been proposed[131,132]. Glucagon-like peptide-1 is the gut peptide involved in the regulation of insulin secretion and weight, currently used for the treatment of diabetes and obesity. Recent in vitro studies have demonstrated that exendin-4, the agonist of glucagon-like peptide-1 receptor reduces secretion of CSF[131]. Additionally, it showed the potential for a significant reduction of ICP in rodents with raised ICP[131]. 11β-HSD1 inhibitors that are involved in the regulation of cortisol availability have been developed to treat obesity and metabolic syndrome; their efficacy and safety in IIH patients are currently being investigated in the randomized controlled trial[132].

1.7.3 Surgical procedures

In most patients, weight reduction and medical management are generally sufficient treatment strategies leading to remission. Surgical procedures are generally required only in IIH cases with severe, rapid or progressive declining of visual function

and in those with an intractable headache despite aggressive medical management[133]. CSF diversion and optic nerve sheath fenestration (ONSF) are the most practiced procedures, however strong evidence from randomized controlled trials is still lacking.

Ventriculoperitoneal shunt (VPS) and lumboperitoneal shunt (LPS) insertion are used to divert CSF from the ventricle or subarachnoid space to peritoneal space. Although both procedures rapidly lower the elevated ICP and improve visual function, the question of the utility of these interventions is raised, as complications are common. They include shunt blockage, infection, back and abdominal pain, tonsillar herniation and intracranial hypotension leading to the shunt revision in more than half of patients or even multiple revisions in 30% within the first 10 years after installation[134].

The goal of ONSF is to reduce papilledema-related visual loss by lowering CSF pressure on the retrolaminar part of the optic nerve. However, the decrease of ICP may not be achieved, which makes this intervention applicable to IIH patients who mainly experience visual symptoms and are not disabled by severe headache[133]. The majority of ONSF studies investigate the visual outcomes (papilledema, visual acuity, visual filed) rather than headache relief. In a retrospective observational study of Chandrasekaran, that evaluated the efficacy and safety of ONSF in IIH patients, visual function is found to be improved significantly, but in 11 of 32 patients, additional CSF diversion was required[135]. It has been suggested that a unilateral ONSF may be sufficient in decreasing papilledema in both eyes[136]. Traumatic optic neuropathy, pupil dilatation, retinal vascular occlusion, and diplopia are reported complications of ONSF[137].

1.7.4 Other interventions

There is growing research on dural venous sinus stenting in IIH owing to a frequent finding of venous sinus stenosis demonstrated by CT/MRI venography in IIH patients. The causal role of venous sinus stenosis in IIH is controversial and the utility of this endovascular procedure is debated. The improvement in symptoms of IIH, especially tinnitus, headache, visual function, and papilledema have been reported in several smaller case series and retrospective studies, but case selection was not

randomized[45,138,139]. The endovascular interventions have the advantage of being minimally invasive; however, multiple complications have been reported including stent migration and thrombosis, restenosis, and vessel perforation[138–140].

Considering a risk of various complications associated with VPS and LPS or endovascular interventions, repeated LPs performed with daily or weekly intervals could be a short-term alternative, but the evidence is entirely clinical. Therapeutic LPs improved headache in 71% of patients, but the improvement is not substantial, and exacerbation of headache is observed in 64% of patients in the week following LP[141]. The role of repeated LPs in IIH treatment could be the protection of vision in patients with fulminant IIH awaiting a CSF diversion[80]. It could be also considered during pregnancy, since the use of acetazolamide is controversial[142,143], and topiramate significantly increases the rate of fetal abnormalities[144].

A systematic review[145] of surgical and interventional procedures could not support the use of any technique in particular due to an absence of evidence; therefore the choice of procedure is largely dependent on resources, local expertise, and preference. Most patients will benefit from a multidisciplinary approach, and close collaboration of neurologist, neuro-ophthalmologist, and dietician, while surgical procedures should be minimized and only reserved for the malignant cases or rapid progression[27].

1.8 IIH prognosis

IIH has not been associated with any specific mortality risk per se, although the increased mortality has been linked with surgical interventions, stenting, and morbid obesity. The morbidity of IIH is mainly related to the persistence of headache and the effects of papilledema on visual function[89]. Visual impairment that could be detected in almost 90% of patients at presentation is often reversible to some extent, while severe or permanent loss of vision occurs in up 10% of patients[14]. Therefore, for many patients, IIH complies with its old name BIH, as a benign disease, not seriously affecting vision in the long-term prognosis. In spite of that, in just as many patients this long-term

illness has been accompanied with the drug adverse effects, potential depression, anxiety, medication overuse, and in some surgical procedures, strongly influencing various aspects of their lives including family life, profession and earning potential[91]. Furthermore, treatment modalities directed at reducing CSF pressure are often insufficient for suppressing headache in many patients with IIH[84,146,147].

Apart from headache, that is the major contributing factor to the quality of life in IIH patients, visual disturbances (TVO, double vision, decreased visual acuity), and neck pain were also identified as independent factors associated with worse quality of life at the time of diagnosis; the same has not been proven for obesity[8]. The improvement of visual fields, TVOs, subjective cognitive dysfunction, and dizziness are on the other hand significantly associated with improvement of the quality of life after 6 months in patients who were treated for IIH[123].

Low prevalence of IIH results in insufficient data regarding the course and long-term outcome of the disease. Prolonged or recurring condition has been reported in several case series of IIH[23,148,149]; however predictors of recurrence or refractory disease have been barely explored.

2. REAEARCH OBJECTIVES

1. Characterizing the presenting symptoms and signs of IIH defined according to the existing diagnostic criteria
2. Correlation of presenting symptoms and signs with the results of diagnostic procedures: ICP measurement, presence of papilledema, and neuroimaging markers of raised intracranial pressure
3. Correlation of presenting symptoms and signs with the course and disease outcome.

3. METHODS AND MATERIALS

3.1 Study protocol, sites and participants

This cohort study was conducted from January 2007 to March 2016 in two tertiary centers: the Danish Headache Center at Rigshospitalet, Glostrup and the Neurology Clinic of the Clinical Center of Serbia. The study included patients that were consecutively referred for the evaluation of possible IIH by an attending neurologist due to chronic headache or ophthalmologist due to papilledema.

The Danish Headache Center is a referral resource for patients with rare headache disorders including IIH that are referred from private practice, outpatient neurology clinics and hospitals in Denmark. Patients with IIH are diagnosed and treated in close collaboration with the Department of Ophthalmology, Rigshospitalet, Glostrup, a tertiary eye care center accepting patients from private ophthalmologists and other Danish ophthalmological departments. Patients with IIH diagnosis from Serbia are evaluated and treated at the Department for cerebrovascular disorders and Headache at the Neurology Clinic of the Clinical Center of Serbia. The Department is receiving patients with treatment-resistant, chronic or rare headache disorders as well as headache patients from the Emergency Department in Belgrade.

The study was conducted in two phases. At first, clinical data were prospectively collected from all study participants in order to evaluate the presenting symptoms and signs of IIH and to estimate their possible role in establishing the diagnosis of IIH. All subjects with possible IIH were than divided into two groups: one group with confirmed IIH diagnosis (IIH group) and one group in whom IIH diagnosis had been rejected (non-IIH). Clinical symptoms and findings that predict the diagnosis of IIH were analyzed and independent predictors were estimated.

The second phase of this study included patients from the IIH group who were followed by neurologist and ophthalmologists at least one year after IIH diagnosis was confirmed. A retrospective chart review of these patients was performed in order to

identify the course and outcome of the disease. Non-IIH patients and those with less than 1-year follow up were excluded from further analysis. Clinical symptoms and findings that predict the course and outcome of IIH were analyzed and independent predictors were estimated. Study procedures and patient disposition are presented at Figure 3.

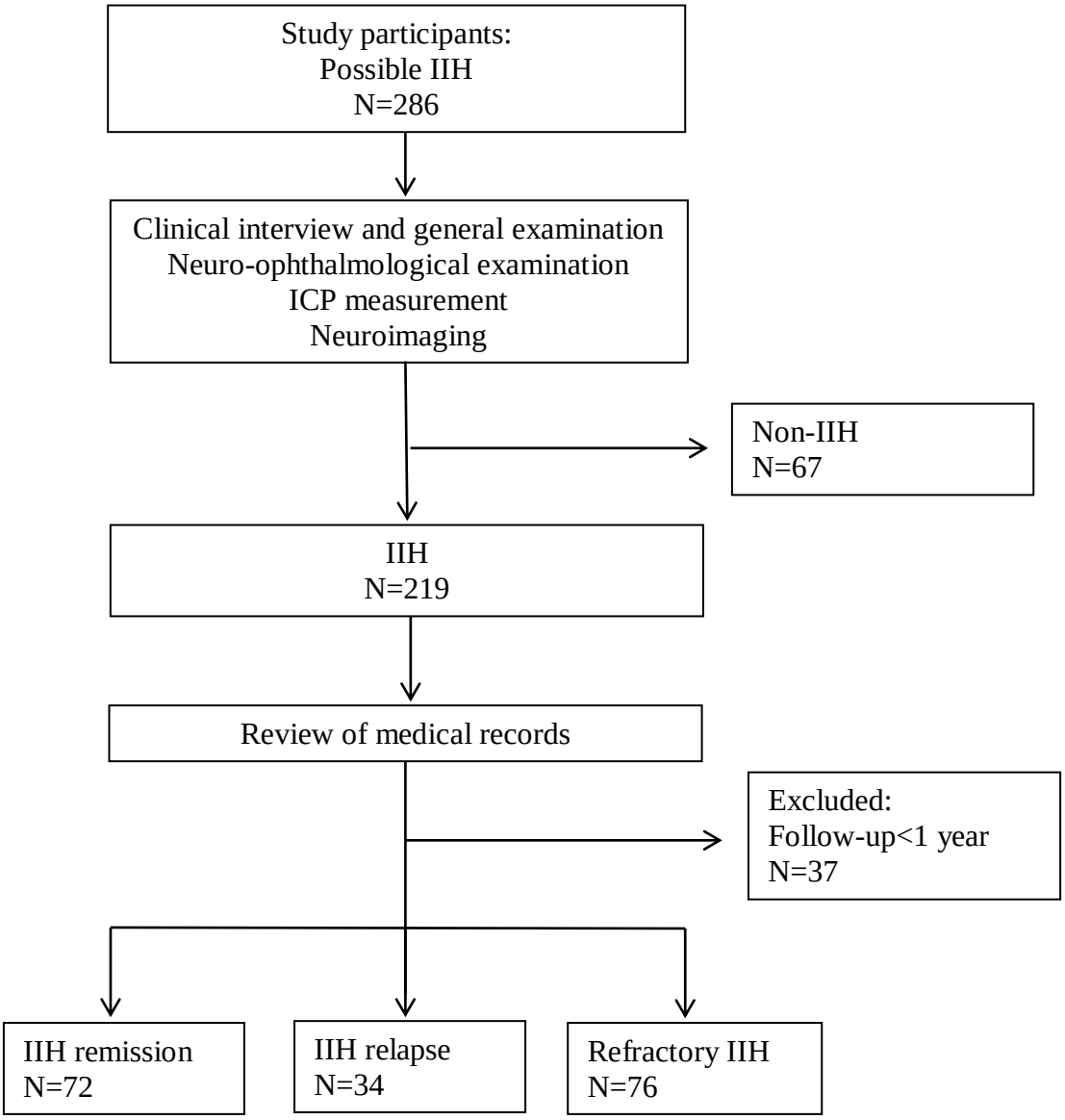

Figure 2. Study design diagram

IIH-Idiopathic intracranial hypertension; ICP-intracranial pressure

3.2 Study procedures

3.2.1 Clinical interview and general examination

A detailed patient history in all participants was assessed by standardized, clinical semi-structured interview supplemented by a comprehensive questionnaire specifically designed for the study.

We collected demographic data: gender, BMI, age at disease onset, presenting symptoms of the disease, medication use prior to disease onset, the presence of comorbid disorders.

The following presenting symptoms were investigated: headache, visual disturbances, tinnitus, nausea, vomiting, photophobia, phonophobia, dizziness, neck pain, concentration, and memory difficulties.

The analyzed headache characteristics were: mode of onset, localization, intensity, pain quality and duration, aggravating factors.

The analyzed visual disturbances were the occurrence of TVO, blurred vision, and double vision. The frequency, localization and possible provoking factors of TVO were also assessed.

Comorbid disorders, including polycystic ovary syndrome, sleep apnea, skin diseases, depression and anxiety, together with pharmacological treatment (tetracyclines, vitamin A preparations, corticosteroids, hormonal contraception), and weight gain were evaluated due to previous reports of their possible role in intracranial hypertension. A history of pre-existing primary headache disorder: migraine, tension-type and other headache was also obtained.

Standardized neurological examination was performed in all participants by neurologist.

3.2.2 Neuro-ophthalmological examination

Visual acuity, eye motility, visual field testing, and ophthalmoscopy were procedures routinely performed in all patients at baseline in both centers. In some patients from Denmark OCT was also performed in order to detect or monitor papilledema.

The assessment of papilledema by direct ophthalmoscopy was done by ophthalmologist. Snellen chart was used to measure visual acuity, and automated perimetry, Humphrey 30-2 for visual fields evaluation. Visual data were not analyzed if patients had other ocular diseases with the potential for causing visual loss.

3.2.3 ICP measurement

ICP measurement was performed in all patients at study entry together with standard cytological and biochemical CSF analysis. We measured ICP by LP manometry with the patient placed in the lateral decubitus position with their legs extended. The patients were given time to relax before a stabilized pressure was recorded. Intracranial hypertension was demonstrated by increased values of opening ICP $\geq$ 25 cm H20. In 4 patients recruited from Danish headache center, ICP measurement was supplemented by direct intracranial pressure monitoring due to uncertain LP manometry measurement. In patients in whom acetazolamide treatment was initiated prior to referral, it was withheld 72 hours prior to lumbar puncture. Patients in whom ICP exceeded standard measure limits were excluded from ICP values analysis. ICP measurement was repeated in some participants with confirmed IIH diagnosis in order to monitor the course and treatment efficacy, but this was not as a part of our study protocol, and the procedure was done entirely for clinical reasons in complex cases. However, ICP values recorded at follow up visits of these patients were used in the study for assessing the course of their disease.

3.2.4 Neuroimaging

Brain CT was performed routinely in all patients in order to exclude space-occupying lesions and other secondary causes. All subjects with confirmed intracranial hypertension had MRI brain scans supplemented by venography to exclude cerebral venous sinus thrombosis. In patients in whom MRI was contraindicated or could not be performed due to claustrophobia or body weight limitation, contrast-enhanced CT with CT venography was done. Neuroimaging markers of raised intracranial pressure were evaluated retrospectively in patients with confirmed IIH diagnosis who underwent brain

MRI. It included empty sella, flattening of the posterior aspect of the globe, distension of the perioptic subarachnoid space and transverse venous sinus stenosis as implied by diagnostic criteria for PTCS from 2013[10]. Descriptions of MRI findings were extracted from medical records.

3.3 Confirmation of IIH diagnosis

The diagnostic criteria proposed by Friedman in 2002[150] and its revision from 2013[10] were applied for diagnostic purpose. Diagnosis of IIH was established by exclusion of secondary causes of intracranial hypertension based on normal results of neuroimaging studies and CSF 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.

3.4 Patient management

In patients with confirmed intracranial hypertension pharmacological treatment was initiated after diagnostic LP in order to lower ICP. According to literature data and being a part of a regular clinical practice in both centers, patients with IIH diagnosis were treated with acetazolamide, topiramate, and/or furosemide. The doses were individualized and adjusted according to tolerance and clinical response, especially the resolution of papilledema, headache and other symptoms. Patents were encouraged to lose weight. Patients with rapid loss of vision were treated with insertion of a VPS or LPS. Dural venous sinus stenting and bariatric surgery were procedures performed in patients treated at Danish Headache Center; these treatment modalities were not available for IIH patients in Serbia.

Follow-up visits were offered to all patients with IIH diagnosis in both centers.

3.5 The assessment of course and outcome of IIH

We performed a retrospective analysis of the clinical data obtained from medical records of IIH patients that met the inclusion criterion for the second part of the study. These patients were examined on regular follow-up visits in a standardized fashion by experienced neurologists and neuro-ophthalmologists. The following data obtained from the end follow-up visit were collected and analyzed: BMI, a presence of chronic headache, visual disturbances (TVO, blurred, double vision), and tinnitus. Visual acuity and visual field testing were also extracted from the latest ophthalmological record, together with the fundoscopic assessment of optic disc for the presence of papilledema or atrophy.

According to the results at the end follow-up visit, three possible outcomes were registered: remission, relapse, and refractory IIH disorder. Remission was defined if the patient was without symptoms of IIH-chronic headache, visual disturbances and tinnitus, and did not have papilledema. Relapse was defined as a return of symptoms (headache, visual disturbances, or tinnitus) and signs of IIH (papilledema, sixth nerve palsy) after resolution and being off medications at least 6 months. Finally, refractory IIH was defined as IIH without significant improvement of symptoms or signs during the total follow-up. Follow-up time was calculated from the time of diagnosis. It varied between 12 and 144 months in our cohort.

3.6 Ethical aspects

The study was approved by the Ethics Committee of Medical Faculty, University of Belgrade. In Denmark, it was approved by the Ethics Committee of Rigshospitalet, Glostrup (protocol H-3-2011-016). The study was conducted in accordance with the Declaration of Helsinki.

Written informed consent was obtained from all participants.

3.7 Statistics

ANOVA and chi-square tests were used for the comparison of two groups depending on data distribution. Multivariate logistic regression (enter method) was applied to determine the diagnostic predictors in the first part of the study. The criterion for the inclusion of variables in the multivariate model was statistical significance at the level of 5% ($p< 0.05$) obtained by univariate analysis. Sensitivity, specificity, and likelihood ratios were calculated for all statistically significant predictors, while receiver operating characteristic curve (ROC) and area under the curve (AUC) were obtained for the multivariate logistic model. Descriptive statistics (ratio, mean value, standard deviation, coefficient of variation) are used to describe the characteristics of the examined IIH group. To determine the correlation between variables, Spearman's correlation test for nonparametric and Pearson correlation tests for parametric data were used. To measure prediction values of individual factors on disease outcome the Cox proportional hazard regression model was applied, using the hazard ratio (HR) with 95% confidence intervals (CI) as the outcome measure. Continuous variables were included in the model without their dichotomization. Time of IIH diagnosis was defined as zero time, while the end point time in this analysis was IIH remission, first relapse or follow-up time in different patient groups. Univariate Cox regression analysis was used to test the influence of different variables on the IIH outcome. Finally, the variables that had reached statistical significance at the level of 5% ($p< 0.05$) were additionally analyzed in the multivariate Cox proportional hazard regression model. The selected predictors were combined into a model by using the forward stepwise method.

The SPSS 17.0 statistical software package (SPSS Inc, Chicago, IL, USA) was used to perform the statistical analysis.

4. RESULTS

4.1 Estimation of the predictive role of presenting symptoms and clinical findings on IIH diagnosis

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).

4.1.1 Demographic data of the study population

Of the 286 patients in the study, 251 (87.8%) were women. The average age at onset of symptoms was 31.7±11.9 years (range 14—71 years). The average BMI was 34.17±7.37 and 168 (71.8%) patients were obese. The comparison between demographic data and referring provider of IIH and non-IIH patients are presented in Table 5.

Table 5. 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**

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

There were no differences between the IIH and non-IIH group 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 5).

4.1.2 Presenting symptoms and signs of the study population

The most common symptom in the whole study population was headache, reported by 254 (89.1%) patients at the initial visit, followed by blurred vision (62.1%) and tinnitus (58.6%). The comparison between presenting symptoms and signs in IIH and non-IIH patients are given in Table 6.

Table 6. 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

TVO, double vision, tinnitus, and neck pain were the presenting symptoms more frequently reported by patients with established IIH diagnosis. In this patient group memory impairment and concentration difficulties were significantly less reported. Papilledema and sixth nerve palsy were noted significantly more often in patients with IIH (Table 6).

4.1.3 A medical history of comorbid disorders, weight gain and medication use prior to the disease onset in the study population

A positive medical history of depression was reported by 66 (23.5%) participants; it was the most frequent comorbidity in the whole study population. The comparison between comorbid disorders, weight gain and medication use prior to the disease onset in IIH and non-IIH patients are presented in Table 7.

Table 7. 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[b], 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

[b]Skin diseases: atopic dermatitis, acne, psoriasis, keratosis, lichen

p values < 0.05 were considered as statistically significant

One third of the whole cohort indicated weight gain preceding the onset of symptoms. A 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, usage of medications prior to disease onset and weight gain within the last 12 months (Table 7).

4.1.4 Diagnostic accuracy of IIH predictors

Sensitivity and specificity for all statistically significant predictors are presented in Table 8.

Table 8. 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

Sensitivity and specificity for all significant symptoms, signs, comorbid disorders and other predictors were low, with the exception of papilledema.

All variables that reached statistical significance at univariate analysis were examined by multivariate logistic analysis as predictors of IIH diagnosis. The results of the multivariate logistic analysis are presented in Table 9.

Table 9. 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

A receiver operating characteristic curve for multivariate logistic predictive model is presented by Figure 3.

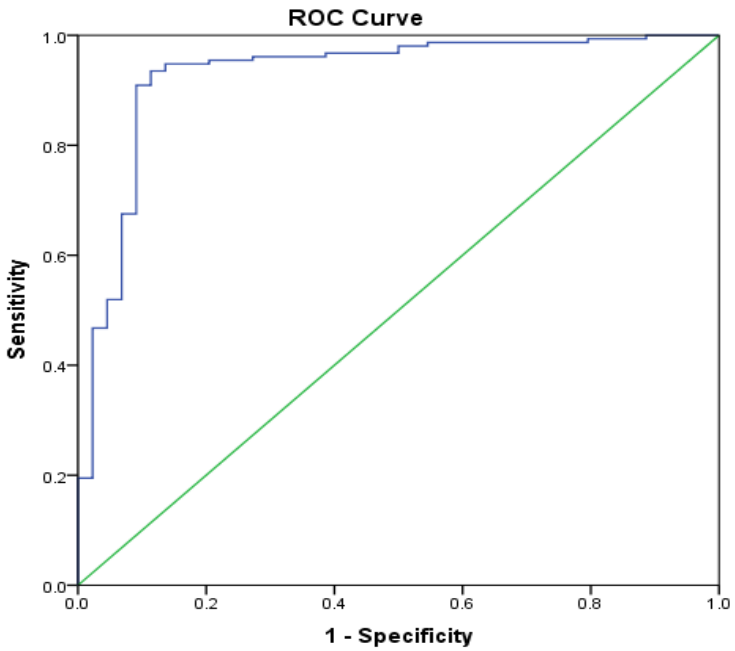

Figure 3. ROC for multivariate logistic predictive model

A multivariate logistic predictive model shows a high capacity for discrimination of IIH and non-IIH patients and a power to identify the patients with IIH mostly due to the high sensitivity and specificity of papilledema (AUC 0.93, 95% CI 0.88 – 0.98) (Figure 3).

4.1.5 Non-IIH diagnosis

In the group of 55 non-IIH patients that were referred by a neurologist, 46.4% were diagnosed chronic headache; the final diagnosis was episodic primary headache (migraine and tension-type headache) in another 14.3% of the patients. Tension-type headache, medication overuse headache, migraine, posttraumatic headache, hemicrania continua, or combinations hereof were the final diagnosis in patients with chronic headache. In these patients elevated ICP was not confirmed. 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 intracranial hypertension were identified (viral meningitis in 3 patients, sinus venous thrombosis in 3 patients, renal failure in 2 patients, Addison's disease in 1 patient, sleep apnea in 1 patient, and oral tetracycline consumption in 1 patient).

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.

4.2 Characterization of presenting symptoms and clinical findings in IIH patients at baseline

Comprehensive baseline characteristics of first symptoms, other symptoms presenting at the time of diagnosis, clinical findings and the results of supplementary investigations were determined in 219 patients with IIH.

The disease most frequently debuted with headache; other initial symptoms are reported in Figure 4.

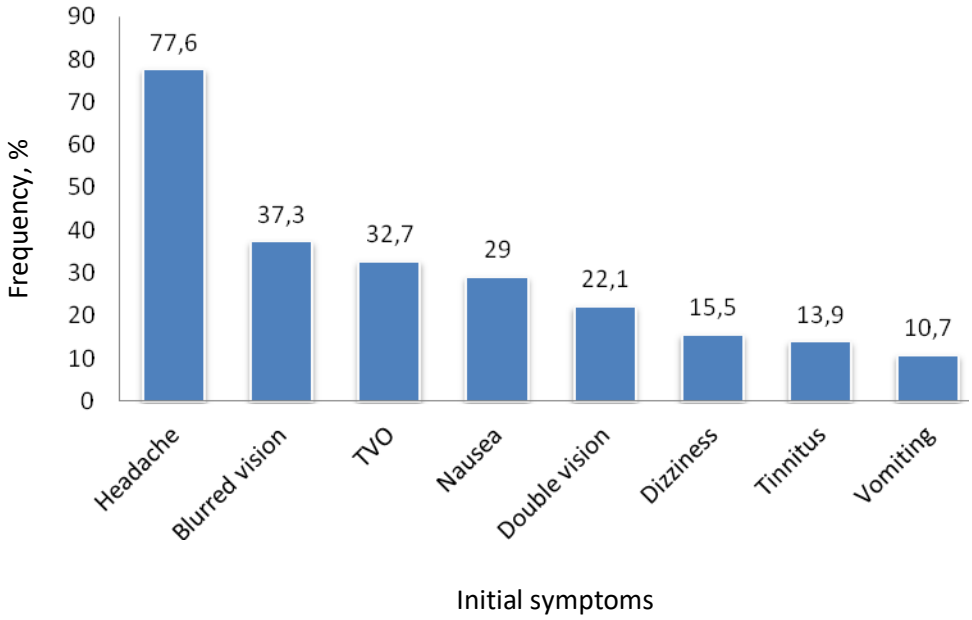

Figure 4. The frequency of initial symptoms in IIH patients.

More than one symptom at the disease onset experienced 72.6% of patients.

4.2.1 Characteristics of headache in IIH

Headache was present in 198 (90.8%) patients at baseline. A history of pre-existing primary headache disorder reported 67 (33.8%) patients. Headache related to IIH was constant (non-remitting) in one-half of the patients prior to diagnosis. The pain character is described as pressure-like by more than 2/3 of patients. In the majority of them headache is localized bilaterally, more frequently in fronto-temporal regions (Table 10).

Table 10. Headache characteristics in IIH patients

Variable	Patients N=219
Headache, n (%)	198 (90.8)
Headache as the first symptom, n (%)	170 (77.6)
Headache debut within, n (%)	
One day	68 (35.8)
One week	30 (15.8)

>1 week – <1month	35 (18.4)
One month and above	54 (28.4)
Pain character, n (%)	
Pulsating quality	62 (33.0)
Pressing quality	126 (67.0)
Headache intensity[b], (mean± SD)	7.28±2.32
Localization, n (%)	
Holocranial	50 (26.0)
Frontal[c]	99 (51.6)
Temporal[c]	79 (41.4)
Parietal[c]	58 (30.4)
Occipital[c]	75 (39.1)
Retrobulbar pain, n (%)	89 (47.6)
Strictly unilateral, n (%)	55 (28.8)
Bilateral, n (%)	153 (80.1)
Constant, n (%)	96 (49.0)
Headache aggravated by, n (%)	
Bending forwards	65 (54.6)
Coughing or straining	52 (43.7)
Other Valsalva-like maneuvers	28 (24.3)
Routine physical activity	91 (47.2)
Morning hours	40 (33.9)
Headache relief after lumbar puncture, n (%)	58 (55.2)
History of pre-existing headache, n (%)	
Migraine with aura	12 (6.18)
Migraine without aura	24 (12.37)
Tension type headache	56 (28.86)

[b]Intensity measured by VAS 0-10,

[c]More than one location possible

4.2.2 Characteristics of visual symptoms and findings in IIH

The frequency and characteristics of the common visual symptoms and signs are given in Table 11.

Table 11. Characteristics of visual symptoms and findings in IIH patients

Variable	IIH N=219
TVO, n (%)	124 (56.6)
Strictly unilateral	18 (24.0)
Frequency≥1 /day	42 (64.6)

Frequency>1/week	19 (29.2)	
Induced by various stimuli[d]	23 (17.8)	
Double vision, n (%)	87 (39.7)	
Blurred vision, n (%)	140 (64.2)	
VI nerve palsy, n (%)	30 (14.9)	
Papilledema, n (%)	195 (93.3)	
Unilateral	7 (3.6)	
Snellen visual acuity[e], n (%)	Right eye	Left eye
≥1	124 (74.7)	120 (74.5)
0.8–0.9	20 (12.0)	18 (11.3)
<0.8	22 (13.3)	23 (14.4)
Visual field defect[e], n (%)		
None	36 (24.83)	
Enlarged blind spot	68 (48.9)	73 (52.5)
Other defect	49 (33.8)	49 (34.0)

[d]assuming the standing position, Valsalva-like maneuvers, bending forward, physical activity

[e]excluded eyes due to vision impairment of etiology other than IIH

Decreased visual acuity or visual field defects resulting from IIH were found in 75% of patients at baseline. An enlarged blind spot was the most often encountered finding in visual field testing (50% of eyes), followed by nasal and peripheral visual field constriction defects (Table 11).

The prevalence of patients without papilledema was 6.7% (n = 13). They were all referred by a neurologist, and headache was by far the most common presenting symptom occurring in all IIH patients without papilledema. In comparison with those with papilledema they less frequently reported TVO (21.4% vs. 58.5%, p= 0.007) and tinnitus (35.7% vs.63.4%, p =0.040).

4.2.3 Characteristics of tinnitus and other presenting symptoms of IIH

Tinnitus is reported by 134 patients with IIH diagnosis. The sound is described like whistling or ringing, while particular pulse-synchronous sounds described 37.5% of patients. The other characteristics of tinnitus are presented in Table 12. The frequency of other presenting symptoms of IIH is recorded in Table 6.

Table 12. Characteristics of tinnitus in IIH patients

Variable	IIH N=219
Tinnitus, n (%)	134 (62.6)
Unilateral	25 (30.1)
Intermittent	43 (64.2)
Dependent on head position	27 (21.4)

4.2.4 CSF opening pressure and neuroimaging findings in IIH patients

The values of CSF opening pressure ranged from 23.5 and 70 cm H2O in IIH patients. In 10 patients the exact value of CSF opening pressure could not be recorded because ICP exceeded standard measure limits. MRI scanning was performed in 212 (96.8%) patients. MRI features of raised ICP were analyzed in 144 (65.7%) patients; in others specified descriptions of venous system, sella turcica and orbits were not available. In one-half of the patients included into the analysis of MRI findings, one or more neuroimaging markers of raised ICP were described by neuroradiologist (Table 13).

Table 13. CSF opening pressure and MRI characteristics in IIH patients

Variable	IIH N=219
CSF opening pressure , (mean±SD),cm H2O	37.85±9.99
MRI features of raised ICP, n (%)	73 (50.0)
Empty sella	47 (31.1)
Flattening of the posterior aspect of the globe	20 (14.0)
Distention of the optic nerve sheet	50 (34.7)
Transverse venous sinus stenosis	18 (12.6)

4.2.5 The correlation of presenting symptoms and signs of IIH with gender

The positive correlation of headache intensity, strictly unilateral headache localization and the presence of retrobulbar pain were found with the female gender. The aggravation of headache by bending forwards, coughing, straining and other

Valsalva-like maneuvers or routine physical activities is also correlated with female gender, along with nausea and complaints of disturbed concentration and memory (Table 14).

The relationship between other symptoms of IIH, visual findings, MRI findings, ICP values and gender are presented in Table 14.

Table 14. The correlation between gender and clinical presentation of IIH

Variable	Gender, female	
	ρ	p-value
Headache as the first symptom	-0.005	0.939
Headache	0.046	0.499
-debut within one day	-0.102	0.163
-debut within one week	0.054	0.456
-debut within >1 week – <1month	0.130	0.678
-debut within one month and above	-0.012	0.869
Pulsating quality	0.126	0.084
Pressing quality	-0.121	0.097
Headache intensity	0.173	**0.021**
Localization: -holocranial	-0.149	0.039
-frontal	0.101	0.161
-temporal	0.001	0.987
-parietal	0.046	0.523
-occipital	-0.089	0.221
Retrobulbar pain	0.202	**0.006**
Strictly unilateral	0.166	**0.022**
Bilateral	-0.116	0.110
Constant	-0.007	0.924
Headache aggravated by bending forwards	0.199	**0.030**
-coughing or straining	0.295	**0.001**
-Valsalva-like maneuvers	0.194	**0.038**
-routine physical activity	0.155	**0.031**
-morning hours	-0.114	0.217
Headache relief after lumbar puncture	-0.002	0.984
TVO	0.001	0.992
Blurred vision	0.117	0.084
Double vision	0.126	0.063
Tinnitus	0.075	0.275
Neck pain	0.040	0.562
Dizziness	-0.024	0.732
Nausea	0.196	**0.004**
Vomiting	0.074	0.277
Photophobia	0.113	0.099

Phonophobia	0.130	0.059
Concentration difficulty	0.211	**0.002**
Memory impairment	0.192	**0.005**
Papilledema	0.158	0.203
VI nerve palsy	0.099	0.155
Visual acuity, right eye, ≥1	-0.014	0.860
0.8–0.9	0.003	0.970
<0.8	0.015	0.850
Visual acuity, left eye, ≥1	0.044	0.579
0.8–0.9	-0.145	0.067
<0.8	0.077	0.332
Enlarged blind spot, right eye	0.045	0.602
Enlarged blind spot, left eye	0.118	0.166
Other visual field defect, right eye	0.056	0.505
Other visual field defect, left eye	0.110	0.187
CSF opening pressure	0.018	0.804
MRI features of raised ICP	0.107	0.200

ρ-Spearman's rank correlation coefficient

4.2.6 The correlation of presenting symptoms and signs of IIH with age at onset

A significant correlation was found between the presence of headache (at the disease onset and in the course of the disease) and younger age at onset. Tinnitus, nausea, vomiting, double vision, sixth nerve palsy, and CSF opening pressure values were also significantly correlated with younger age at onset. The association between other symptoms and visual findings of IIH, MRI findings and age at onset was not found (Table 15).

Table 15. The correlation between age at onset and clinical presentation of IIH

Variable	Age at onset	
	ρ/r[#]	p-value
Headache as the first symptom	-0.148	**0.028**
Headache	-0.201	**0.003**
-debut within one day	-0.066	0.369
-debut within one week	0.018	0.801
-debut within >1 week – <1month	0.053	0.466
-debut within one month and above	0.031	0.666
Pulsating quality	0.000	1.000
Pressing quality	-0.105	0.149
Headache intensity[#]	-0.067	0.376
Localization: -holocranial	-0.044	0.548

-frontal	-0.081	0.266
-temporal	0.019	0.792
-parietal	0.068	0.350
-occipital	0.047	0.522
Retrobulbar pain	-0.085	0.247
Strictly unilateral	0.134	0.064
Bilateral	-0.157	0.030
Constant	-0.017	0.812
Headache aggravated by bending forwards	0.066	0.473
-coughing or straining	-0.017	0.856
-Valsalva-like maneuvers	0.060	0.523
-routine physical activity	-0.051	0.485
-morning hours	0.058	0.536
Headache relief after lumbar puncture	0.070	0.475
TVO	0.010	0.879
Blurred vision	-0.023	0.733
Double vision	-0.205	**0.002**
Tinnitus	-0.159	**0.020**
Neck pain	-0.070	0.305
Dizziness	-0.004	0.949
Nausea	-0.179	**0.008**
Vomiting	-0.308	**<0.001**
Photophobia	-0.023	0.736
Phonophobia	0.023	0.739
Concentration difficulty	0.027	0.694
Memory impairment	0.046	0.512
Papilledema	-0.134	-0.054
VI nerve palsy	-0.140	**0.042**
Visual acuity, right eye ≥1	-0.007	0.926
0.8–0.9	-0.007	0.929
<0.8	0.016	0.838
Visual acuity, left eye ≥1	-0.038	0.632
0.8–0.9	0.021	0.788
<0.8	0.014	0.856
Enlarged blind spot, right eye	-0.115	0.177
Enlarged blind spot, left eye	-0.101	0.239
Other visual field defect, right eye	0.041	0.623
Other visual field defect, left eye	0.134	0.110
CSF opening pressure[#]	-0.183	**0.012**
MRI features of raised ICP	0.127	0.127

ρ- Spearman's rank correlation coefficient, r-Pearson correlation coefficient
p values < 0.05 were considered as statistically significant

4.2.7 The correlation of presenting symptoms and signs of IIH with BMI

A significant positive correlation of visual impairment (double vision, decreased visual acuity and visual field defect at least on one eye) was found with BMI. BMI did not correlate with CSF opening pressure and other presenting symptoms and signs of IIH with the exception of headache aggravation by coughing and straining (Table 16).

Table 16. The correlation between BMI and clinical presentation of IIH

Variable	BMI	
	ρ/r[#]	p-value
Headache as the first symptom	-0.011	0.881
Headache	-0.025	0.730
-debut within one day	-0.022	0.779
-debut within one week	0.123	0.114
-debut within >1 week – <1month	-0.004	0.963
-debut within one month and above	-0.070	0.368
Pulsating quality	-0.014	0.858
Pressing quality	0.072	0.354
Headache intensity[#]	0.046	0.563
Localization: -holocranial	0.138	0.073
-frontal	0.006	0.938
-temporal	0.056	0.476
-parietal	0.065	0.406
-occipital	-0.036	0.648
Retrobulbar pain	-0.100	0.201
Strictly unilateral	0.035	0.657
Bilateral	-0.027	0.731
Constant	0.082	0.287
Headache aggravated by bending forwards	0.082	0.408
-coughing or straining	0.226	**0.021**
-Valsalva-like maneuvers	0.007	0.941
-routine physical activity	0.068	0.368
-morning hours	-0.029	0.769
Headache relief after lumbar puncture	-0.026	0.804
TVO	0.055	0.454
Blurred vision	0.065	0.375
Double vision	0.150	**0.040**
Tinnitus	0.024	0.739
Neck pain	-0.038	0.607
Dizziness	-0.076	0.306
Nausea	-0.029	0.694
Vomiting	-0.052	0.481
Photophobia	-0.023	0.760
Phonophobia	-0.142	0.055
Concentration difficulty	0.069	0.354

Memory impairment	-0.011	0.880
Papilledema	0.000	1.000
VI nerve palsy	-0.013	0.866
Visual acuity, right eye ≥1	-0.157	0.057
0.8–0.9	0.174	**0.034**
<0.8	0.032	0.700
Visual acuity, left eye ≥1	-0.225	**0.007**
0.8–0.9	0.209	**0.013**
<0.8	0.103	0.222
Enlarged blind spot, right eye	0.043	0.624
Enlarged blind spot, left eye	-0.124	0.159
Other visual field defect, right eye	0.083	0.339
Other visual field defect, left eye	0.237	**0.006**
CSF opening pressure[#]	0.055	0.488
MRI features of raised ICP	-0.053	0.556

ρ- Spearman's rank correlation coefficient, r-Pearson correlation coefficient
p values < 0.05 were considered as statistically significant

4.2.8 The correlation of presenting symptoms and signs of IIH with CSF opening pressure

CSF opening pressure positively correlated with the presence of papilledema and sixth nerve palsy. Likewise, a significant positive correlation was established between CSF opening pressure and visual symptoms -TVO and double vision. The appearance of headache at disease onset and occipital localization showed negative correlations with the values of ICP (Table 17.)

Table 17. The correlation between CSF opening pressure and clinical presentation of IIH

Variable	CSF opening pressure	
	ρ/r[#]	p-value
Headache as the first symptom	-0.153	**0.036**
Headache	-0.017	0.814
debut within one day	0.128	0.102
debut within one week	0.004	0.963
debut within >1 week – <1month	-0.090	0.248
debut within one month and above	-0.113	0.075
Pulsating quality	-0.024	0.763
Pressing quality	0.060	0.445
Headache intensity[#]	0.013	0.873
Holocranial	-0.009	0.905
Frontal	0.056	0.473

Temporal	-0.051	0.517
Parietal	-0.083	0.292
Occipital	-0.178	**0.022**
Retrobulbar pain	-0.054	0.499
Strictly unilateral	-0.007	0.926
Bilateral	0.010	0.900
Constant	0.069	0.373
Headache aggravated by bending forwards	0.091	0.344
coughing or straining	0.025	0.793
Valsalva-like maneuvers	-0.047	0.634
routine physical activity	0.053	0.501
morning hours	0.010	0.917
Headache relief after lumbar puncture	0.083	0.412
TVO	0.203	**0.005**
Blurred vision	1.121	0.099
Double vision	0.306	**<0.001**
Tinnitus	0.108	0.143
Neck pain	0.003	0.963
Dizziness	-0.103	0.163
Nausea	0.080	0.278
Vomiting	0.095	0.198
Photophobia	0.069	0.352
Phonophobia	-0.023	0.757
Concentration difficulty	-0.032	0.673
Memory impairment	-0.103	0.171
Papilledema	0.146	**0.049**
VI nerve palsy	0.191	**0.009**
Visual acuity, right eye ≥1	0.043	0.600
0.8–0.9	-0.025	0.756
<0.8	-0.031	0.706
Visual acuity, left eye ≥1	0.070	0.394
0.8–0.9	0.039	0.639
<0.8	-0.111	0.179
Enlarged blind spot, right eye	0.131	0.139
Enlarged blind spot, left eye	0.152	0.085
Other visual field defect, right eye	-0.004	0.964
Other visual field defect, left eye	0.017	0.848
MRI features of raised ICP	-0.032	0.712

ρ- Spearman's rank correlation coefficient, r-Pearson correlation coefficient
p values < 0.05 were considered as statistically significant

4.2.9 The correlation of presenting symptoms and signs of IIH with MRI findings

The presence of at least one of the MRI abnormalities suggestive of raised ICP positively correlated with the presence of papilledema, while negative correlation was found with retrobulbar pain and bilateral headache localization (Table 18). A significant relationship between MRI findings and CSF opening pressure values was not noticed in our IIH cohort.

Table 18. The correlation between MR features of raised ICP and clinical presentation of IIH

Variable	MR markers of raised ICP	
	ρ	p-value
Headache as the first symptom	-0.065	0.437
Headache	0.066	0.433
-debut within one day	-0.040	0.654
-debut within one week	0.065	0.465
-debut within >1 week – <1month	0.116	0.193
-debut within one month and above	-0.141	0.113
Pulsating quality	-0.093	0.295
Pressing quality	-0.127	0.150
Headache intensity	-0.084	0.362
Localization:-holocranial	-0.145	0.616
-frontal	-0.132	0.137
-temporal	-0.093	0.299
-parietal	-0.027	0.761
-occipital	-0.051	0.568
Retrobulbar pain	-0.237	**0.007**
Strictly unilateral	0.214	0.128
Bilateral	-0.241	**0.006**
Constant	-0.093	0.293
Headache aggravated by bending forwards	0.096	0.345
-coughing or straining	-0.073	0.477
-Valsalva-like maneuvers	0.088	0.401
-routine physical activity	0.001	0.993
-morning hours	0.000	0.997
Headache relief after lumbar puncture	0.024	0.829
TVO	0.137	0.099
Blurred vision	0.155	0.061
Double vision	0.000	1.000
Tinnitus	-0.061	0.470
Neck pain	0.000	1.000
Dizziness	-0.071	0.396
Nausea	-0.077	0.359
Vomiting	-0.109	0.192
Photophobia	-0.055	0.511

Phonophobia	0.105	0.209
Concentration difficulty	0.050	0.557
Memory impairment	0.155	0.141
Papilledema	0.170	**0.042**
VI nerve palsy	-0.132	0.113
Visual acuity, right eye ≥1	-0.111	0.217
0.8–0.9	0.010	0.912
<0.8	0.135	0.132
Visual acuity, left eye ≥1	-0.004	0.967
0.8–0.9	-0.123	0.175
<0.8	0.082	0.336
Enlarged blind spot, right eye	-0.045	0.642
Enlarged blind spot, left eye	0.102	0.294
Other visual field defect, right eye	0.075	0.435
Other visual field defect, left eye	0.110	0.252
CSF opening pressure	-0.032	0.712

ρ- Spearman's rank correlation coefficient
p values < 0.05 were considered as statistically significant

4.3 Estimation of the predictive role of presenting symptoms and clinical findings on IIH course and outcome

Presenting symptoms and clinical findings that predict the course and outcome of IIH were analyzed in 182 (83.1%) patients with IIH diagnosis, 165 (90.7%) females and 17 (9.3%) males, who were followed by neurologist and ophthalmologist at least 12 months. The duration of follow-up ranged from 12 to 144 months; the average length of follow-up was 48.73±32.91 months.

The distribution of the patients by the length of follow-up, expressed in months is presented in Figure 5.

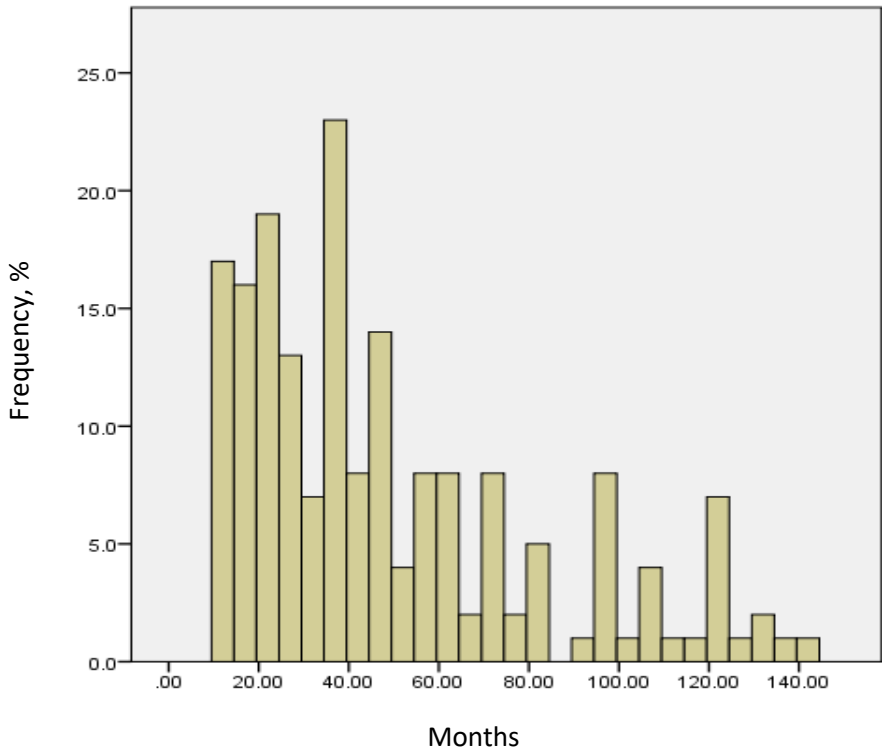

Figure 5. Percentages of IIH patients according to the duration of follow-up periods

4.3.1 Treatment and outcome of IIH cohort

Drug treatment aimed to reduce ICP was introduced to all IIH patients; it consisted of acetazolamide, furosemide, and topiramate. At the end of the follow-up period 87 (47.8%) patients were still taking medications, with 23 of them were using 2 drugs (combination of acetazolamide with topiramate or furosemide). CSF diversion procedures were performed in 28 (15.4%) patients. In most cases VPS and LPS were implemented due to progressive loss of vision within the first months of diagnosis, while in 3 patients CSF diversion was performed due to severe intractable headache. In one patient who did not tolerate drug treatment, dural venous sinus stenting was performed after several VPS revisions.

Weight loss was achieved in 120 (65.9%) patients. Eight patients (4.4%) underwent bariatric surgery for obesity treatment. Mean BMI assessed at the final visit in our cohort was 32.73±7.50 kg/m^2 and was thus significantly lower than on presentation ($p < 0.001$).

The symptom that was most frequently reported at the end of follow-up was headache that persisted in 74 (40.9%) patients in a chronic form, at least 15 days per month. Normal appearance of the optic disk on fundoscopic examination was demonstrated in the majority of patients along with normal corrected visual acuity (88.7% of eyes); however, residual visual field deficit remained in almost 40% of patients, affecting minimum one eye. The frequency of other IIH-related symptoms and visual findings at the final visit is presented in Table 19.

Table 19. IIH-related symptoms and findings at the final follow-up visit

Variable	IIH N=182	
Headache, chronic, n (%)	74 (40.9)	
Tinnitus, n (%)	32 (17.8)	
TVO, n (%)	6 (3.3)	
Blurred vision, n (%)	10 (5.5)	
Double vision, n (%)	2 (1.1)	
VI nerve palsy, n (%)	4 (2.3)	
Papilledema, n (%)	11 (6.1)	
Optic atrophy, n (%)	13 (7.2)	
Snellen visual acuity, n (%)	Right eye	Left eye
≥1	147 (87.5)	146 (90.1)
0.8–0.9	7 (4.2)	4 (2.5)
<0.8	14 (8.3)	12 (7.4)
Visual field defect, any eye, n (%)		
None	99 (60.4)	
Enlarged blind spot, n (%)	25 (15.3)	
Other visual field defect, n (%)	48 (29.3)	

4.3.2 Presenting symptoms and clinical findings predicting IIH remission

Full remission of symptoms and signs of IIH was documented in 72 (39.6%) patients at the final follow-up visit. The mean follow-up time of the patients in IIH remission group was 12.64±14.94 months. In 20 of them, residual visual impairment remained despite a limited course of illness and ultimate cessation of visual and all other symptoms. The remission was established in 70% of patients within the first year from the beginning of treatment; time ranged from 1 to 72 months in the whole group. Time distribution of IIH remission is shown in Figure 6.

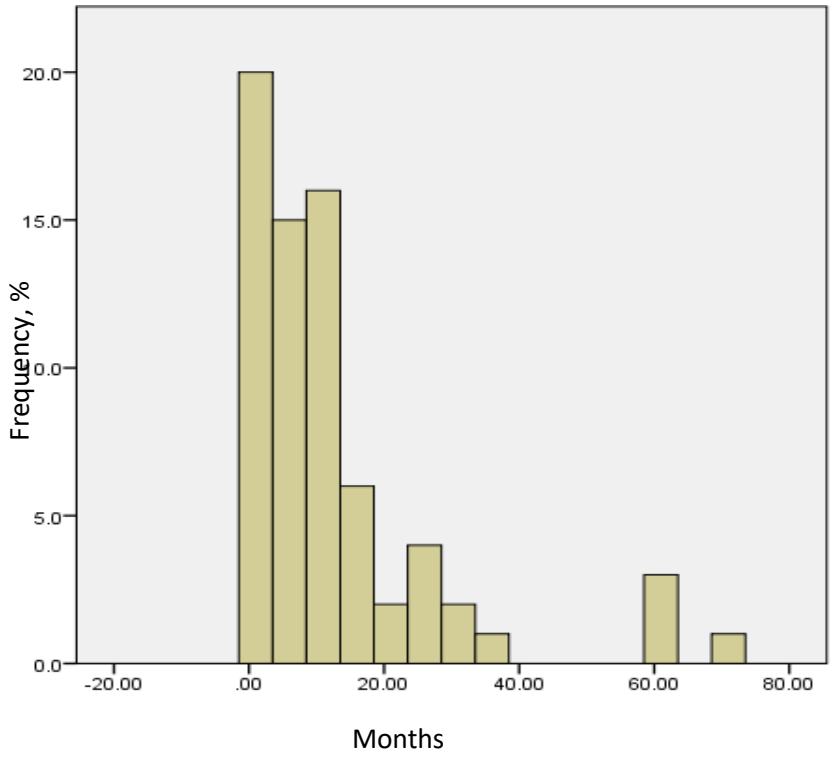

Figure 6. Time distribution of IIH remission

Higher CSF opening pressure and headache reaching maximum intensity within one day were extracted as positive predictors of remission by univariate analysis, while negative predictors were the aggravation of headache by physical activity, the presence of photo-, phonophobia, concentration difficulties and memory complaints. Similarly, comorbid depression and anxiety were negatively associated with IIH remission, as well as MRI finding of empty sella. However, the most important predictors of IIH remission, identified by multivariate analysis, were the presence of neck pain at the disease onset and the absence of phonophobia and concentration difficulties at baseline (Table 20).

Table 20. Variables extracted by univariate and multivariate analysis as predictors of IIH remission

Variables	Univariate HR*	95% CI**	p	Multiva-riate HR*	95% CI**	p
Gender – female	1.562	0.776-3.140	0.211			
Age at onset	1.000	0.980-1.021	0.971			
BMI	0.970	0.930-1.003	0.078			
CSF opening pressure	1.002	1.000-1.005	**0.029**			
Headache as the first	0.810	0.483-1.357	0.423			

symptom						
Headache	0.588	0.301-1.147	0.120			
-debut within one day	2.142	1.289-3.591	**0.003**			
-debut within one week	0.793	0.360-1.746	0.565			
-debut within >1 week – <1month	0.666	0.316-1.404	0.285			
-debut within one month and above	0.588	0.322-1.071	0.083			
Pulsating quality	1.054	0.629-1.724	0.843			
Pressing quality	1.685	0.923-3.075	0.089			
Headache intensity	1.001	0.890-1.125	0.991			
Localization:-holocranial	0.587	0.297-1.161	0.126			
-frontal	0.893	0.530-1.504	0.670			
-temporal	0.724	0.425-1.235	0.236			
-parietal	0.653	0.362-1.177	0.156			
-occipital	1.273	0.760-2.133	0.359			
Retrobulbar pain	0.850	0.506-1.459	0.575			
Strictly unilateral	1.088	0.632-1.875	0.761			
Bilateral	1.210	0.629-2.327	0.568			
Constant	1.338	0.802-2.234	0.265			
Headache aggravated by bending forwards	0.774	0.406-1.476	0.437			
-coughing or straining	0.773	0.401-1.490	0.442			
-Valsalva-like maneuvers	0.451	0.175-1.162	0.099			
-routine physical activity	0.534	0.318-0.898	**0.018**			
-morning hours	1.092	0.556-2.145	0.798			
Headache relief after lumbar puncture	1.580	0.744-3.357	0.234			
TVO	0.827	0.521-1.313	0.421			
Blurred vision	0.915	0.563-1.487	0.721			
Double vision	1.274	0.799-2.032	0.309			
Tinnitus	1.163	0.712-1.898	0.547			
Neck pain	2.935	1.678-5.131	**<0.001**	4.959	2.438-10.087	**<0.001**
Dizziness	0.774	0.437-1.370	0.378			
Nausea	0.766	0.482-1.261	0.259			
Vomiting	0.873	0.517-1.475	0.612			
Photophobia	0.445	0.274-0.723	**0.001**			
Phonophobia	0.303	0.171-0.537	**<0.001**	0.230	0.106-0.501	**<0.001**
Concentration difficulty	0.411	0.249-0.677	**<0.001**	0.360	0.186-0.697	**0.002**
Memory impairment	0.349	0.210-0.579	**<0.001**			
Papilledema	0.737	0.319-1.699	0.437			
Bilateral	3.393	0.471-24.454	0.225			
Unilateral	0.295	0.041-2.124	0.225			
VI nerve palsy	1.459	0.767-2.774	0.249			
Migraine without aura	0.467	0.188-1.159	0.101			
Migraine with aura	0.829	0.302-2.274	0.715			
Tension type headache	1.108	0.660-1.861	0.698			
Skin disease	0.900	0.431-1.878	0.778			
Polycystic ovary syndrome	0.457	0.112-1.871	0.276			
Depression	0.506	0.266-0.963	**0.038**			

Anxiety	0.392	0.170-0.906	**0.028**			
Sleep apnea	0.414	0.058-2.981	0.381			
Tetracyclines	1.275	0.400-4.069	0.681			
Vitamin A preparations	0.049	0.000-6644.101	0.617			
Corticosteroids	0.844	0.384-1.853	0.672			
Hormonal contraception	1.169	0.697-1.963	0.554			
Weight gain	0.766	0.430-1.364	0.365			
Visual acuity, right eye ≥1	1.138	0.646-2.005	0.654			
0.8–0.9	0.744	0.339-1.631	0.460			
<0.8	1.080	0.533-2.187	0.831			
Visual acuity, left eye ≥1	1.448	0.785-2.669	0.236			
0.8–0.9	0.804	0.346-1.867	0.612			
<0.8	0.669	0.304-1.468	0.316			
Enlarged blind spot, right	1.425	0.826-2.458	0.203			
Enlarged blind spot, left	1.113	0.646-1.917	0.701			
Other visual field defect, right eye	0.658	0.359-1.208	0.177			
Other visual field defect, left eye	0.701	0.391-1.254	0.231			
MRI features of raised ICP	0.861	0.499-1.486	0.591			
Empty sella	0.500	0.257-0.974	**0.042**			
Flattening of the posterior aspect of the globe	0.929	0.419-2.060	0.856			
Distention of the optic nerve sheet	0.853	0.478-1.523	0.591			
Transverse venous sinus stenosis	1.031	0.440-2.415	0.944			

*Hazard ratio, **95% confidence intervals

p values < 0.05 were considered as statistically significant

4.3.3 Presenting symptoms and clinical findings predicting IIH relapse

Relapsing course of the disease was identified in 34 (18.7%) patients. The mean follow-up time of these patients was 51.94±41.56 months. During the follow-up period they experienced 39 relapses in total. In three women, the disease recurred during pregnancy. In addition to recurrence of symptoms and signs of IIH, in 30 patients relapse was verified by repeated LP measuring elevated CSF opening pressure; in the remaining 4 patients it was characterized by the reoccurrence of previously resolved papilledema solely. The recurrence of symptoms and signs of IIH in patients being off medications for at least 6 months occurred in a period ranging from 9 to 128 months after the IIH diagnosis. Time distribution of first IIH relapse is shown in Figure 7.

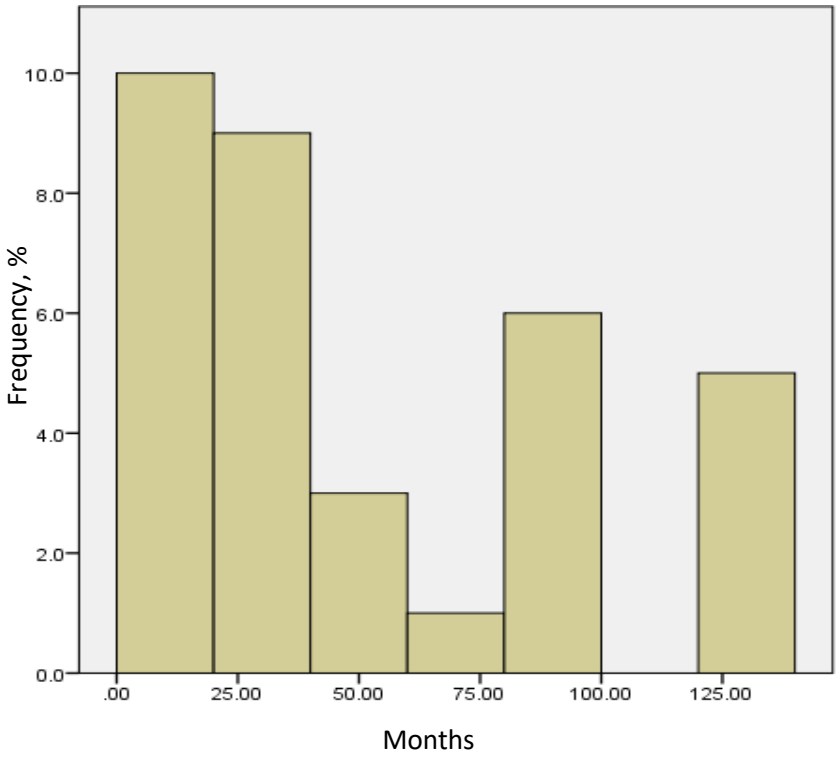

Figure 7. Time distribution of IIH relapses

Headache announcing IIH, occurrence of photophobia, concentration and memory problems, preserved visual acuity bilaterally at the time of diagnosis as well as CSF opening pressure derived from univariate analysis were associated with relapsing IIH course (Table 21). Still, none of the predictors reached statistical significance in multivariate Cox regression analysis.

Table 21. Variables extracted by univariate analysis as predictors of IIH relapse

Variables	Univariate HR*	95% CI**	p
Gender – female	0.639	0.190-2.143	0.468
Age at onset	0.969	0.934-1.004	0.083
BMI	1.014	0.958-1.073	0.624
CSF opening pressure	1.004	1.001-1.007	**0.021**
Headache as the first symptom	5.440	1.292-22.909	**0.021**
Headache	23.053	0.088-6027.961	0.269
debut within one day	0.490	0.186-1.288	0.148
debut within one week	2.018	0.818-4.982	0.128
debut within >1 week – <1month	1.506	0.680-3.336	0.313
debut within one month and above	0.775	0.342-1.756	0.542

Pulsating quality	1.283	0.670-2.459	0.452
Pressing quality	0.574	0.265-1.243	0.159
Headache intensity	0.939	0.814-1.082	0.383
Holocranial	0.678	0.277-1.658	0.394
Frontal	1.479	0.681-3.213	0.323
Temporal	0.510	0.244-1.067	0.074
Parietal	0.814	0.380-1.747	0.598
Occipital	0.797	0.388-1.638	0.537
Retrobulbar pain	0.810	0.403-1.627	0.554
Strictly unilateral	1.110	0.525-2.347	0.786
Bilateral	0.800	0.343-1.864	0.604
Constant	0.934	0.463-1.882	0.849
Headache aggravated by bending forwards	0.614	0.258-1.461	0.270
coughing or straining	0.512	0.206-1.274	0.150
Valsalva-like maneuvers	0.703	0.234-2.109	0.530
routine physical activity	1.834	0.907-3.709	0.091
morning hours	0.983	0.394-2.450	0.970
Headache relief after lumbar puncture	0.748	0.310-1.808	0.519
TVO	0.702	0.453-1.825	0.789
Blurred vision	0.915	0.343-1.435	0.332
Double vision	1.230	0.608-2.488	0.564
Tinnitus	1.167	0.560-2.428	0.680
Neck pain	0.717	0.170-3.027	0.651
Dizziness	0.956	0.451-2.025	0.906
Nausea	1.317	0.649-2.699	0.446
Vomiting	1.288	0.621-2.672	0.496
Photophobia	2.602	1.164-5.816	**0.020**
Phonophobia	1.660	0.829-3.324	0.153
Concentration difficulty	3.519	1.490-8.311	**0.004**
Memory impairment	3.708	1.525-9.015	**0.004**
Papilledema	1.026	0.243-4.326	0.972
Bilateral	1.121	0.152-8.272	0.911
Unilateral	0.892	0.121-6.587	0.911
VI nerve palsy	1.055	0.369-3.017	0.921
Migraine without aura	0.815	0.284-2.335	0.713
Migraine with aura	1.256	0.296-5.338	0.757
Tension type headache	0.574	0.236-1.397	0.222
Skin disease	1.037	0.386-2.791	0.942
Polycystic ovary syndrome	1.204	0.284-5.016	0.801
Depression	1.742	0.786-3.858	0.171
Anxiety	1.999	0.916-4.365	0.082
Sleep apnea	1.314	0.177-9.771	0.789
Tetracyclines	1.130	0.150-8.509	0.906
Vitamin A preparations	0.049	0.000-∞	0.854
Corticosteroids	0.308	0.042-2.290	0.250

Hormonal contraception	1.057	0.486-2.299	0.889
Weight gain	1.607	0.725-3.564	0.243
Visual acuity, right eye ≥1	5.303	1.251-22.482	**0.024**
0.8–0.9	0.641	0.149-2.760	0.551
<0.8	0.033	0.000-2.344	0.117
Visual acuity, left eye ≥1	3.976	1.169-13.517	**0.027**
0.8–0.9	0.814	0.190-3.486	0.782
<0.8	0.113	0.015-0.860	**0.035**
Enlarged blind spot, right eye	1.225	0.540-2.780	0.627
Enlarged blind spot, left eye	1.364	0.599-3.107	0.460
Other visual field defect, right eye	0.751	0.297-1.899	0.546
Other visual field defect, left eye	0.612	0.243-1.538	0.296
MRI features of raised ICP	0.592	0.251-1.395	0.230
Empty sella	0.447	0.160-1.254	0.126
Flattening of the posterior aspect of the globe	0.995	0.290-3.412	0.993
Distention of the optic nerve sheet	0.663	0.265-1.661	0.381
Transverse venous sinus stenosis	1.020	0.302-3.447	0.975

*Hazard ratio, **95% confidence intervals
p values < 0.05 were considered as statistically significant

4.3.4 Presenting symptoms and clinical findings predicting refractory IIH

Refractory IIH was identified in 76 (41.7%) patients at the end follow-up; the complete resolution of symptoms or signs of disease had not been established during the total follow-up period. The mean follow-up time in this group of patients was 51.54 ±33.00 months, lasting between 12 and 120 months.

Higher BMI, comorbid depression, and empty sella sign on MRI scanning were positively associated with refractory disease in univariate analysis, while constant headache of frontal localization and dizziness showed negative correlation. The independent positive predictors of refractory IIH that reached statistical significance in multivariate analysis were older age at onset, aggravation of headache by physical activities, visual field defect other than enlarged blind spot at baseline; pressing headache was extracted as a negative independent predictor of refractory IIH (Table 22).

Table 22. Variables extracted by univariate and multivariate analysis as predictors of refractory IIH

Variables	Univariate HR*	95% CI**	p	Multiva-riate HR*	95% CI**	p
Gender – female	0.881	0.352-2.203	0.786			
Age at onset	1.020	1.002-1.039	**0.031**	1.066	1.025-1.110	**0.002**
BMI	1.067	1.028-1.108	**0.001**			
CSF opening pressure	0.998	0.996-1.001	0.171			
Headache as the first symptom	0.825	0.491-1.387	0.468			
Headache	0.796	0.366-1.734	0.566			
debut within one day	1.107	0.659-1.859	0.701			
debut within one week	1.281	0.633-2.591	0.491			
debut within >1 week – <1month	0.585	0.310-1.102	0.097			
debut within one month and above	1.321	0.804-2.170	0.272			
Pulsating quality	0.892	0.535-1.487	0.662			
Pressing quality	0.282	0.172-0.468	**<0.001**	0.179	0.073-0.437	**<0.001**
Headache intensity	1.046	0.937-1.166	0.423			
Holocranial	1.457	0.879-2.415	0.144			
Frontal	0.373	0.228-0.610	**<0.001**			
Temporal	0.706	0.438-1.138	0.153			
Parietal	0.963	0.592-1.568	0.880			
Occipital	0.738	0.453-1.202	0.222			
Retrobulbar pain	0.976	0.602-1.584	0.923			
Strictly unilateral	0.958	0.562-1.635	0.876			
Bilateral	0.824	0.463-1.467	0.511			
Constant	1.568	0.354-0.913	**0.019**			
Headache aggravated by bending forwards	1.608	0.845-3.063	0.148			
coughing or straining	1.169	0.648-2.206	0.567			
Valsalva-like maneuvers	1.394	0.733-2.652	0.312			
routine physical activity	1.671	1.030-2.711	**0.038**	7.525	2.505-22.604	**<0.001**
morning hours	0.759	0.390-1.477	0.417			
Headache relief after lumbar puncture	0.782	0.399-1.533	0.475			
TVO	1.051	0.669-1.649	0.830			
Blurred vision	1.007	0.616-1.645	0.979			
Double vision	0.757	0.467-1.226	0.258			
Tinnitus	0.856	0.539-1.360	0.511			
Neck pain	0.900	0.361-2.241	0.821			
Dizziness	0.572	0.335-0.977	**0.041**			
Nausea	1.204	0.755-1.921	0.436			
Vomiting	1.022	0.615-1.696	0.934			
Photophobia	1.009	0.631-1.614	0.969			
Phonophobia	1.269	0.800-2.014	0.311			
Concentration difficulty	1.260	0.785-2.020	0.338			
Memory impairment	0.963	0.601-1.543	0.874			
Papilledema	1.193	0.435-3.275	0.732			

Bilateral	0.519	0.208-1.294	0.160			
Unilateral	1.925	0.773-4.798	0.160			
VI nerve palsy	0.677	0.311-1.473	0.325			
Migraine without aura	1.025	0.561-1.872	0.937			
Migraine with aura	1.827	0.779-4.237	0.167			
Tension type headache	1.363	0.824-2,252	0.227			
Skin disease	1.174	0.559-2.464	0.672			
Polycystic ovary syndrome	1.281	0.552-2.972	0.564			
Depression	1.861	1.127-3.076	**0.015**			
Anxiety	1.231	0.695-2.180	0.477			
Sleep apnea	1.816	0.565-5.839	0.317			
Tetracyclines	0.716	0.173-2.961	0.645			
Vitamin A preparations	9.712	1.270-74.274	0.101			
Corticosteroids	1.798	0.904-3.578	0.095			
Hormonal contraception	0.986	0.588-1.656	0.958			
Weight gain	0.768	0.430-1.371	0.372			
Visual acuity, right eye ≥1	0.776	0.450-1.338	0.361			
0.8–0.9	1.228	0.598-2.522	0.575			
<0.8	1.222	0.633-2.359	0.551			
Visual acuity, left eye ≥1	0.737	0.429-1.268	0.270			
0.8–0.9	1.525	0.717-3.243	0.273			
<0.8	1.154	0.618-2.156	0.654			
Enlarged blind spot, right	0.927	0.521-1.649	0.796			
Enlarged blind spot, left	1. 373	0.783-2.408	0.268			
Other visual field defect, right eye	1.773	1.039-3.027	**0.036**	2.550	1.166-5.581	**0.019**
Other visual field defect, left eye	1.606	0.931-2.772	0.089			
MRI features of raised ICP	1.528	0.873-2.674	0.137			
Empty sella	1.749	1.002-3.054	**0.049**			
Flattening of the posterior aspect of the globe	1.484	0.714-3.084	0.291			
Distention of the optic nerve sheet	1.355	0.771-2.382	0.291			
Transverse venous sinus stenosis	0.877	0.371-2.073	0.765			

*Hazard ratio, **95% confidence intervals

p values < 0.05 were considered as statistically significant

5. 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 large prospective study analyzing the baseline clinical characteristics of IIH[15]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.

The most common presenting symptom in our IIH patients was headache, reported by more than 90% of the patients, followed by blurred vision, tinnitus, TVO, and nausea.

Headache was by far the most common presenting symptom in both IIH and non-IIH patients, and there was no difference in headache occurrence between the groups. Headache profile in our IIH cohort is comparable to those previously reported by other authors[14,84,85,146]. In 3 out of 4 patients it was the first symptom of the disease leading to medical assistance. More than one-third of our IIH patients reported headache arising within one day; however, in almost the same proportion of patients, it progressed slowly, during a period lasting over one month. The onset of headache attributed to IIH has not been previously sufficiently investigated, although ICHD3 criteria emphasize headache development or significant worsening in close temporal relation to IIH[81]. In a study of Yri et al. that prospectively assessed headache in newly diagnosed patients with IIH, 47% of patients reported headache debut within hours or one day[84]. The onset of intracranial hypertension cannot be determined in patients with IIH or correlated with headache onset, but our results showed a significant association between acute onset of headache and higher values of CSF opening pressure. Furthermore, the results from our univariate Cox analysis implicate that development of headache within one day as well as higher ICP at presentation may be both associated with better prognosis and stable remission of IIH, but cannot be considered as independent predictors of IIH outcome as they did not reach statistical significance in multivariate analysis. The association between high CSF opening pressure at presentation and better headache outcome has

been noted by Yri et al., which led to the assumption that it may be a marker of short disease duration which would imply a better outcome[84].

Pressure-like headache was reported by 2/3 of patients in IIH group, more frequently than in the recent literature reports that revealed the pulsating quality of pain in the majority of patients[83,84], but consistent with other publications[85,86]. We didn't find any significant correlations of pain quality, localization, intensity and frequency with ICP values, age, gender, BMI, and MRI markers of raised ICP, other than an association between unilateral localization and headache severity with the female gender. The lack of association between headache presence or intensity and CSF opening pressure at IIH diagnosis has been reported by Friedman[83], who postulated that natural daily fluctuations of CSF pressure may be one of the explanations. Patients with IIH are very rarely subjects to continuous monitoring of ICP that has been suggested for a more precise estimation of raised ICP.

Our results indicate that headache attributed to IIH in females is more likely to be associated with worsening by physical activity, bending forwards, coughing and straining, or other Valsalva-like maneuvers. Aggravation of headache by coughing and straining, a feature that has been reported to be the most sensitive and specific to intracranial hypertension[84] was found in 47.3% of our IIH patients. Still, this characteristic is not proved to be related to CSF opening pressure in our IIH cohort, neither anticipate the disease outcome. Contrarily, the aggravation of headache by physical activity that was noted in 47.2% patients is extracted as an important predictor of refractory IIH course, and similarly, if not present at baseline indicates IIH remission in our IIH group.

Approximately 40% of our IIH patients were experiencing chronic headache at the end of the follow-up. Sustained chronic headache after resolution of papilledema and normalization of ICP has been found in 43% of IIH patients at 1-year follow-up in a prospective study of Yri, and supported prior speculations that ICP alone is not responsible for headache in IIH[84].

An independent positive predictor of remission in our IIH cohort was a neck pain. Neck and shoulder pain, sometimes with radicular distribution, have been registered in

other large IIH series[14,15,151], suggesting early spinal nerve root irritation related to raised CSF pressure. In a study of Jones et al.[152], neck pain was recorded in 35% of patients who presented at the emergency department due to IIH. In our study, it occurred significantly more frequently in the IIH group than in non-IIH group. It could be assumed to yield better prognosis as represents an early manifestation of IIH.

Visual disturbances were also frequent complaints in our study population. 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[76]. Even though not unique to IIH, TVO are an important symptom, reported by 56.6% of our IIH patients, which was significantly different from non-IIH patients. We demonstrated unilateral TVO in one of four IIH patients, and provocation by assuming the standing position, bending forward and Valsalva-like maneuvers in 17.8% of patients. Similarly to previous reports[14,76], TVO occurred from one to many times a day in 2/3 of our IIH patients, and their occurrence, but not their frequency, significantly correlated with CSF opening pressure values.

Likewise, a positive correlation was found between ICP and sixth nerve palsy and double vision in our IIH cohort, which confirms that TVO and double vision due to sixth nerve palsy should raise concerns about intracranial hypertension, since these are not symptoms of primary headaches. Our results support previous findings[70] 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. Still, none of these presenting visual symptoms could solely predict correct IIH diagnosis or disease outcome in IIH patients after multivariate analysis in our study.

Tinnitus is generally explained by the flow turbulence within the transverse venous sinus; in our cohort, it occurred in 62.6% of IIH patients, and was significantly more frequent complaint than in non-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[14,15]. The prevalence of tinnitus in the general adult population has shown rates between 10% and 15% and it increases with aging[153]. Less than 10% of tinnitus patients experience pulsatile tinnitus, so if it is present and especially if it is bilateral, it may suggest intracranial hypertension[92]. The characteristics of tinnitus in our

IIH patients were similar to previously reported by Wall; intermittent occurrence reported 2/3 of patients, and unilateral presentation 1/3 of them. We did not demonstrate a significant correlation between tinnitus, CSF opening pressure and transverse venous sinus stenosis or any other MRI finding of raised ICP; these findings indicate that some other mechanisms may be involved in its evolution. Like headache, it is not considered in the literature to be a marker of active IIH and adds little to the evaluation of severity of this condition[120]. Tinnitus was reported by17.8% of our IIH patients at the end follow-up visit, which makes it the most treatment-resistant IIH symptom after headache. The prognostic role of tinnitus in the diagnosis and outcome of IIH has not been demonstrated in our cohort.

Photophobia and phonophobia are considered as typical migrainous phenomena along with nausea/vomiting and are listed in IHS diagnostic criteria for migraine[81]. They may be defined as an aversion to normally non-aversive lights and sounds, and both peripheral and central underlying mechanisms of these symptoms have been suggested[154–157]. High frequency of these migrainous manifestations has been recorded in different IIH cohorts[83,158,159] and their occurrence has been mostly related to headache presence. However, their relations with intracranial pressure have been scarcely studied[160,161], and the significance of these symptoms in IIH is not known. Both photo- and phonophobia were equally presented in our IIH and non-IIH patients, and we did not find any association with ICP levels. Still, IIH remission showed significant and the inverse association with the presence of photo- and phonophobia in our IIH cohort, although phonophobia solely is recognized as an independent predictor of IIH outcome after multivariate analysis.

Self-reported concentration difficulties and memory complaints were more frequent in our non-IIH patients. This result was not a surprise, given that a high proportion of non-IIH group consisted of chronic headache patients. The effects of headache on cognitive functioning has been under debate in the current literature[162–164], while the association of chronic pain conditions and comorbid depression with mild cognitive impairment has been demonstrated in clinical and preclinical studies[165–167]. Recent reports suggest cognitive defects in different domains in IIH patients[71,94], that persisted despite improvement of ICP[94]. Socioeconomic impact of cognitive dysfunction in IIH

has been addressed in a study of Sorensen et al. as prolonged work disability has been noted in their patients with IIH-related mild cognitive deficit[168]. The cause of cognitive decline in IIH is unclear; the proposed explanation included white and gray matter dysfunction due to mechanical compression and the effects of inflammatory mediators[94]. Cognitive aspect of IIH has not been evaluated in our study; however according to our results the remission of IIH is less likely to be accomplished in patients with concentration and memory complaints at the time of diagnosis. The significance of this result is yet to be confirmed in the future studies, as it could be mediated by coexistent depression. A history of depression and anxiety had similar, negative influence on disease outcome in our IIH cohort, although none of these parameters in isolation can be used as predictor of IIH outcome except concentration problems which was confirmed in multivariate analysis. The link between IIH, obesity and psychiatric disorders has been investigated in a case-control study of Kleinschmidt et al.[169]. IIH group expressed significantly higher levels of anxiety, depression, and fatigue than controls, and consequently decreased quality of life measures, which could not be attributed to obesity alone. Although we have not been able to prove an independent effect of psychiatric illnesses on the outcome of IIH, this issue should be further evaluated in comprehensive longitudinal studies.

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 intracranial hypertension due to secondary causes. Appropriately, skin diseases were more frequently reported by our non-IIH patients. Over the years, systemic administration of tetracyclines or vitamin A has been associated with the increase of ICP in several reports[170,171]; 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 exploration of these medications in relation to 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 intracranial hypertension[51]; again, former reports proposed corticosteroids as one of the treatment options for severe papilledema in IIH[172]. In our study, 11.8% of the IIH patients used inhalers and topical steroids, with

only one patient taking prednisone orally for inflammatory bowel disease up to 3 months prior to diagnosis. In this patient, the symptoms debuted 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 raised ICP 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[21]. 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)[173]and in our non-IIH patients, as well. Even though our data are self-reported, this result deserves additional investigation.

Analogous to skin diseases, sleep apnea was more frequently reported by our non-IIH patients. The repercussion of obstructive sleep apnea on ICP is controversial, and possible causality is still debated. The only patient in our cohort of probable IIH in whom intracranial hypertension was attributed to sleep apnea did not have papilledema, and his symptoms revealed with continuous positive airway pressure treatment. In a group of IIH patients who reported sleep apnea, we did not find any correlation with CSF opening pressure values; as previously reported[174–176], the only significant correlation was found with increased BMI.

Correlations between elevated BMI and risk of IIH have been firmly demonstrated[23,177]. 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 IIHTT[15]. There was a significant correlation between obesity and visual impairment (double vision, decreased visual acuity, visual field defects) at the baseline in our IIH cohort. A similar association has been suggested in a case-control study of Bruce at al. that analyzed clinical presentations of IIH in atypical patients: those with normal BMI and older patients[178]. None of their patients with a normal BMI had severe visual loss; otherwise, they did not differ from obese patients in terms of other symptoms and signs of IIH.

Our results suggest that the clinical presentation of IIH may be partly influenced by age differences. Younger age at onset was associated with the higher values of ICP and the presence of all “typical” symptoms of intracranial hypertension at the time of

diagnosis-headache, tinnitus, double vision due to sixth nerve palsy, nausea and vomiting. Literature reports suggest that older patients are less likely to have headache[178] and that they are in general less symptomatic, with better visual prognosis[179]. Still, age at onset has been identified as an important predictor or refractory IIH in our cohort. This result is in line with the study of Yri et al. showing that older age is associated with the poor headache outcome one year after IIH diagnosis[84]. The several explanations have been provided; firstly that young patients might have a more sensitive response to ICP changes, possibly due to more flexible intracranial structures; secondly, that underlying mechanisms of intracranial hypertension differ in younger and older patients[84]. As older patients tend to have fewer symptoms at the baseline, which is also supported by our results, an alternative explanation would be that longer disease duration in oligosymptomatic patients may further result in the refractory condition.

Visual findings in our IIH cohort complement contemporary literature data. 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. The presence of papilledema was identified as a single independent predictor of IIH diagnosis in our study. Still, papilledema is not pathognomonic for IIH and was also observed in our non-IIH patients with raised ICP due to sinus venous thrombosis, viral meningitis, renal failure and tetracycline consumption. Furthermore, bilateral optic disc swelling was registered in one patient with bilateral anterior ischemic optic neuropathy and in a patient with lymphomatous infiltration of the optic nerve in whom ICP measurement was within normal range. The misinterpretation of the results from eye examination has been recognized by Fisayo et al. as one of the main reason for overdiagnosis of IIH in the large neuro-ophthalmology tertiary referral practice[104].

The significance of papilledema has not been specifically emphasized in the modified Dandy criteria; however, it is essential for IIH diagnosis according to the new criteria from 2013[10]. The absence of papilledema despite elevated ICP is an intriguing topic in current headache research. Since IIH is greatly associated with female gender,

chronic headache pattern and obesity, it has been frequently compared in the literature with chronic migraine[180–182]. Similar risk factors and headache features generated the scientific background for further exploration of the role of ICP in migraine chronification. Intracranial hypertension without papilledema has been detected in various studies in up to 14% of patients with chronic and refractory migraine implying the diagnosis of IIH without papilledema[183–185]. In the literature, ICP values in IIH patients without papilledema were found to be lower or fluctuating suggesting that papilledema is greatly influenced by ICP and may not develop in cases with mild or intermittent intracranial hypertension[75,182]. Papilledema correlated with the values of CSF opening pressure in our IIH patients; the positive and significant correlation of CSF opening pressure was also found with other visual findings: sixth nerve palsy, TVO, and double vision. In the subgroup of our 13 IIH patients without papilledema, headache was present in all of them at the diagnosis. They were all recruited from headache centers, and did not differ from IIH patients in whom papilledema was detected in terms of demographic features, past medical history, or comorbid disorders. However, a small number of patients prevented further statistical analysis on disease outcomes in this specific IIH subgroup.

In general, visual acuity was intact in most of our IIH patients at presentation, although visual field defects, usually bilateral, were found in 75% of them which is in accordance with the previous reports[14,15,186]. Blind spot enlargement as a consequence of enlarged optic nerve head from the papilledema was the most frequent finding; it was detected by automated perimetry in every other eye. Reports from the literature indicate that visual symptoms, signs and neuro-ophthalmological findings at the time of diagnosis cannot predict the risk of recurrence or further visual deterioration[14,187]. Our research identified one important visual predictor of the refractory disease outcome-visual field defect that exceeds an enlarged blind spot at the baseline eye examination. This result may suggest that patients presenting with worse visual field status in the advanced disease course, are more likely to be resistant to standard medical or surgical management of IIH.

Brain MRI and MRV demonstrated one or more features of raised ICP in 1/2 of IIH patients. Distension of the optic nerve sheet diameter and empty sella were the most

frequent findings occurring in 36% and 32% of patients respectively. Specificity and sensitivity of these imaging findings in IIH diagnosis have been evaluated in children and adults in several studies[188,189], revealing generally low sensitivity of any of the signs but also high specificity of the posterior globe flattening. Neuroimaging markers of intracranial hypertension are described in our IIH cohort less frequently than in some other prospective and retrospective series which reported MRI abnormalities in up to 85% of IIH patients[190–192]. Brain imaging descriptions in our study are extracted from patients medical charts; some features of raised ICP have not been systematically specified in all neuroimaging reports, as some of these reports were given before the significance of these particular MRI findings in the diagnosis of IIH had been widely recognized. Still, a significant positive correlation was found between the presence of papilledema and the distension of the perioptic subarachnoid space, while empty sella sign correlated with age of onset, TVO and blurred vision in our IIH patients. In the literature, MRI findings in IIH were not found to be predictive of visual outcome[193,194]. In our study, empty sella showed a significant positive association with refractory IIH, and an inverse relationship with IIH remission when considered in univariate analysis; this result could not be reciprocated in multivariate analysis. Empty sella has been described as a classic sign of chronically elevated ICP that enlarges bony structure of pituitary fossa resulting in the partial empty appearance of sella turcica in MRI[195,196]. If noted at presentation it may alarm physicians toward the more chronic and potentially treatment-resistant course, but, according to our results, cannot be used, just like any other MRI parameter, as a reliable predictor of IIH outcome.

The strength of this study is the large number of included patients and the prospective design that is applied for the diagnostic purpose. 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. A reporting bias cannot be excluded and may represent a limiting factor of the present study, but it is likely to be similar in both, IIH and non-IIH group. It is also a one of the longest follow-up study to describe the disease course and clinical outcome, even though this estimation is performed retrospectively.

The first part of our research was intended to question 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 raised ICP together with patients with normal ICP values in whom some of the symptoms, signs, demographic features or comorbidities were suggestive of IIH. An important finding is that despite an abundance of presenting symptoms that have been reported, our results indicate that these symptoms are not diagnostic for IIH. The lack of predictive significance of any presenting symptom for the diagnosis of IIH could be the consequence of our applied design, since some of the analyzed symptoms may reflect ICP regardless of etiology.

Papilledema is found to be the most reliable clinical sign predicting IIH diagnosis. The strongest association between IIH diagnosis and papilledema has been shown in our 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 headache patients without papilledema[10]. The search for another specific diagnostic IIH-marker must continue.

Our study was not able to identify any independent predictor of IIH relapse. None of the presenting symptoms and signs of the disease, demographic features or comorbid conditions could solely contribute to this outcome. The relapsing course has been the least frequent scenario in our IIH cohort. Although studies report IIH recurrence in up to 67% of patients in different age group[23,186,197], the disease relapsed in only 34 (18.7%) of our patients. A possible explanation lies in the different study designs and definition of IIH relapse. This group consisted of patients in whom symptoms and signs of IIH recurred at least 6 months after the cessation of treatment. The similar allocation has been used by Shah et al[149] who demonstrated a recurrence rate of 15% over a mean follow-up of about 13 years. Accordingly, in 2/3 of our patients, the first relapse occurred between 1 and 5 years after being first diagnosed. BMI at the time of recurrence and weight gain of 6% between remission and relapse have been identified as risk factors for IIH recurrence in a study of Ko et al[148].

The refractory IIH has been the most heterogeneous patient group in our cohort. In some patients repeated measurement of CSF opening pressure showed moderately increased of marginally increased values, while in others intracranial hypertension could not be demonstrated; shunt malfunction and overdrainage syndrome have also been detected in some of them contributing to the ongoing clinical manifestations. Furthermore, an interpretation of predictors in this patient group may be limited by an ascertainment or selection bias resulting from tertiary nature of our referral practice and unequal follow-up time. IIH patients referred to our centers may have had a more complicated disease. Also, patients in whom remission has not yet been established because follow-up was not long enough could have been identified as refractory; this effect is minimized by applying Cox regression predictive model. In numerous recent studies[83,84,122,198] one year or even six months after IIH diagnosis and treatment initiation have been considered as an acceptable time frame for the evaluation of specific outcomes including visual and headache. Still, this is an arbitrary limit that may not necessarily correspond well with the clinical improvement, although in most cases the resolution of intracranial hypertension is established much earlier[199].

Another important finding is that a full remission of IIH symptoms is established in only 40% of our cases, predominantly in the first year after the initiation of treatment. It seems encouraging though, that in a small proportion of cases, it can still be achieved within 6 years after the initial diagnosis.

Although the presence of headache per se does not predict the disease outcome, we hypothesize that migraine associated phenomena in IIH might have an important role in the disease prognosis. If IIH presented with photo-, phonophobia, and headache that aggravated by physical activity, the remission was less likely to be achieved in our cohort. Similarly, chronic and refractory course was associated with headache worsening by physical activity and was unlikely if the disease presented with pressing and constant headache. The aggravation of headache related to IIH by physical activity has been reported in the literature in association with the presence of allodynia [147]. Cutaneous allodynia is the perception of discomfort or pain induced by non-noxious stimuli to normal skin resulting from increased sensitization of the central nervous

system and has been well described in primary headaches, especially migraine[200]. In a study of Ekizoglu, allodynia was found in an almost half of the IIH patients, and mostly in those who had migraine-like headache profiles, which led to the hypothesis that IIH may trigger some common mechanisms with migraine in pain pathways[147]. Chronification of headache in IIH despite the apparent normalization of ICP is still an unexplained phenomenon, documented in several different IIH cohorts[84,146,147,149]. The proposed interpretation based on sensitization of the central pain regulating pathways in a subgroup of IIH patients with migrainous features could lead up to different disease outcomes in respect to headache prognosis in different IIH phenotypes. Refractoriness in our IIH patients was mostly influenced by headache persistence despite standardized IIH treatment.

Our findings should draw attention to the symptoms that are more subtle and fairly underestimated in IIH research, and stimulate further investigations focused on the potential beneficial effects of the early introduction of migraine prophylaxis in IIH patients presenting with migrainous phenomena. Further prospective, longitudinal studies are needed to thoroughly explore and categorize different subgroups among IIH patients and to identify the main factors influencing the prognosis of this complex disorder.

5. CONCLUSIONS

1. The most common presenting symptoms of IIH are headache, blurred vision, TVO, tinnitus and nausea.
2. Headache is present in more than 90% of IIH patients at the time of diagnosis, mostly pressure-like and bilateral, localized in fronto-temporal regions.
3. Visual symptoms-blurred vision and TVO occur in more than a half of IIH patients, usually on both eyes repeatedly many times a day.
4. Tinnitus in IIH is bilateral and appears intermittently in 2/3 of patients.
5. The most common clinical sign of IIH is bilateral papilledema, followed by sixth nerve palsy.
6. Not a single presenting symptom of the disease such as headache, blurred vision, TVO, double vision, tinnitus, neck pain, dizziness, nausea, vomiting, photophobia, phonophobia, concentration difficulty, and memory impairment can predict the correct IIH diagnosis in patients with suspected IIH.
7. Papilledema is the most reliable clinical sign predicting IIH diagnosis.
8. Visual symptoms and signs of IIH including the presence of papilledema, sixth nerve palsy, TVO and double vision, positively correlate with CSF opening pressure, while the presence of headache at disease onset and occipital localization showed negative correlations with the values of ICP.
9. A significant relationship was found between the presence of MRI markers of raised ICP and papilledema in IIH.
10. There is a significant correlation between obesity and visual impairment (double vision, decreased visual acuity, and visual field defect) in IIH patients at the time of diagnosis.
11. Younger age at disease onset is associated with the higher values of ICP and the presence of headache, tinnitus, double vision due to sixth nerve palsy, nausea and vomiting at presentation.
12. Long term follow-up of IIH patients revealed three different types of disease course and outcome: remission, relapsing course, and refractory disease.

13. Full remission of symptoms and signs of IIH occurs most frequently within the first year; the predictors of favorable outcome are neck pain at the disease onset and the absence of phonophobia and concentration difficulties.

14. The relapsing disease is the least frequent IIH outcome; none of the presenting symptoms and signs of IIH can predict independently the disease recurrence.

15. The IIH-related symptoms do not significantly improve in over 40% of IIH patients in one to twelve years after the initiation of treatment.

16. Predictors of refractory IIH are older age at onset, aggravation of headache by physical activity and visual field defect that exceeds an enlarged blind spot at the baseline eye examination, while pressing headache is a negative predictor.

17. Migraine associated phenomena in IIH might have an important role in the disease prognosis and deserve further investigations.

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LIST OF ABBREVIATIONS

IIH -idiopathic intracranial hypertension

LP-lumbar puncture

CSF-cerebrospinal fluid

ICP-intracranial pressure

BIH-benign intracranial hypertension

PTCS-pseudotumor cerebri syndrome

BMI-body mass index

MRI- magnetic resonance imaging

MRV- magnetic resonance venography

11β-HSD1-11β-hydroxysteroid dehydrogenase type 1

IIHTT-Idiopathic Intracranial Hypertension Treatment Trial

TVO-transient visual obscurations

OCT-optical coherence tomography

IHS-International Headache Society

TTH-tension-type headache

ICHD-International Classification of Headache Disorders

HIT-6-Headache Impact Test

CT-computed tomography

ONSF-optic nerve sheath fenestration

VPS- ventriculoperitoneal shunt

LPS –lumboperitoneal shunt

BIOGRAPHY

Dr. Aleksandra Radojičić was born on October 16, 1974, in Belgrade. She graduated from School of Medicine, University of Belgrade in 2000. with the overall score of 9,28. She is employed at the Neurology Clinic, Clinical Center of Serbia since 2000, and has been working as a specialist in neurology from 2006. The Master thesis "Medication overuse headache: risk factors, clinical features, and contemporary treatment strategies" Dr. Radojičić defended at School of Medicine University of Belgrade in 2010, under the mentorship of Prof. Dr. Nadežda Šternić. She obtained additional clinical training in the field of headaches at the Department of Neurology and psychiatry for children and adolescents, Medizinische Universität Wien/AKH Wien, and was engaged as a guest researcher at the Danish Headache Center, Department of Neurology, Rigshospitalet Glostrup. In her everyday practice, she is working with chronic and resistant headache patients since 2007. She is a co-founder and secretary of the Serbian Headache Society, and a member of the Society of Serbian Neurologists, Serbian Medical Society, the International Headache Society, and European Academy of Neurology.

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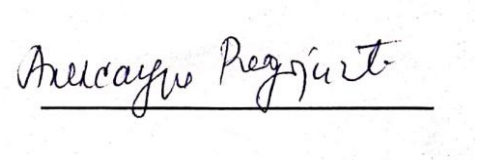

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