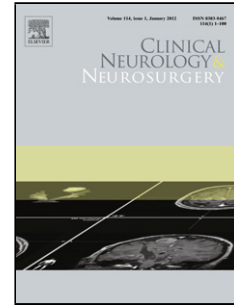


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Psychiatric disorders are a common prognostic marker for worse outcome in patients with idiopathic intracranial hypertension

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Highlights

- Psychiatric disorders are sevenfold more common in IIH patients compared to general population

- The IIH patients with pre-existing psychiatric diagnosis had more often empty sella at diagnosis
- The IIH patients with a pre-existing psychiatric diagnosis have worse subjective outcome

ABSTRACT

Objective: Idiopathic intracranial hypertension (IIH) is aetiologically unknown disorder that associates with endocrinological disturbances, including dysfunction of hypothalamic-pituitary-adrenal-axis. Neuroendocrinological dysfunctions have also been characterized in psychiatric disorders, and therefore we investigated the presence of psychiatric disorders of patients with IIH in a well-defined cohort.

Patients and Methods: A total of 51 patients with IIH were included. Patient demographics, symptoms, imaging data, ophthalmological and clinical findings were collected.

Results: At the time of diagnosis the mean age was 32.5years (SD 10.7), the body mass index was 37.1kg/m² (SD 7.4), and the opening pressure 29.1mmHg (SD 6.2). A total of 88.2% of patients were female and 45.1% were diagnosed with a psychiatric co-morbidity prior to IIH diagnosis. The mean follow-up time was 4.4 years (SD 5.4). The overall treatment outcome was significantly poorer on a group of patients with psychiatric diagnosis when compared to individuals without such history ($p=0.001$), but there were no differences in the resolution of papilledema ($p=0.405$). Patients with IIH and psychiatric disorders had more often empty sella on their imaging at diagnosis when compared to patients without psychiatric co-morbidity ($p=0.044$).

Conclusion: Psychiatric disorders are highly prevalent in patients with IIH and associate with worse subjective outcomes. These findings advocate for monitoring the mental health of patients with IIH and warrant further multidisciplinary research to understand the potentially underlying psychosocial and neuroendocrinological mechanisms.

Key words: Idiopathic intracranial hypertension (IIH), psychiatric disorders, major depressive disorder (MDD), hypothalamic-pituitary-adrenal-axis (HPA-axis), intracranial pressure (ICP)

1. Introduction

Idiopathic intracranial hypertension (IIH) is rare disease with an incidence rate of 0.5-2.0/100,000/year^{1,2}. IIH predominantly affects obese women of fertile age¹, whereas in the paediatric population the gender distribution is equal^{1,3}. The patients with IIH are characterised by chronic headaches, pulsatile tinnitus, diplopia, visual disturbances, bilateral papilledema, and increased intracranial pressure without hydrocephalus or intracranial mass^{1,3}. Classical neuroradiological findings include empty sella turcica, flattening of the posterior sclerae, tortuosity and distension of the subarachnoid perioptic spaces, and protrusion of the optic nerves^{4,5}.

The constantly elevated intracranial pressure threatens the visual system as ischemia from poor perfusion of the optic nerve can result in atrophy, causing permanent visual loss. Therefore, it is paramount to recognise this rare condition early and treat it urgently, as up to 24% suffer from permanent visual loss and 4% report bilateral blindness at the final follow-up^{1,6-8}. The primary treatment goal for IIH is lowering the ICP with weight loss^{1,9} and acetazolamide medication^{1,10}. Acetazolamide is carbonic anhydrase inhibitor limits formation of bicarbonate and hydrogen ions, which may be the mechanism for lowering intracranial and intraocular pressure¹¹. If these conservative treatments are insufficient in resolving the condition, surgical intervention is required. Neurosurgical intervention includes optic nerve sheath fenestration, shunting procedures^{1,3} as well as venous sinus stenting¹². In severely obese patients, gastric bypass surgery may also be an effective treatment of the IIH^{13,14}.

IIH patients frequently display chronic fatigue, depression, anxiety, cognitive decline and lowered quality of life²⁰⁻²⁶. The comorbidity between symptoms of affective disorders and IIH could result from common biological pathways related to hypothalamus-pituitary-adrenal cortex (HPA)-axis dysfunction^{16,27}. IIH populations are also characterized by metabolic comorbidities^{1,3,19} which may contribute to neuroendocrinological homeostasis. Although a few case studies have reported depression in association with IIH several decades ago²⁸, studies have so far not attempted to evaluate the role of psychiatric disorders during the natural course of the disease. In the present study, we characterised the presence of psychiatric disorders and the usage of psychopharmaceutical medications in a well-defined IIH cohort.

2. Material and methods

2.1. Study cohort

This was a retrospective study on patients with International Statistical Classification of Diseases and Related Health Problems (ICD-10) G93.2 diagnosis, collected between January 1, 2000 and December 31, 2018, and formed a part of "Phenotype, Pathophysiology and Prognostic Factors of IIH" study. Clinical data of treatment periods and follow-up visits from referring hospitals and Kuopio University Hospital (KUH) have been included into the Kuopio IIH database. Relevant medical charts, operative reports, laboratory results, imaging findings, and clinical follow-up evaluations were analysed up until April 30th, 2019. Friedman criteria were applied to determine eligibility for inclusion in the database²⁹. After the exclusion of i) ten paediatric patients, under the age of 16 years, ii) two secondary IIH cases caused by venous sinus thrombosis, and iii) two suspected IIH cases that were not true IIH cases in a retrospective review according to the Friedman criteria, we included 51 adult patients with IIH (**Figure 1**).

2.2. Clinical and Treatment variables

The following variables were used in the analyses for patients with IIH:

Before diagnosis of IIH

1. history of psychiatric diseases (diagnoses based on the International Classification of Diseases (ICD-10) and the use of any psychopharmaceutical medication);
2. other medical history (diagnosed co-morbidities);

Baseline at diagnosis of IIH

3. patient demographics (sex, age, body mass index (BMI) presenting symptoms and CSF opening pressure (OP));
4. neuro-ophthalmological findings (visual acuity, papillae and visual fields);
5. magnetic resonance imaging (MRI) data evaluated by a neuroradiologist;

Follow up during treatment of IIH

6. treatment types, either conservative (weight loss, medication), surgical treatments (CSF diversion, gastric by-pass), or combined;
7. treatment outcomes after a) medical and b) both medical and surgical treatments combined;

8. neuro-ophthalmological outcome (degree of papilledema) was classified as a) no papilledema, b) partial resolution of papilledema, and c) no improvement;
9. symptomatic outcome was characterised as follows a) symptomless, b) partial recovery, i.e. on-going symptoms such as headache, tinnitus, fatigue, dizziness, balance problems and need for continuing medical treatment, c) no improvement.

2.3. Statistical analysis

The continuous variables were reported as means with standard deviations (SD), and the categorical variables were reported by using frequencies and percentages. The continuous variables were analysed with Student's t-test or Fisher's exact test. The categorical variables were evaluated using Pearson's χ^2 analysis. In all statistical analyses a p-value of < 0.05 was considered statistically significant. SPSS 22.0 (SPSS, Inc, Chicago, IL) was used.

2.4. Ethical aspects

The study has been approved by the Ethics Committee of the Kuopio University Hospital (284/2016). Informed consent was obtained from all patients. 'The Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) guidelines were used in reporting our findings.

3. Results

3.1. Patient and clinical characteristics of IIH at diagnosis

A total of 51 patients were included in the study, with a mean follow-up time of 4.4 (SD 5.4) years. Majority of patients were females (88.2%), with a mean age of 32.5 (SD 10.7) years at diagnosis. The mean OP was 29.1 (SD 6.2) mmHg. The mean BMI at diagnosis 37.1 (SD 7.4) kg/m². The mean CSF protein count at diagnosis was 277.2 (SD 140.1) mg/l. The most common symptoms at the time of diagnosis were headache (n=40, 78.4%) and visual disturbances (n= 38, 74.5%). Visual loss was reported in (n= 13, 25.5%) of cases, diplopia in (n= 10, 19.6%) of cases, and the rest various visual symptoms such as blurred eyesight. At presentation, tinnitus was reported by 23 (45.1%) patients, and dizziness by seven patients, (13.7%).

3.2. Neuro-ophthalmological and Neuroimaging Findings at diagnosis

Papilledema was found in all patients at the time of diagnosis, and bilaterally papillaedema in n=37, 72.5% of cases. Visual field defects were found in n=18 35.3% of patients. The mean visual acuity in the right eye was 1.05 (SD 0.32) and in the left 1.02 (SD 0.35). Empty sella

turcica was present in 12 (23.5%), and partial empty sella in 12 (23.5%) of the cases. The flattening of the posterior globes was present in 11 (21.6%), and increased CSF around optic nerves was found in 18 (35.3%) of cases. Four (7.8%) patients had protrusion of optic nerve head, and four (7.8%) patients had increased tortuosity of optic nerve.

3.3. Psychiatric comorbidities in patients with IIH

A total of 23 (45.1%) patients with IIH had pre-existing psychiatric diagnosis (**Table 1**). The most common psychiatric diagnosis was major depressive disorder (MDD), which was found in 19 (37.3%) patients. Psychotic disorders, including schizophrenia, psychotic episodes and schizoaffective disorder, were found in three (5.9%) patients. Other psychiatric diagnoses found in this IIH cohort were: personality disorder, suicidal ideations, dissociation disorder, adjustment disorder with anxiety, mixed obsessional thoughts and acts, panic disorder, bipolar disorder and substance abuse (**Table 1**). Multiple psychiatric diagnoses were found in eight (34.8%) patients. The most frequently used psychopharmaceutical drugs, based on clinical indications, were as follows: 1) antidepressant: escitalopram (n=7, 30.4 %), 2) antipsychotics: quetiapine (n=6, 26.1 %), 3) anti-anxiety medication: oxazepam (n=5, 21.7 %), 4) hypnotics: melatonin (n=4, 17.4 %).

3.4. Patients with IIH and psychiatric disorders at diagnosis

The IIH patients with a prior psychiatric diagnosis did not differ in age gender distribution, BMI, or OP at diagnosis from patients with IIH who had no pre-existing psychiatric comorbidity. The CSF protein count was lower for patients with psychiatric disorder, though this difference was not significant. The presenting symptoms and neuro-ophthalmological findings were similarly distributed in both groups. The patients with IIH and pre-existing psychiatric diagnosis had more often empty sella in their initial MRI when compared to the patients with IIH without psychiatric co-morbidity (34.8% vs. 14.3%, p=0.044) (**Table 2**).

3.5. Treatment types and outcomes after treatment

Acetazolamide medication was used in almost all patients (97.9%), with a mean dosage at the beginning of treatment being 885.87 (SD 292.1) mg/day. The acetazolamide treatment was reported beneficial, i.e. complete resolution of all symptoms was observed in 20 (39.2%) of all patients, partial recovery was noted in 19 (37.3%) patients at the end of follow-up. The patients with no psychiatric disorders had better clinical outcome after acetazolamide treatment as compared to patients with IIH and pre-existing psychiatric diagnosis, (57.1% vs. 17.4%, p=0.042) (**Table 2**). Surgical intervention was required for 16 (31.4%) patients, CSF diversion was conducted in 13 (26%) patients, of which ten (76.9%) were lumboperitoneal,

and three (23.1%) were ventriculoperitoneal. Gastric by-pass surgery was done in three (6%) patients. After conservative and operative treatments, the overt outcome improved slightly, as 26 (50.9%) patients reported themselves to be symptomless. In the group of patients with pre-existing psychiatric disorder, the outcomes were significantly worse as compared to patients without such history (26.1% vs. 71.4%, $p=0.002$) (**Table 2**). These patients continued having symptoms, such as headaches, dizziness, visual disturbances and fatigue. However, when neuro-ophthalmological outcome was assessed as a degree of resolution of papilledema, the outcome was equally good for both groups, and up to 71% of all patients had physiological papillae at the end of follow-up. ($p=0.405$) (**Table 2**).

4. Discussion

In the present study, we analysed the prevalence and the type of psychiatric disorders in the patients with IIH. We found that 45% of the patients with IIH displayed pre-existing psychiatric co-morbidities. The most common psychiatric co-morbidity was major depressive disorder (MDD), found in over 37% of the cases. Patients with IIH and pre-existing psychiatric disorder did not differ from IIH-patients with no prior psychiatric diagnoses in terms of age, sex distribution, BMI or CSF opening pressure at diagnosis. Furthermore, their symptoms at presentation and the neuro-ophthalmological findings were similar in both groups. In the patients with psychiatric co-morbidities the only difference observed at the time of IIH diagnosis was higher prevalence of empty sella on the initial MRI scan. The empty sella may reflect propensity for pituitary gland related neuroendocrinological dysfunction and contribute to the development of comorbidities of IIH, including psychiatric conditions such as the affective disorders. However, metabolomic laboratory assays were not included to this study so the extent of hormonal dysfunction could not be assessed.

The development of IIH has been suggested to be accompanied with HPA-axis dysfunction^{16, 27} which has been also implicated in the pathophysiology of a variety of mood and cognitive disorders. For example, neuroendocrine studies have consistently demonstrated HPA axis dysfunction in major depression (32). Another proposed mechanism that could explain why patients with IIH more frequently suffer from anxiety could be related to elevated catecholamine secretion observed in IIH (33). Nevertheless, the pathophysiology of IIH is still unclear and no single theory explains how raised ICP causes the condition. Due to the young and female preponderance, neuroendocrinological dysfunction might have a pivotal role in IIH^{1,9,15,16}. In addition, as obesity is highly prevalent in patients with IIH, it has been suggested that metabolic, inflammatory and hormonal influences contribute to the

development of IIH¹. In particular, the dysfunction of the CSF hydrodynamics and aquaporins have been investigated as key components in understanding the aetiology of IIH^{1,3,17,18}.

The patients with IIH and pre-existing psychiatric disorder were treated similarly as compared to the patients without prior psychiatric diagnoses. When only neuro-ophthalmological outcome was assessed as resolution of papilledema at the end of follow-up, there was no difference in outcome between these groups. However, after the conservative treatment, or both conservative and surgical interventions combined, patients with IIH and pre-existing psychiatric diagnosis had significantly poorer overall outcome. This outcome was a combination of neuro-ophthalmological signs and subjectively reported symptoms, such as headaches, fatigue, visual disturbances. These findings suggest, that the patients with IIH and pre-existing psychiatric disorder suffer from residual symptoms more often although their papilledema has improved, and they have been treated appropriately.

Our results suggest that there is a high risk of MDD co-morbidity in patients with IIH, as recent reviews of epidemiological literature of MDD have established a global point-prevalence (current or past month) of 4.7% and a pooled period prevalence of mood disorder (point of 12-month) of 5.4%^{30,31}, as compared to our cohort the prevalence was sevenfold, 37%. There is little information as to the psychosocial impact of IIH, but there are some hypotheses on how psychiatric disorders might develop in individuals with IIH. The development of IIH has been suggested to be accompanied with HPA-axis dysfunction^{16,27} which has been also implicated in the pathophysiology of a variety of mood and cognitive disorders. For example, neuroendocrine studies have consistently demonstrated HPA axis dysfunction in major depression³². Another proposed mechanism that could explain why patients with IIH more frequently suffer from anxiety could be related to elevated catecholamine secretion observed in IIH³³. MDD was common in patients with IIH and in our study the patients had received their MDD diagnoses prior to the IIH diagnosis. Depressive symptoms may represent prodromal symptoms of IIH rather than a consequence of elevated ICP, but our register-based data did not allow drawing pathophysiology-based conclusions on the causal relationships between the two conditions.

Kleinschmidt et al²⁰ analysed how IIH affects symptoms of depression and anxiety and quality of life in a weight- and age-matched cross-sectional study and showed the patients with IIH suffered from higher levels of depression and anxiety as compared to the control groups. These findings were reflected in poorer quality of life in patients with IIH, and illustrated more analgesics and antidepressant use in the IIH population. Depression

treatment has also led to alleviation of IIH findings and subjective symptoms. Two case reports described electroconvulsive therapy improved both drug-refractory depression and IIH symptoms^{35,36} and one case reported antidepressants together with IIH treatment improved not only the IIH symptoms but also depression³⁷. There are also cases when resolution of major depression has triggered IIH^{28,38}.

Our study is limited by factors inherent to a secondary analysis of retrospectively collected data as well as the small sample size. Nevertheless, there is a limited amount of previous data on this issue. This study represents a detailed investigation based on a well-defined cohort, which ensures a clinically comprehensive analysis and follow-up time for these patients, which we regard as a strength of this study. Nevertheless, further studies, focusing on the role of mental health adversities and the quality of life in patients with IIH in larger patient cohorts are needed. In 2017, we initiated a prospective collaborative multicentre study on IIH (www.iih.fi). In this study, we prospectively administer validated questionnaires, including Beck Depression Inventory, Beck's Anxiety Inventory, Perceived Stress Scale, Headache Impact test-6 and Quality of Life (15D) questionnaires to screen and follow-up on mental well-being of patients with IIH, quality of life, and impact of their possible residual symptoms. Our aim is to increase the knowledge on pathophysiological mechanisms of IIH disease and to improve the diagnostics and management of IIH. We want to ameliorate the assessment of effectiveness of different treatment modalities, their follow-up protocol, and overall treatment outcomes. Finally, we also want to explore possible novel metabolic pathways as diagnostic or prognostic tools, and to unravel possible genomic variants of IIH. In this prospective study, in addition to gathering all clinical variables, we perform continuous lumbar ICP measurement, collect biological samples for further metabolomics and genetic studies to advance understanding of the complex pathophysiology of the IIH disease (**Figure 2**).

5. Conclusion

Almost half of the patients with IIH suffered from psychiatric disorders, and these individuals continued to have residual symptoms although their ophthalmological outcomes improved. Psychiatric disorders appear to be common in IIH. They should be screened and treated promptly, as they may have an impact of treatment outcomes. IIH associates to neuroendocrinological disturbances, and therefore further multidisciplinary research on IIH is warranted.

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Disclosure

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Figure legends

Fig 1. Flowchart of the study population: 65 patients with IIH from 2000 to 2018. Identification of the patients with IIH and comorbid psychiatric diseases. (*In a retrospective review)

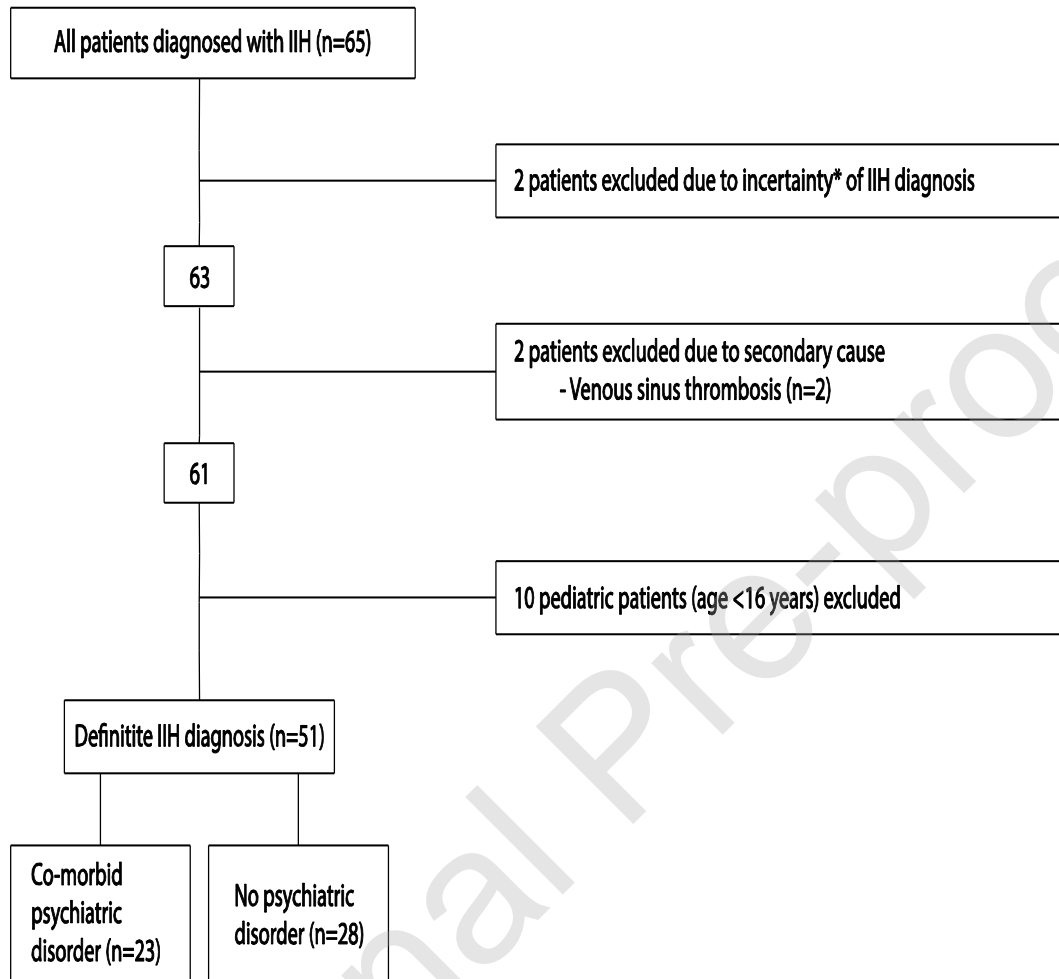


Fig. 2. Prospective IIH Research Protocol in Kuopio University Hospital. (Abbreviations: 15D = Quality of Life, BAI = Beck's Anxiety Inventory, BDI = Beck's Depression Inventory, cICP = continuous intracranial pressure, COHEN = Cohen's Perceived Stress Scale, CRF = Clinical Research Form, CSF = Cerebrospinal fluid, ENT = Ear-Nose-Throat, GYN = Gynaecology, IIH = Idiopathic intracranial hypertension, KUH = Kuopio University Hospital, MRI = Magnetic Resonance Imaging, NEU = Neurology, PACS = Picture archiving and communication systems, PUL = Pulmonology)

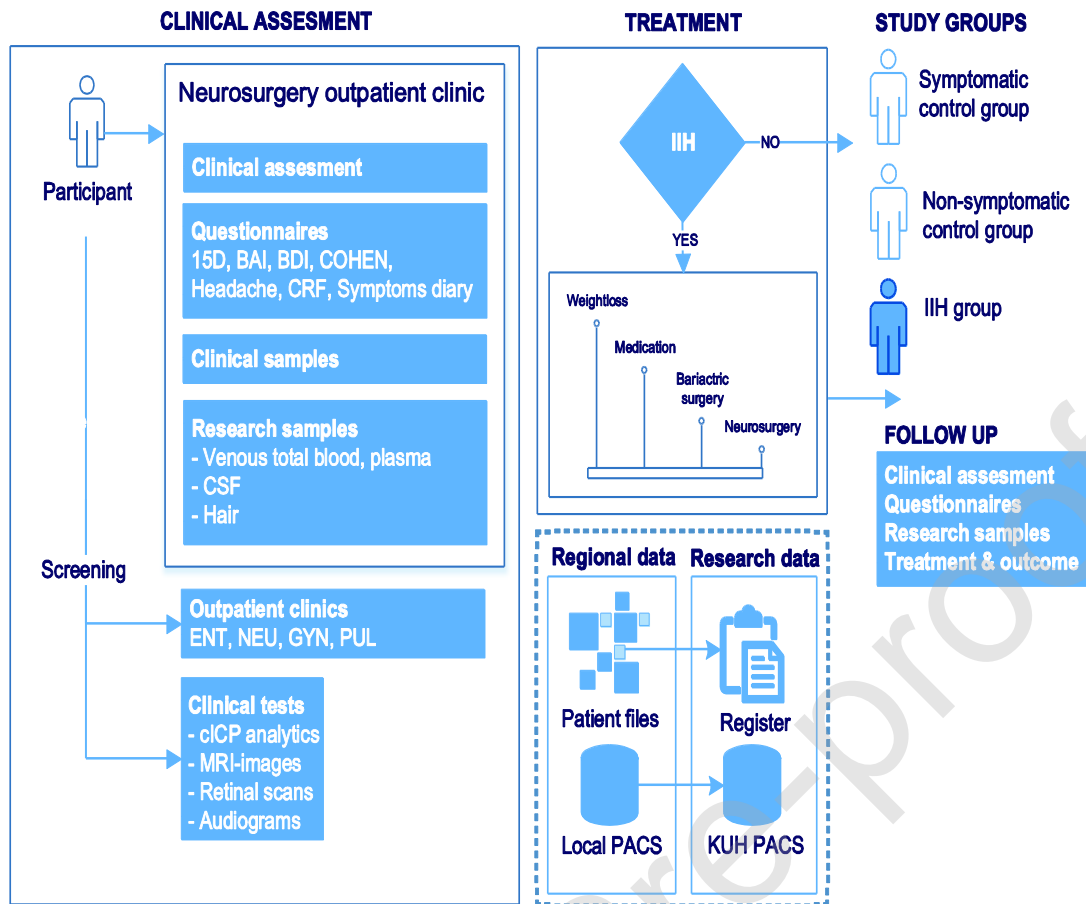


Table 1. All psychiatric diagnoses of the IHH patients			
ICD-10 Diagnosis	Description	n	(%)
F10-F19 Mental and behavioral disorders due to psychoactive substance use			
F10.19	Substance abuse	1	(2)
F20-F29 Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders			
F20	Paranoid schizophrenia	1	(2)
F25.9	Schizoaffective disorder, unspecified	1	(2)
F29	Unspecified psychosis not due to a substance or a known physiological condition	1	(2)
F30-39 Mood (affective) disorders			
F31.8	Bipolar II disorder	1	(2)
F33	Major depressive disorders	19	(37.3)
F40-F48 Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders			
F41.0	Panic disorder	1	(2)
F42.2	Mixed obsessional thoughts and acts	1	(2)
F43.22	Adjustment disorder with anxiety	1	(2)
F44.9	Dissociation disorder	1	(2)
F60-F69 Disorders of adult personality and behavior			
F60.3	Personality disorders	2	(3.9)
Symptoms and signs constituting part of a pattern of mental disorder			
R45.8	Suicidal ideations	1	(2)

Table 2. Adult IIH patients with psychiatric disorders compared to IIH patients without psychiatric disorders

	Patients without psychiatric disorder		Patients with psychiatric disorder		p-value
	n	%	n	%	
TOTAL	28	(54.9)	23	(45.1)	
Females	24	(85.7)	21	(91.3)	0.538
Mean age in years (SD)	33.6 (12.6)		31.0 (7.9)		0.400
Mean BMI kg/m² (SD)	39.6 (7.2)		34.7 (7.0)		0.067
Mean OP mmHg (SD)	28.4 (5.3)		29.4 (7.4)		0.768
Mean CSF protein count mg/l (SD)	308.52 (169.8)		242.6 (89.9)		0.139
Neuroradiological findings at diagnosis					
Presence of empty sella					
None	11	(39.3)	10	(43.5)	0.044*
Partial	10	(35.7)	2	(8.7)	
Yes	4	(14.3)	8	(34.8)	
Flattened sclera	6	(21.4)	5	(21.7)	0.922
Increased CSF around CN II	8	(28.6)	10	(43.5)	0.203
Intraocular protrusion of CN II head	2	(7.1)	2	(8.7)	0.806
Increased tortuosity of CN II	3	(10.7)	1	(4.3)	0.417
Presenting symptoms					
Headache	21	(75.0)	19	(82.6)	0.601
All visual symptoms	19	(67.9)	19	(82.6)	0.313
Tinnitus	12	(42.9)	11	(47.8)	0.615
Dizziness	3	(10.7)	4	(17.4)	0.536
Neuro-ophthalmological findings at diagnosis					
Optic nerve edema					
Slight	2	(7.1)	5	(21.7)	0.366
Unilateral	4	(14.3)	2	(8.7)	
Bilateral	19	(67.9)	15	(65.2)	
Visual field defects	8	(28.6)	10	(43.5)	0.412
Mean visual acuity (SD)					
Right eye	1.05 (0.31)		1.04 (0.33)		0.874
Left eye	1.03 (0.36)		1.01 (0.35)		0.841
Neuro-ophthalmological outcome after all treatments					
No papilledema	20	(71.4)	16	(69.6)	0.394
Partial resolution of papilledema	6	(21.4)	7	(30.4)	
Papillar atrophy	2	(7.1)	0	(0)	
Effect of acetazolamide on papillae and symptoms					
Complete resolution of symptoms	16	(57.1)	4	(17.4)	0.042*
Slight improvement	7	(25.0)	12	(52.2)	
No improvement	5	(17.9)	5	(21.7)	
Effect of conservative and surgical treatments combined on papillae and symptoms					
Complete resolution of symptoms	20	(71.4)	6	(26.1)	0.002*
Slight improvement	8	(28.6)	16	(69.6)	
Abbreviations: BMI = Body mass index, CN = Cranial nerve, CSF = Cerebrospinal fluid, IIH = Idiopathic intracranial hypertension, OP = Opening pressure, SD = Standard deviation. p values were calculated by X2-test or Student's t-test, as appropriate.					

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