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Original Article

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Headache Phenotypes in Idiopathic Intracranial Hypertension and Its Short-Term Outcomes: A Retrospective Case Series Study

Miguel Serodio[a, c], Goncalo Cabral[a], Bruna Meira[a], Andre Caetano[a, b], Miguel Viana-Baptista[a, b]

Abstract

Background: Idiopathic intracranial hypertension (IIH) presents a complex physiopathology, leading into diverse manifestations, notably variable headache phenotypes. Furthermore, its frequent overlap with migraine complicates the evaluation of treatment benefit for IIH-related headache. Our aim was to investigate if there is any relationship between demographic factors, clinical patterns of headache, treatment response, and headache short-term outcome with the headache phenotype of IIH.

Methods: This study was a retrospective analysis of demographic, clinical, and treatment features of patients with idiopathic intracranial hypertension presenting with headache and evaluation of headache outcomes in the first 12 months following treatment.

Results: Thirty-two patients were included (median age of onset 29.0 years (interquartile range 25.0 - 38.5), 90% females, median body mass index 32.5 kg/m^2; 87.5% (n = 28) with papilledema; median cerebrospinal fluid opening pressure 36.5 cm H_2O). Patients presented with migraine (n = 11, 34.4%), tension-type (n = 9, 28.1%), or a not-classifiable headache (n = 12, 37.5%). Regarding treatment and short-term follow-up (12 months), there was a failure of medical treatment in 43.8% (n = 14) and a reduction of headaches (≥ 50%) in 62.5% (n = 20) of the patients. Among headache phenotypes, there were no significant differences regarding demographics, clinical features, clinical patterns, or treatment response at baseline. Also, there were no differences regarding response to treatment or headache outcomes in 1, 3, 6, and 12 months of follow-up.

Conclusions: In our study, migraine and unclassifiable types were the most commonly reported headache phenotypes. Headache phenotype does not appear to be an essential factor in allowing clinical distinction, treatment response, or predicting the short-term headache outcome of this intriguing entity.

Keywords: Idiopathic intracranial hypertension; Headache phenotype; Short-term outcomes

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[a]Department of Neurology, Hospital Egas Moniz, Centro Hospitalar Lisboa Ocidental, Lisboa, Portugal
[b]Chronic Diseases Research Center (CEDOC) - Nova Medical School, Universidade Nova de Lisboa, Lisboa, Portugal
[c]Corresponding Author: Miguel Serodio, Servico de Neurologia, Centro Hospitalar Lisboa Ocidental, 1349-019 Lisboa, Portugal.
Email: miguelserodio.457@gmail.com

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Introduction

Idiopathic intracranial hypertension (IIH) is a rare entity characterized by an increased intracranial pressure in the absence of any secondary cause, typically manifesting as progressive visual deterioration from papilledema and chronic headache [1]. Headache is reported as the most common symptom and the most frequent initial manifestation of IIH [2]. Its phenotype may be variable, but the majority of patients' headache is migraine-like or tension type-like [3]. The International Classification of Headache Disorders, third edition (ICHD-3) provides criteria for IIH-related headache [3] as being a new headache or a significant worsening of a pre-existing headache in temporal relation to the IIH, with the diagnosis of IIH and a documented cerebrospinal fluid (CSF) opening pressure greater than 25 cm, and it can be accompanied by pulsatile tinnitus and papilledema. As the most common reason for seeking medical advice and having an impact on quality of life [4], understanding the pathophysiology of IIH-related headache would allow for better treatment and outcomes. Although there is commonly an improvement in IIH-related headache after normalization of CSF pressure, it may persist in the long term and several other studies even report that there is no correlation between CSF pressure and the presence and intensity of headache [4].

Treatment strategies for IIH include reduction of body weight and reduction of the CSF production. Acetazolamide is the only medication proven beneficial in IIH investigated in a randomized controlled trial (RCT), but no effect was proven for headache severity [5]. Topiramate is another medication increasingly used in IIH for its carbonic anhydrase inhibition, anti-migraine, and appetite suppression effects, but it has still no proven benefit in headache relief from an RCT [4]. Surgical management of IIH is needed when there is an important decline in visual function. Emerging treatments such as venous sinus stenting have been also used for refractory IIH. The treat-

ment benefit of IIH-related headache is still difficult to assess, given the complexity of its pathophysiology and its frequent overlap with chronic migraine [4].

In the present study, we aimed to study if there was any relationship between demographic factors, clinical pattern of headache, treatment response, and headache outcome with the headache phenotype of IIH.

Materials and Methods

We conducted an observational, retrospective case series study of patients with definitive IIH and headache as a manifestation, evaluated in the headache clinic from our hospital center from January 1, 2008 to December 31, 2021.

The diagnosis of IIH was established using the modified Friedman criteria, whether with associated papilledema and/or VI cranial nerve palsy [6]. The presence of headache and its phenotype was classified according to ICHD-3 [3], as either migraine, tension-type, or unclassifiable. Patients were included if they were at least 18 years old, had a diagnosis of definite IIH according to the modified Friedman criteria, presented with headache, underwent medical or surgical treatment for IIH according to best practice, and had a minimum follow-up of 12 months. The presence of a predominant headache explained by another condition and incomplete descriptions of clinical variables were exclusion criteria.

Demographic and clinical data were collected through electronic records. Headache characteristics were obtained at the time of IIH diagnosis, specifying headache time course, pain location, headache phenotype, associated symptoms, previous history of headache, and analgesic overuse. IIH characteristics were also obtained at the time of diagnosis, regarding CSF opening pressure, the presence of papilledema, associated symptoms, radiological aspects suggestive of IIH, and time to IIH diagnosis. A 1-year follow-up was assured for collecting information regarding treatment made, the presence of papilledema, and headache improvement (defined as a $\geq$ 50% reduction in headache frequency or a patient reported improvement in quality of life and decreased need for acute treatment).

We performed descriptive statistics with the calculation of absolute and relative frequencies, means, standard deviations, and ranges. For testing the hypothesis of the existence of an association between headache phenotype and demographic factors, clinical pattern of headache, treatment response, and headache outcome, non-parametric tests (Kruskal-Wallis and Chi-square) were used, with a statistical significance defined as a P-value < 0.05 (two-tailed). The analyses were made with SPSS® Statistics version 23.0.

The study was approved by the local Ethics Review Board (number of approval 2389), and was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

Demographics, clinical characteristics and treatment response of the study subjects are shown in Tables 1 and 2.

Thirty-two patients were included, with a median age of 29.0 years (interquartile range (IQR) 25.0 - 38.5 years). Twenty-nine (90.6%) were female and the median body mass index (BMI) was 32.5 kg/m^2 (IQR 27.9 - 35.0 kg/m^2). The time to IIH diagnosis took a median of 2.5 months (IQR 0.6 - 12.0 months). At the time of diagnosis, 28 (87.5%) patients had papilledema. The median CSF opening pressure was 36.5 cm H_2O (IQR 29.0 - 45.3 cm H_2O); suggestive IIH imaging findings were present in 14 (43.8%). Besides headache, additional IIH-associated symptoms were described in 28 (87.5%): 14 (43.8%) reported transient visual obscurations (TVOs), 10 (31.3%) reported diplopia and 10 (31.3%) reported tinnitus. A VI nerve palsy was observed in six (18.8%).

Headache phenotypes were migraine (11, 34.4%), tension-type (9, 28.1%), and unclassifiable (12, 37.5%). Pain location was anterior in eight (25.0%), posterior in five (15.6%), on the vertex in two (6.3%), and holocranial in 11 (34.4%). Unilateral pain was reported in six (18.8%). Accompanying symptoms were nausea and vomiting in six (18.8%) each, photophobia in 15 (46.9%), and phonophobia in three (9.4%). Worsening with recumbency was reported in eight (25.0%) and with Valsalva maneuvers in three (9.4%). Most patients (17, 53.1%) had an acute headache and 24 (75.0%) patients reported daily headache. Three (9.4%) patients reported analgesic overuse. Thirteen (40.6%) had a history of previous primary headache (migraine being the most common, in nine patients).

Regarding treatment, weight loss was proposed in 29 (90.6%) cases and pharmacological treatment was initiated in 30 (93.8%) with acetazolamide (500 - 2,000 mg/day). Due to persistent headache or adverse effects/intolerance, 10 (31.3%) patients switched to topiramate (50 - 400 mg/day). The two remaining patients were directly proposed to surgical therapy due to their severe visual dysfunction, being submitted to ventriculoperitoneal shunt. Initial medical treatment failed in 14 (43.8%) cases. A ventriculoperitoneal shunt was the most common surgical procedure (13, 40.6%) in patients whose medical therapy failed; optic nerve fenestration was performed in one patient. The median time to surgery was 2.6 months (1.0 - 10.5 months). During a 12-month period of follow-up, 20 (62.5%) patients experienced a $\geq$ 50% improvement in headache frequency and improvement of papilledema was documented in 25 (78.1%).

Non-parametric statistical tests showed a statistically significant difference comparing headache phenotypes and the presence of diplopia (P = 0.016), in which patients with the unclassifiable headache type showed more frequent diplopia than expected (and tension-type phenotype showing less diplopia than expected). No statistically significant differences were observed regarding age (P = 0.060), time to diagnosis (P = 0.153), BMI (P = 0.725), CSF opening pressure (P = 0.343), presence of papilledema (P = 0.192), VI nerve paresis (P = 0.153), TVO (P = 0.982), tinnitus (P = 0.154), pain location (P = 0.900) and worsening with Valsalva/recumbency (P = 0.416) at the time of the diagnosis. No differences were also observed between headache phenotype and history of analgesic overuse (P = 0.383), previous primary headache (P = 0.401), and presence of suggestive IIH imaging findings (P = 0.625). Regarding the follow-up period, no differences were equally ob-

Table 1. Demographic and Clinical Characteristics at Time of Diagnosis of the 32 Patients Included

Characteristics	
Median age (years)	29.0 (IQR 25.0 - 38.5)
Female sex	29 (90.6%)
Median body mass index (kg/m^2)	32.5 (IQR 27.9 - 35.0)
Idiopathic intracranial hypertension characteristics	
Papilledema	28 (87.5%)
Median CSF opening pressure (cm H_2O)	36.5 (IQR 29.0 - 45.3)
Radiological aspects suggestive of IIH	14 (43.8%)
Transient visual obscurations	14 (43.8%)
Diplopia	10 (31.3%)
Tinnitus	10 (31.3%)
VI nerve palsy	6 (18.8%)
Headache characteristics	
Migraine phenotype	11 (34.4%)
Tension-type phenotype	9 (28.1%)
Unclassifiable phenotype	12 (37.5%)
Acute headache	17 (53.1%)
Subacute headache	2 (6.3%)
Chronic headache	5 (15.6%)
Intermittent headache	8 (25.0%)
Daily headache	24 (75.0%)
Nausea and vomiting	6 (18.8%)
Photophobia	15 (46.9%)
Phonophobia	3 (9.4%)
Analgesic overuse	3 (9.4%)
History of previous primary headache	13 (40.6%)

CSF: cerebrospinal fluid; IIH: idiopathic intracranial hypertension; IQR: interquartile range.

Table 2. Treatment Characteristics and Outcomes of the 32 Patients Included

Treatment and outcomes	
Therapies proposed	
Weight loss	29 (90.6%)
Pharmacological treatment	30 (93.8%)
Acetazolamide alone	16 (50.0%)
Acetazolamide and subsequent topiramate	10 (31.3%)
Acetazolamide and subsequent furosemide	1 (3.1%)
Acetazolamide and subsequent corticotherapy	2 (6.3%)
Surgical treatment	14 (43.8%)
Ventriculoperitoneal shunt	13 (40.6%)
Optic nerve fenestration	1 (3.1%)
12 months follow-up	
Initial medical treatment failure	14 (43.8%)
Papilledema improvement	25 (78.1%)
≥ 50% improvement in headache frequency	20 (62.5%)

served in initial medical treatment failure (P = 0.741) and ≥ 50% improvement in headache frequency at the first month (P = 0.384), 3 months (P = 0.814), 6 months (P = 0.856) and 12 months (P = 0.798). These results are summarized in Table 3. A subanalysis including only patients in whom surgery was not offered (n = 18) showed a statistically significant correlation between the headache phenotype and headache improvement at 1-month follow-up (where patients with migraine headache phenotype showed a ≥ 50% headache frequency reduction less frequently than expected, P = 0.014), but no significant differences at 3-, 6- and 12-month follow-up.

Discussion

In IIH patients admitted to our institution, the unclassifiable type was the most commonly reported headache phenotype, and headache frequency showed a favorable evolution in the first year of follow-up. Our results show some differences when compared to a prospective study from the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) [2]. De-

Table 3. Headache Phenotypes and Differences in Clinical and Outcome Variables

Variables	Migraine (n = 11)	Tension-type (n = 9)	Unclassifiable (n = 12)	P-value
Median age (years)	28.0 (IQR 18.0 - 42.0)	33.0 (IQR 29.5 - 50.5)	26.5 (IQR 25.0 - 29.8)	0.060
Median time to diagnosis (months)	3.0 (IQR 1.8 - 8.0)	12.0 (IQR 0.5 - 12.0)	0.8 (IQR 0.4 - 1.4)	0.153
Median body mass index (kg/m^2)	32.5 (IQR 28.8 - 33.8)	32.5 (IQR 32.0 - 33.9)	31.3 (IQR 27.0 - 37.0)	0.725
Median CSF opening pressure (cm H_2O)	33.0 (IQR 30.0 - 40.3)	30.0 (IQR 28.0 - 45.0)	43.0 (IQR 29.8 - 50.0)	0.343
Papilledema	11 (34.4%)	8 (25.0%)	9 (28.1%)	0.192
Radiological aspects suggestive of IIH	6 (18.8%)	3 (9.4%)	5 (15.6%)	0.625
Transient visual obscurations	5 (15.6%)	4 (12.5%)	5 (15.6%)	0.982
Diplopia	3 (9.4%)	0 (0.0%)	7 (21.9%)	0.016*
Tinnitus	3 (9.4%)	1 (3.1%)	6 (18.8%)	0.154
VI nerve palsy	2 (6.3%)	0 (0.0%)	4 (12.5%)	0.153
Analgesic overuse	0 (0.0%)	1 (3.1%)	2 (6.3%)	0.383
History of previous primary headache	5 (15.6%)	2 (6.3%)	6 (18.8%)	0.401
Initial medical treatment failure	5 (15.6%)	3 (9.4%)	6 (18.8%)	0.741
≥ 50% improvement in headache frequency at 1 month	3 (9.4%)	5 (15.6%)	6 (18.8%)	0.384
≥ 50% improvement in headache frequency at 3 months	5 (15.6%)	5 (15.6%)	5 (15.6%)	0.814
≥ 50% improvement in headache frequency at 6 months	6 (18.8%)	6 (18.8%)	7 (21.9%)	0.856
≥ 50% improvement in headache frequency at 12 months	6 (18.8%)	6 (18.8%)	8 (25.0%)	0.798

*Statistically significant P-value. CSF: cerebrospinal fluid; IIH: idiopathic intracranial hypertension; IQR: interquartile range.

spite a fairly similar frequency of TVO and diplopia, headache phenotypes were more frequently unclassifiable in our study, which also reflects less frequent reports of photo/phonophobia and nausea/vomiting. Indeed, a migraine phenotype was much more common in IIHTT (67.6% vs. 34.4%), which can be explained by the fact that the IIHTT study included patients with criteria for probable migraine in the migraine phenotype. Both our study and IIHTT show similar frequency of previous primary headache (40.6% and 43.1%, respectively). Although a daily headache was much more common in our study (75.0% vs. 23.0%), our patients report less medication overuse, which might be the reflection of a more frequent acute headache course compared to IIHTT patients (53.1% vs. 28.1%).

Considering headache presence on short-term follow-up, we report a ≥ 50% improvement in headache frequency in 62.5% after 12 months, a value greater than that reported in a study by Yri et al [7], but smaller than the results provided by Bsteh et al [8]. In the latter, 76.5% achieved headache improvement (frequency and/or severity) and 27.8% attained freedom of headache. A headache improvement using HIT-6 scores in IIHTT was also reported by Friedman et al [2], but the majority of patients in these studies maintained headaches at the end of follow-up, despite an improvement in papilledema. No migraine or tension-type headache prophylactic drugs (other than topiramate) were initiated within the follow-up period in our study.

Our study shows a significant difference regarding the presence of diplopia and headache phenotype, where patients with unclassifiable phenotype show a greater than expected frequency of diplopia. To our best knowledge, this result was not shown in any other study. Diplopia in IIH patients is present in about 18-38% and the most common cause for it is VI nerve palsy [4]. While statistically significant differences in VI nerve palsy were not observed in our study, the unclassifiable headache group displayed a higher frequency of VI nerve palsy compared to what would be expected by chance. This finding might be attributed to the limitations of a small sample size and possibly due to other causes of diplopia not further explored in our study, requiring further investigation with larger cohorts. We report no differences regarding the remaining clinical/paraclinical characteristics, similar to what the IIHTT study showed. The IIHTT study showed no statistically significant relationship between headache disability and CSF opening pressure, BMI, papilledema grade, and headache characteristics at baseline or at 6 months [2]. However, when excluding patients not submitted to surgical treatment, patients with a migraine-like phenotype showed less than expected headache improvement at 1-month follow-up, with no differences at 3, 6 and 12 months. A recent study by Bsteh et al [8] reveals lower rates for headache improvement and freedom of headache in patients with IIH and a migraine-like phenotype, even with resolved papilledema, with 23% of patients having a preexisting diagnosis of migraine. Whether our result reflects a real trend for lower rate of headache frequency improvement, the natural history of the medical treatment of a migraine-like headache or just a limitation due to a low number of patients, is unknown and merits additional studies.

IIH-related headache is clinically diverse and overlaps with preexisting headache (mainly migraine) [1]. Despite normalization of CSF pressures and improvement in papilledema,

headache remains present and leads to great disability; additionally, it appears that IIH-directed therapies are not ideal for achieving headache freedom, although they may lead to an improvement in the frequency of headaches [2, 7-9]. Whether this is due to a preexisting headache not being optimally treated or another pathophysiological mechanism yet to be understood is currently unknown, reflecting the need for additional studies with larger cohorts and efficacy studies of phenotype-specific drugs.

Our study has some limitations. Its small sample size limits its generalizability to a broader IIH population and hinders the creation of an age- and sex-matched non-headache control group, despite reflecting our clinical practice. Information bias may also impact our results. Additionally, no structured interview was performed to assess all the clinical variables collected, which might under/overestimate some clinical characteristics and misdiagnose headache phenotypes. Also, probable migraine and probable tension-type headache were not included as migraine and tension-type phenotypes in our study, unlike previous studies, which might be difficult for direct comparisons.

Conclusions

In conclusion, in our sample, migraine and unclassifiable headache were the most common phenotypes in IIH. Most patients manifested with daily headache and a considerable number of patients had preexisting headache. At 1-year follow-up, a favorable evolution of headache was shown, despite a persisting headache in the majority. Finally, headache phenotype does not appear to be an essential factor in allowing clinical distinction, treatment response, or predicting the short-term headache outcome of this intriguing entity. However, it would be important to understand if this persists in the long term.

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None to declare.

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Conflict of Interest

The authors have no potential conflict of interest do disclose.

Informed Consent

Written informed consents have been obtained.

Author Contributions

Miguel Serodio: concept and design of the work; acquisition, analysis and interpretation of data; drafting of the article. Goncalo Cabral: concept and design of the work; acquisition, analysis and interpretation of data; drafting of the article; critical revision of intellectual content. Bruna Meira: acquisition, analysis and interpretation of data; critical revision of intellectual content. Andre Caetano: acquisition, analysis and interpretation of data; critical revision of intellectual content. Miguel Viana Baptista: acquisition, analysis and interpretation of data; critical revision of intellectual content. All authors approved the version to be published and take public responsibility for appropriate portions of the content.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

BMI: body mass index; CSF: cerebrospinal fluid; ICHD-3: International Classification of Headache Disorders, third edition; IIH: idiopathic intracranial hypertension; IIHTT: Idiopathic Intracranial Hypertension Treatment Trial; RCT: randomized controlled trial; TVOs: transient visual obscurations

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