J Korean Med Sci. 2025 Oct 27;40(41):e278
https://doi.org/10.3346/jkms.2025.40.e278
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Neuroscience

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A Prospective Multicenter Study on the Evaluation of Frequency of Idiopathic Intracranial Hypertension in Korea

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OPEN ACCESS

Received: Jan 20, 2025
Accepted: Mar 18, 2025
Published online: Sep 12, 2025

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ABSTRACT

Background: Idiopathic intracranial hypertension (IIH) is a complex neurological disorder that primarily affects obese women of reproductive age. Epidemiological data on IIH in Asia are scarce, and previous small retrospective studies in Asia have reported a significantly different patient profile from what is known for this disorder. We aimed to prospectively examine the frequency of IIH in headache clinics and to assess the presence of red flag signs in patients with IIH.

Methods: We prospectively collected data on consecutive first-visit patients with IIH who visited the headache clinics of 11 hospitals in Korea between January 2022 and March 2024. Data on clinical characteristics, lumbar puncture opening pressure, and neuroimaging were collected. The SNNOOP10 list was administered to patients with IIH to assess the presence of red flags.

Results: Among the 13,028 new headache patients, 22 were diagnosed with IIH (frequency, 0.17%; 95% confidence interval [CI], 0.11–0.25%; women, 0.19%; 95% CI, 0.12–0.30%; men, 0.11%; 95% CI, 0.04–0.28%). The median age of the patients was 33 years (interquartile range, 27–44 years), and 18 patients (81.8%) were women. Sixteen (72.7%) patients were obese (≥ 25 kg/m^2) according to the Asian-Pacific classification, with only

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Funding

This research was funded by Korean Headache Society (2021).

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim BS, Cho SJ, Chu MK, Lee MJ. Data curation: Kim BS, Cho SJ, Chu MK, Lee MJ. Formal analysis: Kim BS, Cho SJ, Chu MK, Lee MJ. Funding acquisition: Cho SJ, Cho KH. Investigation: Kim BS, Cho SJ, Baek SH, Sohn JH, Song TJ, Lee W, Park HK, Cho S, Cha MJ, Chu MK, Lee MJ. Methodology: Kim BS, Cho SJ, Han J, Rhiu S, Chu MK, Lee MJ. Project administration: Cho SJ, Cho KH. Resources: Cho SJ. Supervision: Cho SJ, Cho KH, Han J, Rhiu S, Chu MK, Lee MJ. Validation: Han J, Rhiu S. Visualization: Kim BS, Cho SJ, Chu MK, Lee MJ. Writing - original draft: Kim BS, Cho SJ, Lee MJ. Writing - review & editing: Kim BS, Cho SJ, Cho KH, Baek SH, Sohn JH, Song TJ, Lee W, Park HK, Cho S, Han J, Rhiu S, Cha MJ, Chu MK, Lee MJ.

11 (50%) having a body mass index ≥ 30 kg/m^2. All patients with IIH reported one or more red flags in the SNNOOP10 list, with papilledema being the most common (n = 14; 63.6%). When patients with papilledema and red flags irrelevant to IIH were excluded, 10 patients (45.5%) had no red flags. Among the headache-related red flags, pattern change or new-onset headache (n = 6; 27.3%) were the most common. Positional headache (n = 2; 9.1%) and precipitation due to sneezing, coughing, or exercise (n = 1; 4.5%) were uncommon.

Conclusion: The frequency of IIH in headache clinics in Korea was low. Typical obesity profiles, clinical characteristics, and papilledema are less common in Korean patients with IIH. Although the SNNOOP10 list seems to be feasible, clinical suspicion alone may not be sufficient to screen for IIH, particularly in Asians.

Keywords: Idiopathic Intracranial Hypertension; Headache; Frequency; Papilledema; Obesity

INTRODUCTION

Idiopathic Intracranial Hypertension (IIH) is caused by increased intracranial pressure without obstructive or space occupying lesions and predominantly affects obese women of reproductive age.[1] IIH often presents with chronic headaches, vision loss, or pulsatile tinnitus and significantly reduces quality of life. The global increase in obesity has exacerbated the severity of IIH.[2-4] Additionally, glucagon-like peptide-1 receptor agonists prescribed for weight loss may influence IIH outcomes, either by inducing IIH after discontinuation or by improving IIH when used, making an accurate diagnosis of IIH more important.[5,6]

Asian populations have a markedly lower incidence of IIH than Western populations, with studies indicating that a lower prevalence of obesity is a potential contributing factor.[7-10] Despite its growing importance, data from Asia remain scarce, with few prospective, multicenter studies available.

This study aimed to evaluate the frequency of IIH in patients with new headaches across multiple headache clinics in Korea, using a prospective, multicenter approach. Along with clinical characteristics and patient profiles, we evaluated the red flags in our IIH cases using the SNNOOP10 checklist to assess whether clinical suspicion alone is sufficient to screen for IIH.[11]

METHODS

Study design and inclusion criteria

In this prospective observational study, we collected data from new consecutive outpatients with headaches at the headache clinics of 11 hospitals in Korea between January 2022 and March 2024. Assuming that IIH is rare and relatively milder in severity in the Asian population, we decided to use inclusion criteria that can encompass a broader clinical spectrum of IIH. In this context, our diagnostic inclusion criteria were modified from the revised Friedman criteria[12] as follows: 1) elevated lumbar puncture opening pressure of ≥ 25 cm cerebrospinal fluid (CSF) or 2) elevated lumbar puncture opening pressure of ≥ 20 and < 25 cm CSF with at least one of papilledema, abducens nerve palsy, or neuroimaging findings indicative of intracranial hypertension (empty sella, flattening of the posterior globe, enlarged perioptic subarachnoid space and/or tortuous optic nerve,

and transverse sinus stenosis). Based on a comprehensive diagnostic work-up, patients with IIH were diagnosed by experienced headache neurologists based on the inclusion criteria. The exclusion criterion was the presence of structural intracranial lesions that could potentially lead to secondary intracranial hypertension.

Data collection and measurement

The comprehensive diagnostic workup for the diagnosis of IIH consisted of in-depth medical interviews with headache neurologists, neurological examinations, neuro-ophthalmological examinations, lumbar punctures, and neuroimaging studies. In this regard, we investigated information on demographics, medical comorbidities (migraine, anemia, hypertension, polycystic ovary syndrome, sleep apnea, renal failure, chronic obstructive pulmonary disease, systemic lupus erythematosus, pregnancy, adrenal insufficiency, Cushing's syndrome, hypo- or hyperthyroidism, hypoparathyroidism, Down syndrome, Turner syndrome, and craniosynostosis), medication usage (systemic steroids, fluoroquinolones, tetracycline antibiotics, levothyroxine, cyclosporine, tamoxifen, danazol, vitamin A derivatives, nalidixic acid, levonorgestrel implant, lithium, growth hormone, indomethacin, and cimetidine), and clinical manifestations (headache, pulsatile tinnitus, transient visual obscuration, blurred vision or visual impairment, dizziness, double vision, photophobia, cognitive impairment, abducens nerve palsy, and neck/back pain). Based on the International Classification of Headache Disorders, 3rd edition, headache phenotyping was conducted, which was dichotomously classified into migraine or tension-type headache with sub-phenotyping of episodic, chronic, or probable.[10] Lumbar puncture was performed to measure the CSF opening pressure and to conduct routine CSF analysis. Lumbar puncture opening pressure was measured using a standard manometer with the patient in a relaxed, lateral decubitus position with the neck and legs extended (cm CSF). A neuro-ophthalmological examination was conducted by an experienced ophthalmologist at each hospital to determine the functional and structural abnormalities of the optic nerves (fundus photography, optical coherence tomography, visual acuity, visual field perimetry, and/or transorbital sonography). Three-Tesla brain magnetic resonance (MR) imaging scans with contrast were performed in all patients to determine the neuroimaging signs of intracranial hypertension, as specified in the inclusion criteria. MR or computed tomography (CT) venography was selectively performed based on clinical needs and availability.

Application of framework of headache red flags

After the diagnosis of IIH, we investigated the presence of red and orange flags in patients with IIH using the SNNOOP10 list.[13] A total of 15 items, including 1) systemic symptoms including fever; 2) neoplasm in history; 3) neurologic deficit including decreased consciousness; 4) onset of headache is sudden or abrupt (thunderclap headache); 5) older age (after 50 years); 6) pattern change or recent onset of new headache; 7) positional headache; 8) precipitated by sneezing, coughing, or exercise; 9) papilledema; 10) progressive headache and atypical presentations; 11) pregnancy or puerperium; 12) painful eye with autonomic features; 13) posttraumatic onset of headache, 14) pathology of the immune system such as human immunodeficiency virus; and 15) painkiller overuse (medication overuse headache) or new drug at onset of headache, were evaluated through SNNOOP10 in this study.

Statistical analysis

The frequency of IIH was calculated as the ratio of the number of patients diagnosed with IIH to the total number of new patients visiting the headache clinic during the study period. The 95% confidence intervals (CIs) were calculated using the Wilson score method.[14] The IIH

https://doi.org/10.3346/jkms.2025.40.e278

frequency and the corresponding 95% CI were calculated separately for the overall patient population, female patients, and male patients.

Continuous variables are presented as medians with interquartile ranges (IQRs). Categorical variables are reported as numbers (percentages), and the test statistics were based on the Fisher's exact or linear-by-linear association test, as appropriate.

The presence and number of SNNOOP10 cells are summarized. We conducted the Fisher's exact test to evaluate whether the total number of red flags differs according to each diagnostic inclusion criterion (elevated lumbar puncture opening pressure of ≥ 25 cm CSF, papilledema, and neuroimaging sign). To identify IIH-relevant red flags based on the clinical history, we also evaluated the presence and number of SNNOOP10 items, excluding papilledema and flags irrelevant to IIH (e.g. systemic symptoms, neoplasm history, older age, painful eye with autonomic features, post-traumatic onset, and immune compromise). All statistical analyses were performed using R software version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/), Python 3.8 (Python Software Foundation, Wilmington, DE, USA; https://www.python.org/), and SPSS 18.0 (SPSS Inc., Chicago, IL, USA). All reported *P* values were two-tailed, and $P < 0.05$ were considered to indicate statistical significance.

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of each hospital (Bundang Jesaeng General Hospital, Dongtan Sacred Heart Hospital, Korea University Anam Hospital, Chuncheon Sacred Heart Hospital, Ewha Womans University Seoul Hospital, Yongin Severance Hospital, Inje University Ilsan Paik Hospital, Uijeongbu Eulji Medical Center, Seoul National University Hospital, Severance Hospital, and National Police Hospital; approval No. of main research hospital DH 2021-11-011). Informed consent was submitted by all subjects when they were enrolled.

RESULTS

Diagnostic frequency of IIH

Over a two-year period, 13,028 new patients with headaches visited to the participating headache clinics (9,403 women and 3,625 men). Of these, 22 patients were diagnosed with IIH (frequency, 0.17%; 95% CI, 0.11–0.25%). The median age of the patients was 33 years (IQR, 27–44 years), and 18 (81.8%) were women. The diagnostic frequency of IIH according to sex was 0.19% (95% CI, 0.12–0.30%) in women and 0.11% (95% CI, 0.04–0.28%) in men, respectively. The diagnostic frequency of IIH according to age and duration of outpatient visits is shown in **Fig. 1**.

Opening pressure and signs of intracranial hypertension

The median lumbar puncture pressure was 30 (IQR, 26.5–38) cm CSF. Nineteen (86.3%) patients had lumbar puncture opening pressure of ≥ 25 cm CSF, and three (13.6%) had lumbar puncture opening pressure of ≥ 20 and < 25 cm CSF (**Fig. 2**). Fourteen patients (63.6%) had papilledema, including 12 (63.1%) among 19 with opening pressure of ≥ 25 cm CSF and two (66.6%) out of three with opening pressure of ≥ 20 and < 25 cm CSF. Abducens nerve palsy was reported only for 2 patients in the group of elevated lumbar puncture opening pressure of ≥ 25 cm CSF.

https://doi.org/10.3346/jkms.2025.40.e278

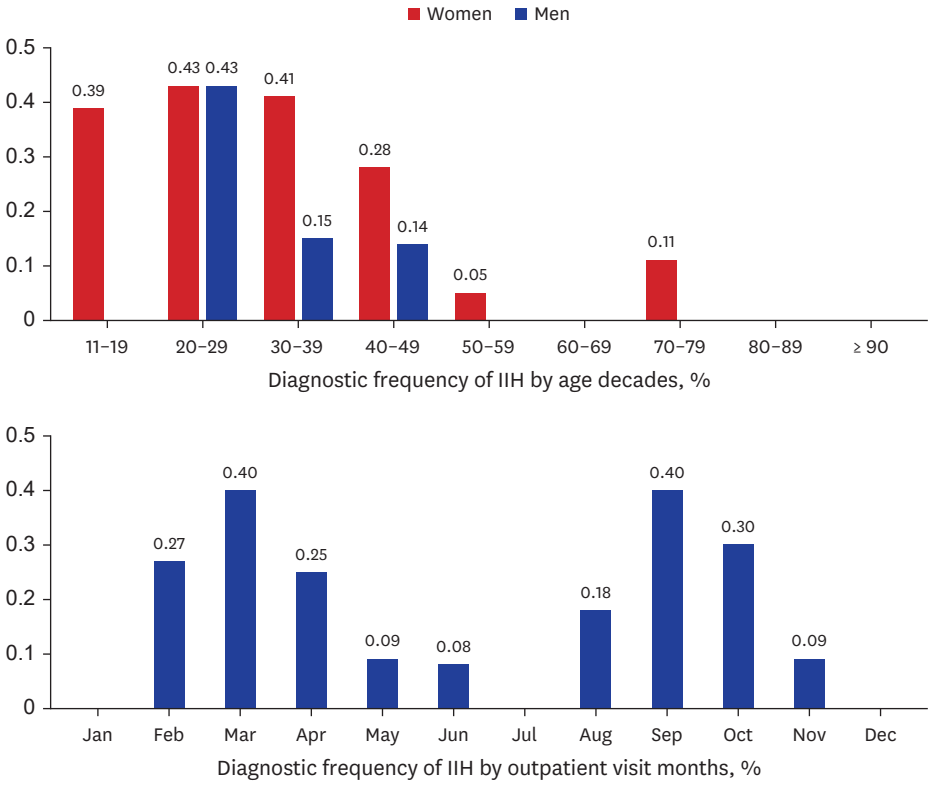

Fig. 1. The diagnostic frequency of idiopathic intracranial hypertension by age (decades) and outpatient visit (months).
IIH = idiopathic intracranial hypertension.

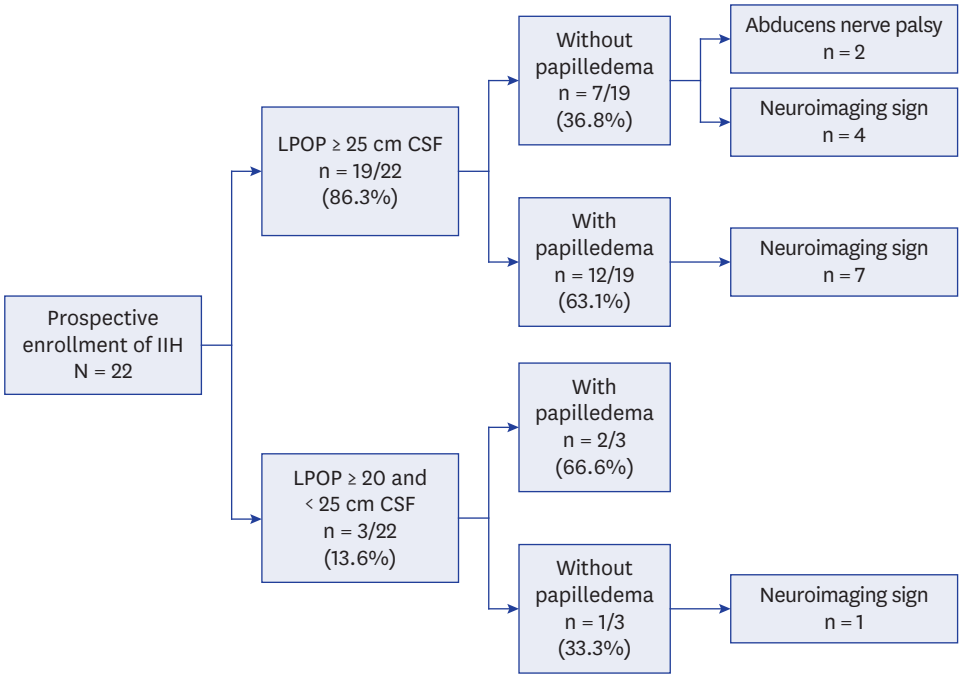

Fig. 2. Flowchart on the prospective enrollment of patients with idiopathic intracranial hypertension according to diagnostic inclusion criteria.
IIH = idiopathic intracranial hypertension, LPOP = lumbar puncture opening pressure.

https://doi.org/10.3346/jkms.2025.40.e278

Neuroimaging abnormalities were identified in 12 (54.5%) patients. Tortuosity of the optic nerve or distension of the perioptic subarachnoid spaces was the most frequent finding, identified in 11 patients (50.0%), followed by cupping or flattening of the posterior globe (n = 7, 31.8%) and empty sella (n = 3, 18.2%). Transverse sinus stenosis was observed in seven (63.6%) out of 11 patients who underwent MR or CT venography.

Clinical manifestations

The median body mass index (BMI) was 29.0 (IQR, 24.2–34.2) kg/m^2. Sixteen (72.7%) patients were obese (≥ 25 kg/m^2) according to the Asia-Pacific classification. Only 11 (50%) had a BMI ≥ 30 kg/m^2.

A total of 20 patients (90.9%) reported headache. Headache was the only presenting symptom in 3 patients (13.6%; **Table 1**). The headache phenotype was classified into migraine-like in 12 patients (54.5%; 4 with episodic, 5 with chronic, and 3 with probable subtypes), tension-type-like in 3 patients (13.6%; 2 with episodic and 1 with probable subtype), and unclassified in 5 patients (22.7%). Medication overuse was identified in only 2 patients (9.1%). Nine patients had preexisting migraine history (40.9%). The frequency of the migraine phenotype was significantly higher in patients with preexisting migraine history than in those without (88.9% vs. 36.3%; $P = 0.008$; **Supplementary Table 1**).

Nineteen patients (86.3%) reported non-headache symptoms (**Table 1**). Dizziness (45.5%), blurred vision (36.4%), and pulsatile tinnitus (36.4%) were relatively frequently reported, whereas photophobia (18.2%), cognitive impairment (13.6%), and abducens nerve palsy (9.1%) were rarely reported.

Application of SNNOOP10

Table 2 summarizes the clinical history of SNNOOP10 and the flags potentially relevant to IIH. All patients with IIH exhibited one or more red flags (**Table 2**). Papilledema was

Table 1. Clinical manifestations of a total of 22 patients with idiopathic intracranial hypertension

Clinical manifestations	Values
Headache	20 (90.9)
Isolated headache	3 (13.6)
Phenotype of headache	
Episodic migraine	4 (18.2)
Chronic migraine	5 (22.7)
Probable migraine	3 (13.6)
Episodic TTH	2 (9.1)
Probable TTH	1 (4.5)
Unclassified	5 (22.7)
Medication overuse	2 (9.1)
Non-headache symptoms	19 (86.3)
Blurred vision	8 (36.4)
Dizziness	10 (45.5)
Pulsatile tinnitus	8 (36.4)
Double vision or diplopia	5 (22.7)
Transient visual obscuration	5 (22.7)
Photophobia	4 (18.2)
Abducents nerve palsy	2 (9.1)
Neck pain	6 (27.3)
Cognitive impairment	3 (13.6)

Values are presented as number (%).
TTH = tension-type headache.

https://doi.org/10.3346/jkms.2025.40.e278

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Table 2. Red and orange flags observed in patients with idiopathic intracranial hypertension

Variables	Values
Systemic symptoms including fever	1 (4.5)
Neoplasm history	1 (4.5)
Neurologic deficit (including decreased consciousness)	4 (18.2)
Onset is sudden or abrupt	4 (18.2)
Older age (onset after age 50 yr)	2 (9.1)
Pattern change or recent onset of new headache	6 (27.3)
Positional headache	2 (9.1)
Precipitated by sneezing, coughing, or exercise	1 (4.5)
Papilledema	14 (63.6)
Progressive headache and atypical presentations	4 (18.2)
Pregnancy or puerperium	0 (0.0)
Painful eye with autonomic features	0 (0.0)
Post-traumatic onset of headache	1 (4.5)
Pathology of the immune system or immunosuppressive therapy	1 (4.5)
Painkiller overuse (includes analgesics, ergot, triptans)	2 (9.1)
Flags potentially relevant to IIH manifestation excluding papilledema	
0	10 (45.5)
1	5 (22.7)
2	4 (18.2)
3	3 (13.6)
4+	0 (0)

Values are presented as number (%).
Flags potentially relevant to idiopathic intracranial hypertension are marked in bold.

the most common red flag (n = 14; 63.6%). Among the headache-related red flags, pattern change or new-onset headache (n = 6; 27.3%) was the most common, followed by progressive headache (n = 4; 18.2%). Positional headache (n = 2; 9.1%) and precipitation by sneezing, coughing, or exercise (n = 1; 4.5%) were uncommon. Detailed findings from each patient are presented in **Table 3**.

The median number of red flags was two (IQR, 1–3) in the patients with IIH. The total number of red flags in all patients and subgroups is shown in **Fig. 3**. The composition did not differ between the subgroups of elevated lumbar puncture opening pressure of ≥ 25 cm CSF vs. < 25 cm CSF (P = 0.672) and neuroimaging signs suggestive of IIH present vs. absent (P = 0.322). Patients without papilledema had more red flags than those with papilledema (P = 0.042).

DISCUSSION

This study presented several key findings that contribute to our understanding of IIH in Asian populations. First, the frequency of IIH in our multicenter study was notably low: 0.17% among new patients with headaches in Korea. Second, our patients showed different profiles in terms of BMI and the prevalence of obesity compared to studies from regions other than Asia. Third, all patients reported one or more red flags on the SNNOOP10 checklist; papilledema was the most common, and red flags reflecting the temporal course of headaches were the most important clues from history.

This was the first prospective multicenter study to investigate the frequency of IIH in headache clinics. The frequency of IIH in our multicenter study was 0.17% among new patients visiting headache clinics in Korea. Given that the participating clinics were mostly university-based, the frequency of IIH in our hospital-based sample was notably low.

https://doi.org/10.3346/jkms.2025.40.e278

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https://doi.org/10.3346/jkms.2025.40.e278

Table 3. The full list of SNNOOP10 in all the included patients

No.	Age, yr	Women	BMI, kg/m²	Lumbar puncture opening pressure, cm CSF	1. Systemic symptoms	2. Neoplasm history	3. Neurologic deficit	4. Sudden onset	5. Onset age ≥ 50 yr	6. Pattern change or new onset headache	7. Positional headache	8. Precipitated by sneezing, coughing, or exercise	9. Papilledema	10. Progressive headache and atypical presentations	11. Pregnancy or puerperium	12. Painful eye with autonomic features	13. Post-traumatic onset of headache	14. Pathology of the immune system	15. Painkiller overuse	Sum
1	27	✓	31.4	27									✓							1
2	42	✓	13.8	30						✓			✓						✓	3
3	21	✓	24.1	24.5									✓							1
4	19	✓	34.3	38									✓							1
5	22	✓	35.8	40									✓							1
6	42	✓	30.1	46	✓						✓		✓	✓						4
7	33	✓	34.9	22									✓					✓		2
8	28		34.9	41				✓					✓							2
9	20	✓	30.9	32									✓							1
10	33	✓	24.3	25									✓							1
11	30	✓	34.2	30.5						✓										1
12	46	✓	28.0	27			✓			✓				✓						3
13	47		32.2	28			✓							✓						2
14	32	✓	37.7	38									✓							1
15	53	✓	27.8	30					✓	✓	✓		✓							4
16	33	✓	24.3	25			✓	✓					✓							3
17	44	✓	15.6	40						✓									✓	2
18	72	✓	26.1	24		✓			✓											2
19	33		27.6	32										✓			✓			2
20	30		27.2	27			✓	✓												2
21	32	✓	23.3	33									✓							1
22	44	✓	33.3	27				1		1		✓								3

BMI = body mass index, CSF = cerebrospinal fluid.

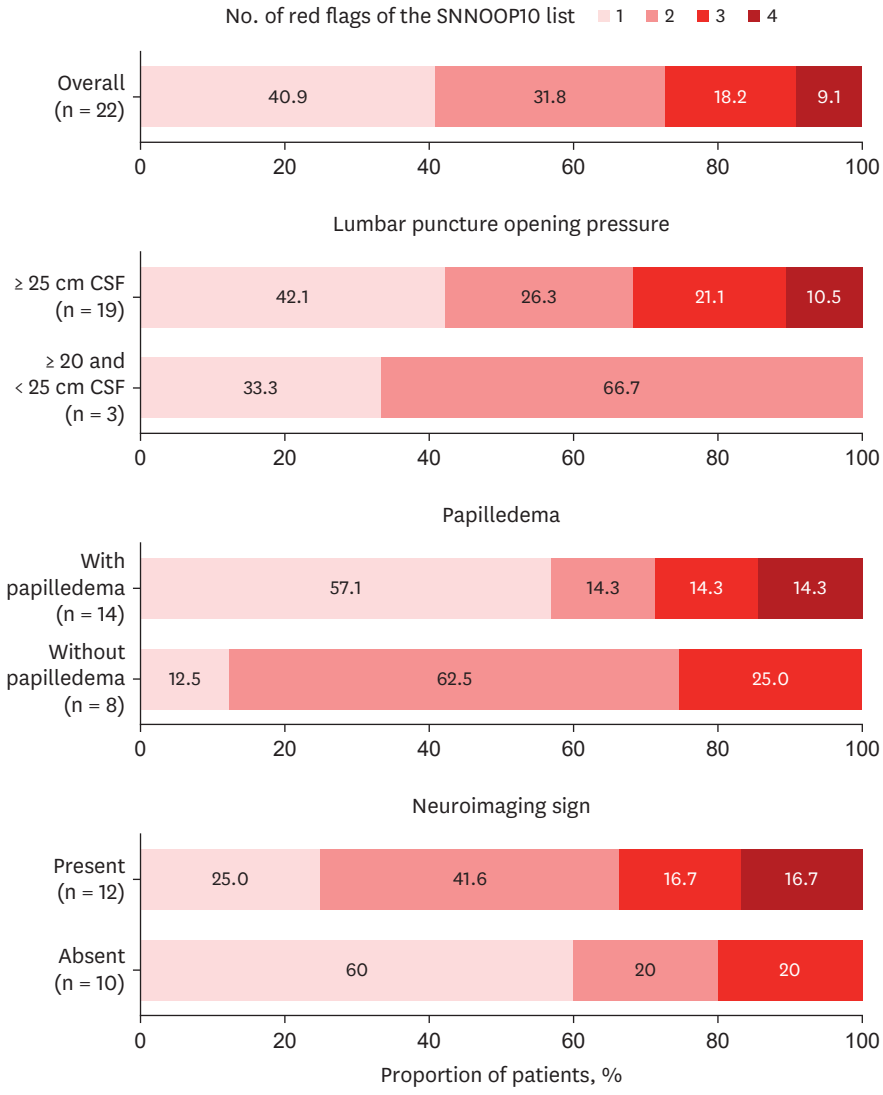

Fig. 3. Headache red flags of the SNNOOP10 list in a total of 22 patients with idiopathic intracranial hypertension, stratified by diagnostic inclusion criteria of elevated lumbar puncture opening pressure of ≥ 25 cm CSF, papilledema, and neuroimaging sign.
CSF = cerebrospinal fluid.

Population-based studies have shown that the incidence of IIH is low in Asia compared to that of the United Sates (US) or Europe: 0.9–1.07 per 100,000 per year in the US, 0.28–2.36 in Europe, and 0.03 in Japan. The low frequency of IIH in our study aligns with previous case studies, patient cohort-based studies, or the prevalence estimates from Asia.[7,9]

Given that obesity is a well-established risk factor for IIH, the lower incidence of IIH in Asians can be partially explained by the lower prevalence of obesity in Asians.[15,16] The obesity profile of patients with IIH in our study differed from that typically reported in modern studies from "Western" countries such as the US, Australia, New Zealand, and European countries. The median BMI was 29.0 kg/m^2 in this study, whereas mean BMIs reported from these countries ranged from 35.9–36.1 kg/m^2 in cohort studies and 38.1–43.9 kg/m^2 in Idiopathic Intracranial Hypertension Treatment Trial and other clinical trials.[6,17-20] Only half the patients had a BMI ≥ 30 kg/m^2 in our study, whereas 88% of study participants had

https://doi.org/10.3346/jkms.2025.40.e278

a BMI ≥ 30 kg/m^2 in Idiopathic Intracranial Hypertension Treatment trial.[17] When obesity was defined using the Asia-Pacific criterion of 25 kg/m^2,[21] our study showed an obesity prevalence of 72.7%, which is still lower than modern studies from Europe and North America but comparable to older studies from these regions.[22-24] In contrast, the obesity rate was surprisingly low in previous Asian studies on IIH: 6% (2/33) in an Indian study, 33% (4/12) in a Taiwanese study, and 45.8% (27/59) in a retrospective study in Korea.[8,10,16] Taken together, the obesity rate in the present study reflects both secular trends of increasing obesity and true ethnic differences. Our study better represents typical IIH in Asians, suggesting that obesity is still closely related to IIH, despite of lower BMIs in the Asian populations.

In this study, we showed that headache phenotypes in patients with IIH resemble primary headaches. Intracranial hypertension, a neurological manifestation of SARS-CoV-2 infection, can present with similar features of headache.[25-27] This may be a barrier to the early diagnosis of IIH. In addition, only two-thirds of the patients in this prospective study reported experiencing papilledema, which is in line with our previous retrospective study and much lower than the recent studies of IIH from non-Asian regions, where papilledema was reported in > 90% of patients.[19,28] Non-headache symptoms also differed; blurred vision and tinnitus were less prominent.[28] These findings support the notion that "atypical" IIH is more prevalent in Asians and may contribute to diagnostic delays. Interestingly, a recent Taiwan dual-center study reported similar findings: lower prevalence of obesity (BMI ≥ 27.5 kg/m^2; 45.1%) and papilledema (62.6%).[29] Therefore, the diagnostic criteria for IIH should be modified to reflect these characteristics in Asian populations.

The SNNOOP10 checklist proved to be a valuable tool in our study. Papilledema was the most common red flag in our cohort. All patients had at least one red flag other than papilledema, which supports the role of SNNOOP10 in screening for IIH. However, approximately half of the patients lacked flags relevant to IIH manifestations, indicating that the clinical features are not sufficient or typical for suspecting IIH. Pattern change in preexisting headache and new onset headache were more frequent than positional worsening of headaches and precipitation by sneezing, coughing, or exercise. Interestingly, regarding the total number of red flags, patients without papilledema seemed to have more secondary headache features than those with papilledema. Conversely, these findings may implicate IIH without papilledema and with few secondary headache features as a high-risk factor of misdiagnosis.[30] In addition to clinical red flags, subtle neuroimaging findings such as an empty sella were important for the diagnosis of IIH in our study, as in previous studies.[31-33] Our study suggests that red flags from the SNNOOP10 checklist, as well as subtle neuroimaging findings, should not be missed, particularly in Asian populations.

This study has several limitations. The small sample size and potential selection bias due to the study being conducted in headache clinics limit the generalizability of the findings, having possibly overlook milder cases. Additionally, focusing on a single nation, particularly Korea, reduces the applicability of the results to other regions where genetic, healthcare, and diagnostic differences can impact outcomes. The use of modified diagnostic criteria further complicates the comparisons with other studies.

In conclusion, IIH is uncommon in Korean patients visiting headache clinics, and clinical manifestation was more atypical with lower obesity rates. Tailored diagnostic approaches may be required to screen Asian populations for IIH.

https://doi.org/10.3346/jkms.2025.40.e278

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Comparison of headache phenotype according to preexisting migraine history of a total of 22 patients with idiopathic intracranial hypertension

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