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Idiopathic intracranial hypertension in Asians: a retrospective dual-center study

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Abstract

Background There have been limited data on idiopathic intracranial hypertension (IIH) in Asians and there remain uncertainties whether a cerebrospinal fluid (CSF) pressure of 250 mm CSF is an optimum diagnostic cutoff. The aims of the present study included (1) characterization of IIH patients in Taiwan, (2) comparisons among different diagnostic criteria for IIH, and (3) comparisons between patients with CSF pressures of > 250 and 200–250 mm CSF.

Methods This retrospective study involved IIH patients based on the modified Dandy criteria from two tertiary medical centers in Taiwan. Clinical manifestations were retrieved from electronic medical records, and findings on ophthalmologic examination and magnetic resonance images (MRIs) were reviewed.

Results A total of 102 patients (71 F/31 M, mean age 33.4 ± 12.2 years, mean CSF pressure 282.5 ± 74.5 mm CSF) were identified, including 46 (45.1%) with obesity (body-mass index ≥ 27.5), and 57 (62.6%) with papilledema. Overall, 80 (78.4%), 55 (53.9%), 51 (50.0%), and 58 (56.9%) patients met the Second and Third Edition of International Classification of Headache Disorders, Friedman, and Korsbæk criteria, respectively. Patients in the 200–250 mm CSF group ($n=40$) were less likely to have papilledema (48.5% vs. 70.7%, $p=0.035$), transient visual obscuration (12.5% vs. 33.9%, $p=0.005$), and horizontal diplopia (10.0% vs. 30.6%, $p=0.006$), and had fewer signs on MRIs (2.2 ± 1.3 vs. 2.8 ± 1.0 , $p=0.021$) when compared with those with CSF pressures > 250 mm CSF ($n=62$). However, the percentages of patients with headache (95.0% vs. 87.1%, $p=0.109$) at baseline, chronic migraine at six months (31.6% vs. 25.0%, $p=0.578$), and visual field defect (86.7% vs. 90.3%, $p=0.709$) were similar.

Conclusions It was found that obesity and papilledema were less common in Asian IIH patients when compared with Caucasian patients. Although patients with CSF pressures of 200–250 mm CSF had a less severe phenotype, the risks of having headache or visual loss were comparable to those in the > 250 mm CSF group. It is possible that a diagnostic cutoff of > 200 mm CSF could be more suitable for Asians, although further studies are still needed.

Keywords Idiopathic intracranial hypertension, Ethnicity, Criteria, Papilledema, Magnetic resonance imaging

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Introduction

Idiopathic intracranial hypertension (IIH) is most commonly seen in obese women of childbearing age, and typically presents with headache and ophthalmologic manifestations [1, 2]. Headache is reported by 75–94% of IIH patients, and migrainous features are common [2, 3]. Visual symptoms, such as transient visual obscuration (TVO), metamorphopsia, and horizontal diplopia, are reported by 68–72% of patients [2, 3]. One of the most notable signs on ophthalmologic examination is papilledema [4, 5], and visual loss is among the most dreaded complications of IIH [2, 3, 6, 7]. To date, most the current understandings of IIH are based on reports from Caucasian populations, and the clinical pictures of IIH in Asians are less clear.

There is some evidence indicating the presence of racial or ethnic differences in the clinical manifestations of IIH. IIH is much less common in Asians than in Caucasians. The incidence of IIH is about 0.5–7.8 per 100,000 person-years in the literature [8], although it was estimated at 0.03 per 100,000 person-years in Japan [9], and 0.16 per 100,000 person-years for Asians and Pacific Islanders in the United States [10]. Besides, even though obesity, typically defined as a body-mass index (BMI) of over 30 kg/m² [11], is a well-known risk factor for Caucasians [12], its association with IIH is not as definite in Asians [13, 14]. Limited data are available for IIH in Asians [9, 13, 14], and whether the clinical and radiological presentations in Asians could be different from those in Caucasians need to be further elucidated.

Although increased intracranial pressure (IICP) is one of the defining features of IIH, the diagnostic cutoff levels of CSF pressure vary among different diagnostic criteria. It is defined as a CSF pressure of >200 mm water or CSF in the modified Dandy criteria [15, 16], and those in the International Classification of Headache Disorders (ICHD), Second Edition (ICHD-2) [17], although there is a separate threshold of >250 mm CSF for obese patients in the ICHD-2 [17]. A cutoff of >250 mm CSF, irrespective of the presence of obesity, is used in the Friedman criteria [18], and in the criteria of the ICHD, Third Edition (ICHD-3) [19] for adult patients. On the other hand, according to the recently proposed criteria by Korsbæk et al., in the presence of papilledema and ≥ 3 neuroimaging signs defined in the Friedman criteria, a diagnosis of IIH could be made regardless of the CSF pressure [20]. The thresholds for CSF pressure are based on the normal ranges in the general population [21, 22], and prior studies in IIH patients [5, 23, 24]. However, the vast majority of participants in these studies were Caucasians, and Asians typically constituted only less than 1% [25, 26]. Whether 250 mm CSF is the optimum diagnostic cutoff level for CSF pressure for IIH in Asians deserves clarifications.

The aims of our study included characterization of the clinical, ophthalmologic, and radiological profiles in Asian IIH patients, comparisons among different diagnostic criteria, and comparisons between patients with a CSF pressure of >250 mm CSF and those with a CSF pressure of 200–250 mm CSF.

Methods

Participants

This was a retrospective study involving consecutive patients hospitalized in the Departments of Neurology of two tertiary medical centers in Taiwan, namely Taipei Veterans General Hospital and Taichung Veteran General Hospital, between January, 1999 to January, 2021. The diagnosis of IIH was based on the modified Dandy criteria [15, 16]. Patients were included if they (1) were hospitalized for diagnostic work-up for suspected IICP, and (2) had a discharge diagnosis of IIH, benign intracranial hypertension, pseudotumor cerebri, or intracranial hypertension. Patients were excluded if they (1) had no CSF opening pressure documented or clinical manifestations available in the medical records, (2) had secondary causes for IICP, such as brain tumors or metastases, central nervous system (CNS) infection, subarachnoid hemorrhage, cerebral venous sinus thrombosis, etc. demonstrated by the diagnostic work-up, or (3) had a CSF pressure ≤ 200 mm CSF. The study protocols were approved by the Institutional Review Boards of Taipei Veterans General Hospital (TVGH IRB No. 2022-04-005AC) and Taichung Veterans General Hospital (TCVGH IRB No. CE23493C), which waived the need for informed consent because of the retrospective nature of the study.

Clinical manifestations and treatment

Clinical profiles were retrieved by comprehensive chart review of electronic medical records, including demographics (sex, age at diagnosis, body weight [BW] and height, etc.), headache characteristics, time to diagnosis, the presence of transient visual obscuration (TVO), metamorphopsia, horizontal diplopia, pulsatile tinnitus, or other relevant symptoms, and CSF opening pressure at lumbar puncture. Patients were categorized as obese if they had a body-mass index (BMI) of ≥ 27.5 kg/m² [11]. For patients who had been examined by ophthalmologists, the presence of papilledema or visual field defect was included in the analysis. For patients in whom the original digital photographs of fundi were available for review, the severity of papilledema was rated based on the Frisén grades [27]. The presence of visual field defect on the Humphrey visual field analyzer (Swedish Interactive Threshold Algorithm Standard 30–2 or 24–2 test pattern) or G1 program of the Octopus perimeter was analyzed based on the protocols described in the Idiopathic

Intracranial Hypertension Treatment Trial (IIHTT) [28, 29]. The findings of the worse eye of each individual patient were used in the analysis. Average perimetric mean deviations (MDs) of each patients were derived from the results of Humphrey visual field analyzer (30–2 test pattern), and as defined in the IIHTT, a value of less than -2 dB indicated the presence of visual loss [16, 28, 29]. Patterns of visual field patterns were analyzed. The interpretation of ophthalmologic examinations was carried out by an experienced neuro-ophthalmologist (H.C.C.). Medical and interventional treatments were retrieved from medical records, and comparisons were made between patients with and without interventions.

Radiologic findings

Magnetic resonance images (MRIs) were reviewed for the four signs of IIH included in the Friedman criteria [18], including (1) empty sella, (2) flattening of the posterior aspect of the globe, (3) distention of the perioptic subarachnoid space with or without a tortuous optic nerve, and (4) transverse sinus stenosis (TSS) [18]. Empty sella was defined as a pituitary gland height of <4.8 mm on midline sagittal T1-weighted images, and distention of perioptic subarachnoid space was labeled as present if the optic nerve sheath diameter was >5.5 mm on axial T2-weighted images [30, 31]. TSS sinus stenosis was defined as $>50\%$ stenosis on at least one side of the transverse sinus in comparison with the immediate pre-stenosis segment [32, 33]. Empty sella and flattening of the posterior aspect of the globe were evaluated on sagittal T1-weighted and axial T2-weighted images, respectively. Distention of the perioptic subarachnoid space was rated on coronal and axial T2-weighted images. TSS was rated on magnetic resonance venography (MRV), and patients without MRV were labeled as not having TSS. The interpretation of the images was carried out by a neurologist (H.T.H.) and verified by an experienced neuroradiologist (J.F.L.).

Statistical analysis

Statistical analysis was conducted by IBM SPSS Statistics 26.0. Patients were divided into two groups based on the CSF pressure, i.e., 200–250 mm CSF and >250 mm CSF. Categorical variables were presented as n number (percentage), and were compared by using the chi-square test. Continuous variables were shown as mean \pm standard deviation, and were compared by using the Student's t test, or by using the Mann-Whitney U test for non-normally distributed variables. Logistic regression modeling (enter) was carried out to determine the association between CSF pressure and interventional treatment, and to estimate the odds ratios (ORs) and 95% confidence intervals (CIs), with interventional treatment as the binary dependent variable and CSF pressure as the

independent variable. Further analysis was made to control for potential confounders. Age and sex were included in the model as covariates, along with factor that were significant in univariate analysis, including BMI and papilledema (present/absent). The variance inflation factor was used to evaluate the presence of collinearity, and the goodness of fit of the model was evaluated by using the Nagelkerke's R^2 . Subjects with missing values were excluded from the analysis. A two-tailed p value <0.05 was considered statistically significant.

Data availability

Anonymized data can be made available to qualified investigators on reasonable requests.

Results

Study participants

In total, 159 patents (51 M/108F, mean age 37.3 ± 12.2 years) were screened. After excluding patients without available medical records ($n=1$) or CSF pressure in their medical records ($n=11$), those with secondary causes (brain tumor in 13, CNS infection in 6, cerebral venous thrombosis in 4, and subarachnoid hemorrhage in 1), and those with a CSF pressure of ≤ 200 mm CSF ($n=26$), 102 patients (31 M/71F, mean age 33.4 ± 12.2 years) were included in the analysis (Fig. 1). Ninety-one (89.2%) were initially recruited by neurologists, and 99 (97.1%) had been evaluated by headache specialists. The mean BW and BMI were 76.6 ± 18.9 kg and 29.3 ± 6.4 kg/m², respectively, and 46 (45.1%) patients were obese, i.e., $\text{BMI} \geq 27.5$ kg/m². The mean CSF opening pressure was 282.5 ± 74.5 mm CSF. Headache was the most common symptom, and was present in 92 patients (90.2%). Other clinical manifestations included TVO ($n=26$, 25.5%), pulsatile tinnitus ($n=24$, 23.5%), horizontal diplopia ($n=23$, 22.5%) and metamorphopsia ($n=14$, 13.7%) (Table 1).

Comparisons among different diagnostic criteria

Overall, 80 (78.4%), 55 (53.9%), 51 (50.0%), and 58 (56.9%) fulfilled the ICHD-2 [17], ICHD-3 [19], Friedman [18], and Korsbæk criteria [20], respectively. Patients were subsequently divided into two groups based on the CSF pressure, i.e. 200–250 and >250 mm CSF. For patients in the >250 mm CSF group ($n=62$), all of the patients (100%) met the ICHD-2 criteria, and 47 (75.8%), 55 (88.7%), and 51 (82.3%) fulfilled the ICHD-3, Friedman, and Korsbæk criteria, respectively (Fig. 2). For patients in the 200–250 mm CSF group ($n=40$), 18 (45.0%) met the ICHD-2 criteria, and 19 (47.5%) and 25 (62.5%) could fulfill the ICHD-3 and Friedman criteria, respectively, when the criterion for CSF pressure >250 mm CSF, i.e. criterion B-2 of the ICHD-3 criteria, and criterion E of the Friedman criteria, was neglected. Besides, 7 patients (17.5%) in this group met the Korsbæk criteria.

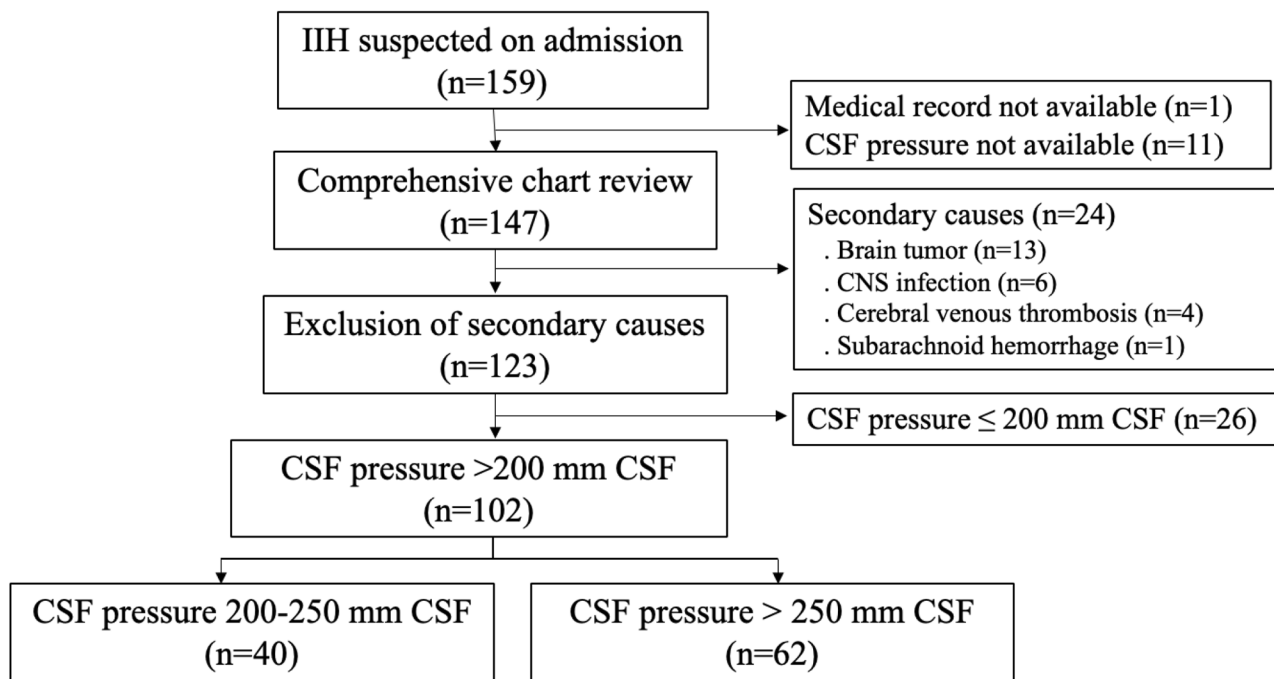


Fig. 1 Patient selection. Abbreviations: CNS = central nervous system, CSF = cerebrospinal fluid, IIH = idiopathic intracranial hypertension

Table 1 Demographics and clinical symptoms

	All patients (n = 102)	CSF pressure > 250 mm CSF (n = 62)	CSF pressure 200–250 mm CSF (n = 40)	p value
Age (years)	33.4 ± 12.2	32.3 ± 11.3	35.1 ± 13.4	0.192
Female	69.6% (71/102)	72.6% (45/62)	65.0% (26/40)	0.416
Body weight (kg)	76.6 ± 18.9	76.4 ± 18.7	77.0 ± 19.5	0.997
BMI (kg/m ²)	29.3 ± 6.4	29.2 ± 6.2	29.6 ± 6.7	0.979
BMI ≥ 30 kg/m ²	34.3% (35/102)	33.9% (21/62)	35.0% (14/40)	0.610
BMI ≥ 27.5 kg/m ²	45.1% (46/102)	45.2% (28/62)	45.0% (18/40)	0.630
Time to diagnosis (months)	10.0 ± 17.1	10.7 ± 18.4	9.0 ± 15.1	0.816
CSF pressure (mm CSF)	282.5 ± 74.5	324.8 ± 68.9	220.0 ± 14.3	<0.001
Headache	90.2% (92/102)	87.1% (54/62)	95.0% (38/40)	0.109
Migrainous phenotype	67.4% (62/92)	66.7% (36/54)	68.4% (26/38)	0.142
Severity (NRS)	8.1 ± 2.1	8.0 ± 2.0	8.2 ± 2.2	0.493
Bilateral	20.6% (21/102)	27.4% (17/62)	10.0% (4/40)	0.010
Exaggerated by lying down	20.6% (21/102)	21.0% (13/62)	20.0% (8/40)	0.716
Awakening from sleep	27.5% (28/102)	30.6% (19/62)	22.5% (9/40)	0.467
Diurnal change	23.5% (24/102)	24.2% (15/62)	22.5% (9/40)	0.682
Induced by Valsalva maneuver	20.6% (21/102)	21.0% (13/62)	20.0% (8/40)	0.886
Visual symptoms				
Metamorphopsia	13.7% (14/102)	19.4% (12/62)	5.0% (2/40)	0.023
TVO	25.5% (26/102)	33.9% (21/62)	12.5% (5/40)	0.005
Horizontal diplopia*	22.5% (23/102)	30.6% (19/62)	10.0% (4/40)	0.006
Pulsatile tinnitus	23.5% (24/102)	29.0% (18/62)	15.0% (6/40)	0.053

Abbreviations: CSF = cerebrospinal fluid, NRS = numerical rating scale, TTH = tension-type headache, TVO = transient visual obscuration

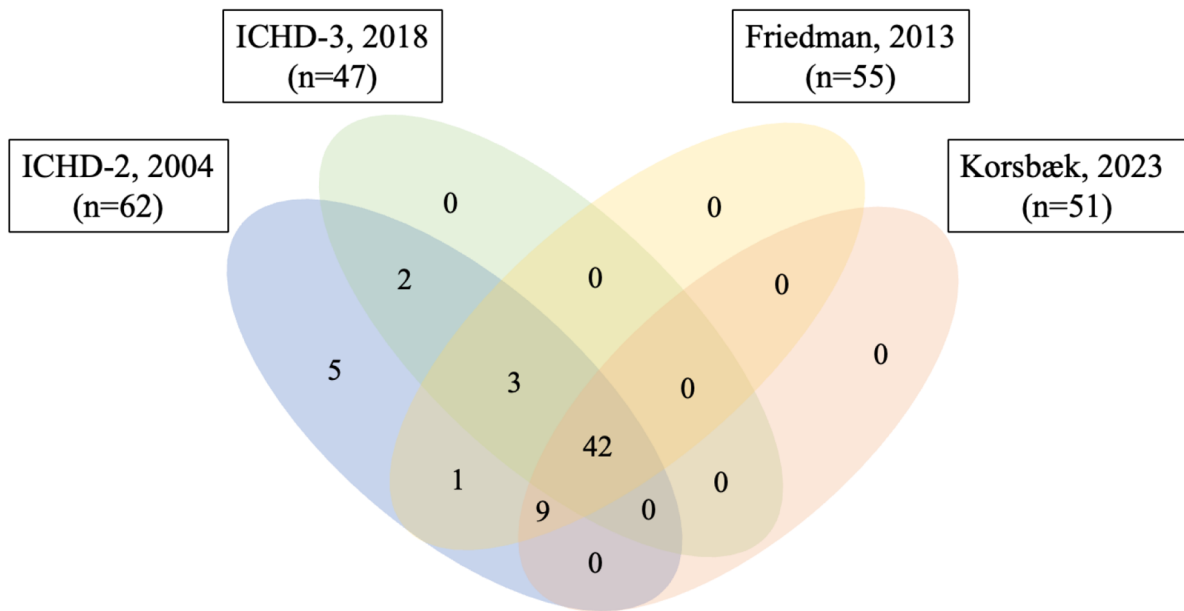
*All of these patients were found to have abducens palsy on neurological examination.

Higher vs. lower CSF pressures: demographics and clinical presentations

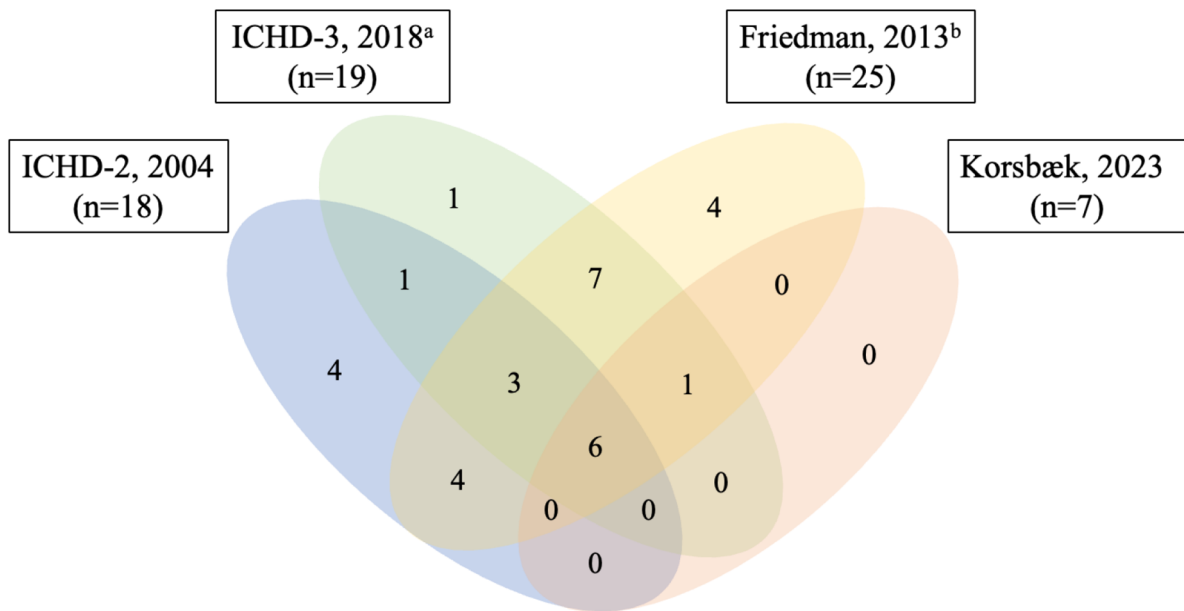
Patients with a CSF pressure > 250 mm CSF were more likely to have bilateral headaches (27.4% vs. 10.0%,

$p=0.010$), TVO (33.9% vs. 12.5%, $p=0.005$), horizontal diplopia (30.6% vs. 10.0%, $p=0.006$), and metamorphopsia (19.4% vs. 5.0%, $p=0.023$) (Table 1), and there was a trend toward a higher percentage of pulsatile tinnitus

A. CSF pressure >250 mm CSF (n=62)



B. CSF pressure 200-250 mm CSF (n=40)



^a Neglecting criterion B-2.

^b Neglecting criterion E.

Fig. 2 The distribution of patients who fulfilled different criteria stratified by CSF pressure

(29.0% vs. 15.0%, $p=0.053$) when compared with those in the 200–250 mm CSF group. However, the demographics, BMIs, the proportions of patients reporting headache (87.1% vs. 95.0%, $p=0.109$), migrainous headache (66.7% vs. 68.4%, $p=0.142$), and the other clinical features were not different between these two groups. All of the patients ($n=23$) who reported horizontal diplopia were found to have abducens palsy on neurological examination.

Higher vs. lower CSF pressures: ophthalmologic examinations

Of the 91 patients who had results of funduscopy documented in their medical records, 57 (62.6%) had papilledema, and the proportions were higher in the >250 mm CSF group (70.7% vs. 48.5%, $p=0.035$) (Table 2). The original photographs of funduscopy were available in 61 patients, including 35 with papilledema (57.4%). Based to the modified Frisén grades (Supplementary table) [34, 35], 12 of the 30 patients (40.0%) in the higher pressure group had grade 0 or 1 papilledema, and all of the 5 patients (100%) in the lower pressure group were categorized as grade 0 or 1. In other words, all of the patients ($n=18$) with papilledema of modified Frisén grade ≥ 2 had CSF pressure >250 mm CSF. The original data of visual field examination were available in 46 patients, including 31 and 15 in the >250 and 200–250 mm CSF groups, respectively. The proportions of patients with visual

field defects (90.3% vs. 86.7%, $p=0.709$) and the patterns of visual field defects ($p=0.378$) were similar between these two groups (Table 2). Besides, the average perimetric MDs were comparable between patients with higher and lower pressures (-6.51 ± 7.58 dB vs. -5.00 ± 6.60 dB, $p=0.697$), and the proportions of patients with visual loss, i.e., average perimetric MD < -2dB, were not different (75.9% vs. 85.7%, $p=0.457$).

Higher vs. lower CSF pressures: MRI features

MRIs were available for review in 89 patients (87.3%), including 66 with magnetic resonance venography (MRV). Patients with a CSF pressure >250 mm CSF had more MRI signs (2.8 ± 1.0 vs. 2.2 ± 1.3 , $p=0.021$) compared with those in the 200–250 mm CSF group (Table 3), and there was a trend toward higher frequencies of empty sella (63.6% vs. 44.1%, $p=0.071$) and flattening of posterior aspect of the globe (72.7% vs. 52.9%, $p=0.057$). Patients with a CSF pressure of >250 mm CSF were more likely to have ≥ 3 imaging signs compared with those in the 200–250 mm CSF group (67.3% vs. 47.1%, $p=0.045$).

Treatment

The use of acetazolamide was more common in the >250 mm CSF group when compared with the 200–250 mm CSF group (59.7% vs. 37.5%, $p=0.023$), and there was a trend toward a higher average dose in those treated

Table 2 Results of ophthalmologic examinations

	All patients	CSF pressure > 250 mm CSF	CSF pressure 200–250 mm CSF	p value
Papilledema	62.6% (57/91)	70.7% (41/58)	48.5% (16/33)	0.035
Modified Frisén grade	($n=35$)	($n=30$)	($n=5$)	0.095
0	17.1% (6/35)	10.0% (3/30)	60.0% (3/5)	
1	31.4% (11/35)	30.0% (9/30)	40.0% (2/5)	
2	5.7% (2/35)	6.67% (2/30)	0% (0/5)	
3	8.6% (3/35)	10.0% (3/30)	0% (0/5)	
4	29.6% (10/35)	33.3% (10/30)	0% (0/5)	
5	8.6% (3/35)	10.0% (3/30)	0% (0/5)	
Modified Frisén grade ≥ 2	51.4% (18/35)	60.0% (18/30)	0% (0/5)	0.006
Presence of VF defect	89.1% (41/46)	90.3% (28/31)	86.7% (13/15)	0.709
Patterns of VF defect				0.378
No visual field defect	10.9% (5/46)	9.7% (3/31)	13.3% (2/15)	
Enlarged blind spot	41.3% (19/46)	41.9% (13/31)	40.0% (6/15)	
Enlarged blind spot with mild general depression	26.1% (12/46)	22.6% (7/31)	33.3% (5/15)	
Enlarged blind spot with moderate general depression	4.3% (2/46)	6.5% (2/31)	0.0% (0/15)	
Severe constriction with only central island preserved	2.2% (1/46)	0.0% (0/31)	6.7% (1/15)	
Total obscuration	4.3% (2/46)	6.5% (2/31)	0.0% (0/15)	
Constriction	2.2% (1/46)	3.2% (1/31)	0.0% (0/15)	
Superior and inferior arcuate defect	6.5% (3/46)	9.7% (3/31)	0.0% (0/15)	
Superior arcuate defect	2.2% (1/46)	0.0% (0/31)	6.7% (1/15)	
Perimetric MD (Humphrey 30–2)	-6.02 ± 7.23 ($n=43$)	-6.51 ± 7.58 ($n=29$)	-5.00 ± 6.60 ($n=14$)	0.697
Visual field loss (MD < -2 dB)	79.1% (34/43)	75.9% (22/29)	85.7% (12/14)	0.457

Abbreviations: CSF=cerebrospinal fluid, MD=mean deviation, VF=visual field

Table 3 Magnetic resonance imaging features

	All patients (n = 89) (MRV n = 66)	CSF pressure > 250 mm CSF (n = 55) (MRV n = 46)	CSF pressure 200–250 mm CSF (n = 34) (MRV n = 20)	p value
MRI features				
Empty sella	56.2% (50/89)	63.6% (35/55)	44.1% (15/34)	0.071
Flattening of the posterior aspect of the globe	65.2% (58/89)	72.7% (40/55)	52.9% (18/34)	0.057
Distention of the perioptic subarachnoid space with or without a tortuous optic nerve	80.9% (72/89)	83.6% (46/55)	76.5% (26/34)	0.302
Transverse sinus stenosis	71.2% (47/66)	71.7% (33/46)	70.0% (14/20)	0.674
No. of MRI signs of IIH				
0	6.7% (6/89)	3.6% (2/55)	11.8% (4/34)	0.141
1	12.4% (11/89)	7.2% (4/55)	20.6% (7/34)	
2	21.3% (19/89)	21.8% (12/55)	20.6% (7/34)	
3	37.1% (33/89)	40.0% (22/55)	32.4% (11/34)	
4	22.5% (20/89)	27.2% (15/55)	14.7% (5/34)	
Average	2.6 ± 1.2	2.8 ± 1.0	2.2 ± 1.3	0.021

Abbreviations: CSF = cerebrospinal fluid, IIH = idiopathic intracranial hypertension, MRI = magnetic resonance imaging, MRV = magnetic resonance venography

Table 4 Factors associated with intervention

Characteristic	Intervention (n = 11)	Conservative treatment (n = 91)	p value
Age (years)	25.2 ± 8.5	34.4 ± 12.2	0.017
Sex	3 M/8F	28 M/63F	0.812
Body weight (kg)	65.5 ± 10.0	77.6 ± 19.2	0.106
BMI (kg/m ²)	24.5 ± 3.4	29.8 ± 6.4	0.035
BMI ≥ 27.5 kg/m ²	18.2% (2/11)	48.4% (44/91)	0.179
Time to diagnosis (months)	3.6 ± 4.0	10.5 ± 17.7	0.307
Headache	90.9% (10/11)	90.1% (82/91)	0.888
Papilledema	90.9% (10/11)	58.8% (47/80)	0.039
Presence of visual field defect	83.3% (5/6)	90.0% (36/40)	0.625
CSF pressure (mm CSF)	402.5 ± 101.2	271.9 ± 62.1	< 0.001

Abbreviations: BMI = body-mass index, CSF = cerebrospinal fluid, VF = visual field

with acetazolamide (789.5 ± 346.5 vs. 616.7 ± 228.9 mg/day, $p=0.057$) in the higher pressure group. On the other hand, the proportions of patients treated with topiramate and the average daily dose of topiramate were similar (data not shown). At six months, the headache outcomes were available in 62 patients, including 38 in the >250 mm CSF group and 24 in the 200–250 mm CSF group. The proportions of patients who developed chronic migraine (CM) were similar between patients in the higher and lower pressure groups (31.6% vs. 25.0%, $p=0.578$).

A total of 11 patients (10.8%) underwent interventions, including ventriculoperitoneal shunting in 3, lumboperitoneal shunting in 6, and stenting for transverse sinus stenosis in 2. Ten of them (90.9%) were in the group of >250 mm CSF. Patients who received interventions were younger (mean age 25.2 ± 8.5 vs. 34.4 ± 12.2 years, $p=0.017$) and had a lower BMI (24.5 ± 3.4 vs. 29.8 ± 6.4 kg/m², $p=0.035$), a higher CSF pressure (402.5 ± 101.2 vs. 271.9 ± 62.1 mm CSF, $p<0.001$), and a higher percentage of papilledema (90.0% vs. 58.8%, $p=0.039$) compared with those treated conservatively (Table 4). However, the

other demographic and clinical features were similar. Surgical intervention was associated with a higher CSF pressure (OR = 1.22 per 10 mm CSF, 95% CI = 1.09–1.33, $p=0.001$), and the finding was consistent after controlling for age, sex, BMI, and the presence of papilledema (OR = 1.17 per 10 mm CSF, 95% CI = 1.01–1.35, $p=0.037$) (VIF < 10 for all variables, Nagelkerke $R^2=0.466$). Of note, patients with missing variables were excluded from the logistic regression modeling, and 80 patients were included in the analysis.

Discussion

In the present study, it was found that IIH in Asians was characterized by lower BMIs, less pronounced female preponderance, and lower frequencies of papilledema and TVO when compared with Caucasian patients. A significant proportion of patients with a CSF pressure of 200–250 mm CSF had classical manifestations of IIH, and could meet commonly used diagnostic criteria for IIH. Although these patients had a less severe phenotype when compared with those in the >250 mm CSF group, the risks of headache or visual field defect were similar.

The findings bring up the issue whether a CSF pressure of >250 mm CSF is the optimum cutoff for a diagnosis of IIH in Asian populations.

One of the most important strengths of the present study is the sample size. More than 100 patients were included, which constituted the largest cohort in Asian populations to date. A larger sample size could give more accurate estimates, and made comparisons between patients with CSF pressures >250 and 200–250 mm CSF feasible. More importantly, data in Asian patients were under-presented in the literature, and there could be concerns whether the current diagnostic criteria and treatment guidelines could be suitable for IIH in Asians [6, 36]. Besides, ophthalmologic findings were re-evaluated in a standardized fashion, and interpretation of MRIs was carried out systemically based on the criteria proposed by Friedman et al. [18] and morphometric parameters reported in the literature [30–33]. In addition, all of the patients had been hospitalized, and secondary causes for IICP were excluded by meticulous diagnostic work-up.

According to the findings of the present study, obesity was less common in Asian IIH patients, and the female predominance was less significant when compared with Caucasian patients. The findings were consistent with the trend observed in prior small-scale studies from Korea ($n=14$) [13], Taiwan ($n=12$) [14], and China ($n=9$) [37]. In those studies, the mean BMI ranged from 25.4 to 29.43 kg/m², and the proportions of patients with obesity, i.e., BMI ≥ 30 kg/m², were between 7.1% and 33.3%. In the present cohort, even in those with a CSF pressure of >250 mm CSF, the mean BMI was 29.2 \pm 6.2 kg/m². Overall, 34.3% had a BMI of ≥ 30 kg/m², and even when a threshold of ≥ 27.5 kg/m² was used [11], only 45.1% were categorized as obese. In comparison, obesity was present in 75.6–85.0% in Caucasian cohorts, and the reported BMIs were between 35.0 and 39.9 kg/m² [8, 29, 38, 39]. In the current study, men constituted 30.4%, which was close to those in other Asian series (35.7–41.7%) [13, 14]. In contrast, there has been a well-known female predominance in IIH, and in some of the largest IIH cohorts from Europe, the United States, Middle East, and North Africa, only 5.1–18.2% of the patients were men [2, 10, 40]. The demographic profile in Asian IIH patients could be different from those in other parts of the world, although further studies are needed to verify our findings.

It was found that ophthalmologic manifestations associated with IIH were less prominent in Asian IIH patients, and IIH without papilledema (IIHWOP) was not uncommon. In the literature, papilledema was seen in 93.1–95.8% in Caucasian and Middle East patients [4, 5, 41], and IIHWOP has been believed to be a relatively rare entity [41, 42]. However, papilledema was present in 62.6% in the current cohort, and it was 70.7% even among those with a CSF pressure of >250 mm CSF. Also,

TVO was less common in Asian patients (32.8% in those with a CSF pressure >250 mm CSF) compared to their Caucasian counterparts (68.0–72%) [2, 16, 43]. Although the frequencies of papilledema and TVO were higher in some Asian studies [13, 14, 37], patients in those studies were recruited by ophthalmologists, and could have papilledema and other visual symptoms as the presenting symptoms which led to the diagnosis of IIH. As IIHWOP constituted nearly 40% of Asian IIH patients, the absence of papilledema could not be used as a reliable indicator to preclude the need for lumbar puncture when other clinical or radiological features suggestive of the diagnosis of IIH are present.

Patients in the >250 mm CSF group had more MRI features typical of IIH, and there were trends toward higher frequencies of empty sella and flattening of the posterior aspect of the globe when compared with those in the 200–250 mm CSF group. In the current study, the proportions of patients with individual MRI signs were mostly within the ranges reported in the literature [20, 31, 33, 44], although distension of the perioptic sub-arachnoid space was more common (80.9%) than in other reports (51.0–69.8%) [20, 31]. The trend that MRI features were more commonly seen in patients with higher CSF pressures is in keeping with the report by Bono et al. [45]. However, the clinical relevance of these MRI features remains an issue of debate [46, 47], and needs to be further clarified.

In the present study, although patients with higher pressures had more severe manifestations, the differences were not huge. In fact, when the criterion on CSF pressure was neglected, a significant proportion of patients in the 200–250 mm CSF group could meet other commonly used diagnostic criteria for IIH, such as the ICHD-3 [19] and Friedman criteria [18]. In other words, they could have clinical presentations indistinguishable from those in classical cases with a CSF pressure of >250 mm CSF. More importantly, the proportions of patients with headache or visual field defect, and the average perimetric MDs in such patients were not only similar to those with CSF pressures >250 mm CSF included in the present study, but also within the ranges reported in the literature [2, 48, 49]. Therefore, for Asian patients with a CSF pressure of 200–250 mm CSF and typical clinical features of IIH, it is not without doubt whether the diagnosis should be excluded based on the ICHD-3 [19] or the Friedman criteria [18] since such patients are still at substantial risks of developing headache and visual complications. Race or ethnicity should be taken into consideration in the evaluation of IIH patients, as clinical decisions based on traditional wisdom might not always be the best strategy. In particular, patients with lower CSF pressures were less likely to receive interventions in the current study. Whether such patients could benefit from a more

aggressive approach in the diagnosis and management deserves further study.

There are some limitations. First, there could be concerns about generalizability, since patients in the present study were recruited from two tertiary medical centers, and only patients who were hospitalized were included in the analysis. However, IIH is a disorder that could lead to significant neurologic or ophthalmologic consequences, and most of the patients would be referred to medical centers for further evaluation and management. On the other hand, it is the common practice in Taiwan that lumbar punctures be done in an inpatient setting, and hospitalization does not necessarily correspond to greater disease severity. Besides, our National Health Insurance system has a ~99% coverage of the citizens in Taiwan, and copayment is generally limited [50]. Therefore, whether patients could be hospitalized was not related to their socioeconomic status. Second, the study participants are mostly ethnic Chinese, whether the findings could be applied to other Asian populations needs to be further confirmed. However, the findings were consistent with those in some small-scale Asian studies [13, 14, 37]. Third, the study involved patients admitted to neurology service, and it is possible that the patient characteristics could be different from those recruited by ophthalmologists. In fact, 89.2% of the current cohort were initially recruited for neurological presentations. Nevertheless, most of our patients were also evaluated by ophthalmologists, and all of the patients fulfilled the modified Dandy's criteria, which are widely used in clinical practice and studies, including the IIHTT [16]. Fourth, data reliability could be another source of bias due to technical or methodological concerns. Because of the retrospective nature of the study, it could not be ascertained whether the CSF pressures were measured in a consistent manner or whether the results could have been influenced by treatment. Besides, there were no predefined protocols or platforms for perimetry and MRI, and the inter-rater reliability of ophthalmologic and radiologic signs has not been formally evaluated. However, 61.8% of the patients were treatment-naïve, the results of fundus photographs and MRIs were interpreted by an experienced neuro-ophthalmologist (H.C.C.) and a senior neuroradiologist (J.F.L.), respectively. Finally, as a retrospective study, some of the data variables were not available in a variable proportion of patients. For instance, digital photographs of optic discs were available in 61 patients only, whether the findings on funduscopy could be consistent in the entire study population is uncertain. Besides, MRV was available for review in 66 patients. Since only patients with TSS on MRV were rated as having that sign, underdiagnosis could be a concern for those in whom MRV was not available. However, the rates of papilledema between the medical record and data from re-evaluation

by a neuro-ophthalmologist were generally consistent (agreement rate=82.0%), which indicates the medical records were reliable to a certain extent. Besides, the rate of papilledema in these patients was close to the estimate of the entire study population.

In conclusion, in this relatively large cohort, it was found that obesity, papilledema, and TVO were less common in Asian IIH patients when compared with Caucasians. Besides, a significant proportion of patients with a CSF pressure of 200–250 mm CSF had clinical and radiologic features typical of IIH, and the risks of having headache or visual field defect were similar to those in the >250 mm CSF group. A threshold of >250 mm CSF could be more specific for the diagnosis, but is at the cost of missing a significant proportion of patients at risk of developing complications. It is possible that a diagnostic cutoff of >200 mm CSF could be more suitable for Asian patients, although further studies are still needed to verify our findings.

Abbreviations

BMI	Body-mass index
BW	Body weight
CM	Chronic migraine
CNS	Central nervous system
CSF	Cerebrospinal fluid
ICHD	International Classification of Headache Disorders
ICHD-2	International Classification of Headache Disorders, Second edition
ICHD-3	International Classification of Headache Disorders, Third edition
IICP	Increased intracranial pressure
IIH	Idiopathic intracranial hypertension
IIHWOP	Idiopathic intracranial hypertension without papilledema
MDs	Mean deviations
MRIs	Magnetic resonance images
MRV	Magnetic resonance venography
NRS	Numerical rating scale
TVO	Transient visual obscuration
VF	Visual field

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s10194-024-01852-w>.

Supplementary Material 1

Author contributions

H.T.H. and Y.F.W. conceived and designed the study, and completed the first draft. H.C.C., T.W.H., Y.S.T., J.F.L., S.P.C., W.T.C., W.J.L., Y.W.P., Y.C.L., J.F.L., S.J.W., and Y.F.W. acquired the data. H.T.H., Y.S.T., and Y.F.W. analyzed the data. H.T.H., H.C.C., S.J.W., and Y.F.W. participated in the discussion and critical revision of the manuscript. The authors have read and approved the manuscript.

Funding

The study was sponsored in part by Taiwan National Science and Technology Council [110-2321-B-010-005, 111-2321-B-A49-004, 111-2314-B-075-086-MY3, 111-2321-B-A49-011, and 112-2321-B-075-007 (to S.J.W.) and 109-2314-B-075-054 and 110-2314-B-075-041-MY3 (to Y.F.W.)], Taiwan Ministry of Health and Welfare [MOHW112-TDU-B-211-144001 (to S.J.W.)], and Taipei Veterans General Hospital [V108C-092, V109C-096, V110C-111, V111C-161, V112C-078, V113C-123, and V112D67-003-MY3 (to Y.F.W.)]; this work was also supported by the Brain Research Center, National Yang Ming Chiao Tung University from The Featured Areas Research Center Program within the framework of the Higher

Education Sprout Project by the Ministry of Education (MOE) in Taiwan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study protocols were approved by the Institutional Review Board of Taipei Veterans General Hospital (TVGH IRB No. 2022-04-005AC, and TCVGH IRB No. CE23493C).

Consent for publication

Not applicable.

Competing interests

W.T.C. has received honoraria as a speaker from Allergan/AbbVie, Hava Bio-Pharma, Orient EuroPharma, Pfizer, and Viatrix. He has received research grants from the Taiwan National Science and Technology Council, and Taipei Veterans General Hospital. S.J.W. has received personal fees as an advisor or speaker from AbbVie, Orient EuroPharma, Pfizer, and Percept; and has been the PI in trials sponsored by Allergan/AbbVie, Lundbeck, Novartis, Pfizer, and Orient EuroPharma. He has received research grants from the Taiwan National Science and Technology Council and Taipei Veterans General Hospital. Y.F.W. has received personal fees as an advisor or a speaker from Allergan/AbbVie, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, Eli Lilly, Hava Bio-Pharma, Lundbeck, Novartis, Orient EuroPharma, Pfizer, Sanofi, Teva, UCB, and Viatrix. He has received research grants from the Taiwan National Science and Technology Council, and Taipei Veterans General Hospital. H.T.H., H.C.C., T.W.H., Y.S.T., J.L.F., S.P.C., W.J.L., Y.W.P., Y.C.L., and J.F.L. reported no relevant disclosure.

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Received: 22 July 2024 / Accepted: 29 August 2024

Published online: 04 September 2024

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