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Differing presenting features of idiopathic intracranial hypertension in the UK and US

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Conflict of interest

The authors declare no conflict of interest.

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Abstract

Demographic factors potentially influencing the presentation and severity of IIH in US vs UK populations include obesity and ethnicity. We aimed to compare the presenting features of IIH between populations in UK and US tertiary referral centres, to assess what population differences exist and whether these cause different presentations and impact on visual function.

Methods

Clinical data were collected on 243 consecutive UK IIH patients and 469 consecutive US IIH patients seen after 2012 in two tertiary centers. Visual function was defined as severe visual loss when HVF-MD was <-15dB, GVF showed constriction or visual acuity was less than 20/200.

Results

US patients were more commonly of self-reported black race (58.9%vs7.1%) than UK patients, but had a similar mean BMI (38.3±0.63 kg/m2 UK vs 37.7±0.42 kg/m2 US; p=0.626). The UK cohort had lower presenting Frisén grade (median 1 vs 2; p<0.001) and severe visual loss less frequently (15.4%vs5%; p=0.014) but there was no difference in mean CSF-OP (35.8±0.88 cmH2O UK vs 36.3±0.52 cmH2O US; p=0.582). African-Americans had poorer visual outcomes compared with US-whites (19.4% vs 10% severe visual loss; p=0.011). Visual function was weakly associated with CSF opening pressure (R^2=0.059; p=0.001), which was similar between UK and US patients.

Conclusions

The UK and the US cohorts had a similar average presenting BMI. However, the worse presenting visual function in the US IIH cohort was partially attributable to differences in the black populations in the two countries.

Introduction

Idiopathic Intracranial Hypertension (IIH) is a rare disease, where there is international acceptance on diagnosis,[1] but until recently less consensus on management.[2, 3] Thus management may vary amongst treatment centres and, in addition, the presenting phenotype may be location-specific.

Demographic factors that potentially influence the phenotype between IIH populations are body mass index (BMI) and ethnicity. IIH is known to have a marked association with those who are obese. In particular truncal fat mass and higher BMI has been associated with more severe visual loss.[4, 5] Obesity affects 30.4% of British women and 38.2% of American women[6] (Table 1). Previous work has identified that those of African-American descent with IIH are more likely than white US IIH patients to have severe visual loss,[7] and 2.81% of the British population identified as black on the latest census data, compared with 13.4% in the US.[8, 9]

IIH incidence is rising in England and worldwide [10 11], presumed to be related to the increasing global prevalence of obesity (Table 1).[11, 12] The rise in CSF shunting procedures in the US between 1998 and 2002, paralleled the rise in obesity rates over that same period.[13] The international prevalence of IIH associates with the prevalence of obesity.[11, 14] However, the proportion of obesity in IIH cohorts may vary independently of the overall population prevalence of obesity (Table 1). Given the differences between the UK and US populations, we aimed to compare two large neuro-ophthalmology IIH clinic cohorts from prospectively held databases in the two countries to assess for differences in the presenting phenotype.

Methods

The study was approved by the University Institutional Review Board at Emory and the local NHS National Research Ethics Committee (14/LO/1208) and conformed to the tenets of the Declaration of Helsinki.

We included consecutive patients over the age of 16 with a diagnosis of IIH, seen in one US and one UK tertiary referral centres. Only patients with a diagnosis of IIH according to the modified Dandy criteria were included [1]: specifically papilledema, normal neurologic examination except cranial nerve palsies, normal neuroimaging, normal CSF constituents and elevated lumbar puncture opening pressure (>25cm CSF). The US cohort was a retrospectively collected cohort of consecutive patients evaluated in a standardised fashion by VB, NN and BB. The UHB cohort was prospectively collected in consecutive patients with a diagnosis of IIH who consented to recruitment in the IIH: Life database.

All patients were evaluated in a standardised manner by experienced neuro-ophthalmologists including complete neuro-ophthalmic history and examination with formal visual fields, fundus photography, neuro-imaging, height and weight. UK data were collected and entered prospectively into the IIH:life database. US data was entered retrospectively from the electronic patient record and written notes.

Data collected included age, race, gender, BMI, recent weight gain, presenting symptoms (headache, tinnitus, diplopia, transient visual obscurations), visual acuity (VA), visual fields (VF), and CSF-opening pressure (CSF-OP).

US patients' fundus images taken at or close to the time of initial presentation were Frisén-graded by 3 different neuro-ophthalmologists, all masked to clinical details. For the UK dataset, 2 different neuro-ophthalmologists performed Frisén-grading on slit lamp examination at presentation [28]. Disagreements were settled by referral to two additional observers. UK patients' disc appearance was graded in clinic at the time of recruitment by two experienced neuro-ophthalmologists. Visual fields were graded as severe visual loss when the Humphrey Visual Field Mean Deviation was <-15 dB or when Goldmann visual fields showed severe constriction.

Patients who reported use of medications that have been associated with intracranial hypertension were excluded (fluoroquinolone and tetracycline antibiotics, cyclosporin, vitamin A preparations, recent steroid discontinuation). Alternative causes for intracranial hypertension were excluded at the time of diagnosis by full blood count checking for anaemia and review of imaging, including venography.

Statistical analysis was performed in SPSS 21 (IBM Corp., Armonk, NY) and used t-test for continuous numeric data and Chi-squared for categorical data except for visual fields and visual acuity data. Because visual fields (MD) and visual acuity had two measurements per patient, they were analysed using generalised estimating equations. To allow model fit, groups with few patients (e.g. transgender, South Asian race) were collapsed and combined. In particular missing race data were combined with white race, because most patients with missing race data were from the UK cohort. To assess systemically the effect of these missing data, the data were also replaced with multiple imputation and pooled analyses are reported. To minimise the risk of type 1 error, we analysed Frisén grading and severe visual field loss analysis, which are non-numeric data, for the worse eye only using Chi-squared tests. Means are reported as mean ± standard error of the mean unless otherwise specified.

Results

Presenting Demographics

Consecutive cohorts of 243 UK patients and 469 US patients presenting for evaluation of IIH after 2012 in two tertiary centers were included. One patient in the UK cohort was not included because she did not consent to inclusion in IIH: Life.

US patients were more commonly of self-reported black race (58.9%vs7.1%; Table 2) and UK patients were more commonly of South Asian descent (8.8%vs1.0%), reflecting the ethnicity of the local populations surrounding the treatment centres.

There was no evidence that the UK and US patients differed in BMI (38.3±0.63 kg/m^2 UK vs 37.7±0.42 kg/m^2 US; p=0.626; 95% CI for the difference -0.8 to 2.1) or in the proportion of obese patients (84.4% UK vs 79.7% US; p=0.147).

The gender proportions were similar between UK and US patients (6% males US vs 4.1% UK; p=0.284).

Visual Function

Compared with US patients (Table 2), the UK cohort had better presenting VA (logMAR 0.09±0.02 vs 0.15±0.02; p<0.001) and mean deviation (-4.74±0.40 vs -6.52±0.35 dB; p<0.001). Frisén grade was also lower in UK patients (median 1 vs 2; p<0.001). Because of the potential for systematic differences in how visual acuity and visual fields are assessed, we also looked at the proportion with severe visual loss, defined as diffusely constricted Goldmann visual fields or a MD<-15dB, as previously described. [16] The US patients were more likely to have severe VF loss at presentation (15.4%vs5%; p=0.014).

There was no evidence of a difference in mean CSF-OP between UK and US patients (35.8±0.73 cmH_2O UK vs 36.3±0.46 cmH_2O US; p=0.582).

History

Among symptomatic US patients, the mean reported duration of symptoms was 10.0±0.64 weeks; equivalent data on symptom duration were not available in the UK cohort. The prevalence of headache as a presenting symptom was higher in UK than US patients (Table 3; 85vs65%; p<0.001). Incidental finding of papilledema on routine examination was also more common in UK than US patients (Table 3; 48%vs30%; p<0.001). About half of the patients reported recent weight gain (54% UK vs 46% US; p=0.236).

Variation in visual function at presentation

When the US and UK datasets were analysed together, Frisén grade and CSF opening pressure were weakly associated (R^2=0.109, p<0.001). CSF opening pressure was available on 539/712 patients (76%) and initial Frisén grade on 288/712 patients (40%). When Frisén grade, CSF opening pressure, race, country, BMI and duration of symptoms were analysed together, CSF opening pressure and the interaction between race and country were independently associated with visual function at presentation (Table 4), assessed as mean deviation (R^2=0.042, p<0.001).

The binary measure of visual function "severe visual loss in either eye" associated with race (p=0.02) and CSF opening pressure (p<0.001), but a model could not be fitted for the interaction term. (p<0.001; GEE binomial logit).

To assess the effect of missing data, multiple imputation of the missing values with pooled analysis of the 10 imputed datasets yielded results consistent with the primary analysis: every 1cmH_2O increase in CSF opening pressure was associated with a 0.168dB reduction in MD (p<0.001) and visual function was worse in African-American than white US patients by an average of 1.60dB (p=0.018), whereas UK African Caribbean visual function was, on average, 3.15dB better than in US white patients (p=0.039).

Race

Within the US cohort, African-American patients had a higher proportion of severe visual loss at presentation (19.4% vs 10%; p=0.011) and a worse mean deviation on visual field testing (-7.38±0.52 vs -5.58±0.49 dB; p=0.003). There was weak evidence of a difference in CSF opening pressure, which was higher in African-American patients (37.69±0.720 cmH_2O vs 34.95±0.794 cmH_2O; p=0.055), though minimal evidence of a difference in Frisén grade (median 3 African American vs 2 white; p=0.205). There was no difference in presenting visual acuity (logMAR 0.14±0.03 white vs logMAR 0.17±0.03 African American; p=0.857). On average white patients had a longer duration of symptoms before presentation (11.5±1.13 weeks vs 9.02±0.75 weeks; p=0.042), but no difference in the proportion of patients with incidentally discovered papilloedema (24.1% African American vs 26.3% white; p=0.624).

There were 8 African Caribbean patients in the UK dataset, who had lower CSF opening pressures (33.4±1.81 vs 39.6±2.11 cmH_2O; p=0.037) and better mean deviations on Humphrey visual field testing (-2.02 dB±0.63 vs -6.02 dB±0.85; p=0.001).

Discussion

This collaborative study compared two large neuro-ophthalmology IIH clinic cohorts from prospectively held databases in the UK and the US and assessed for differences in the presenting phenotype between the two centres. US patients with IIH presented with significantly worse visual function, being more likely to have severe visual loss at presentation. African-American patients in the US cohort had worse visual function than white patients, who had similar baseline features in both the US and UK cohorts.

The more severe disease in African-American patients has been previously reported,[7] and does not seem to be explained by different access to care in our cohort, because duration of symptoms and incidentally discovered papilledema was not different between white and African-American ethnicities. Although duration of symptoms was not available in the UK cohort, there was a higher rate of incidental papilledema compared with the US cohort. The higher prevalence of incidental papilloedema in the UK cohort is in contrast to the higher reported rate of headache in the UK and could be explained by access to care, as greater access to eye examinations may be expected to associate with greater incidental detection of papilloedema. .

Visual function was similar in white US and white UK patients (0.76dB worse in US, p=0.192), in contrast to a previous comparison between white US and white French patients with IIH, [16] which found that white US patients had a longer pre-diagnosis duration of symptoms and were more likely to have visual field constriction and poor visual acuity at presentation.

Table 1 shows a weak relationship between population obesity in the general population and IIIH patients. A recent English paper reports not only an increase in the incidence of IIH between 2002 and 2016, but the association with obesity over this time.[10] In Iowa in 1988, the mean weight in an IIH population was 38% above ideal weight for height (BMI 34.5) and 67% were obese.[29] At that time, 17.5% of the US population was obese. Comparison with the recent IIIH cohorts suggests that the average weight of IIH patients has increased over time in concert with the increased prevalence of obesity in the population. In the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), the

mean initial BMI was much higher, at 39.9, and in this trial recruitment was restricted to mild visual field defects with mean deviations less than 7 dB, although the study did not report the characteristics of patients declining to participate or failing screening.[30]

The US has higher prevalences of both overweight and obesity than the UK (UK 68.6% male and 58.9% female overweight, 26.9% male and 28.6% female obese; US 72.7% male and 63.2% female overweight, 35.5% male and 37% female obese). The similar weights and proportions of obesity between US and UK IIH patients probably reflects that fact that only obese patients suffer from IIH and we do not have data on the average BMI of obese patients in the UK and US. The equivalent average BMI in our US and UK IIH cohorts excludes degree of obesity as an explanatory factor in the more severe presentation of US patients.

Similar to previous studies, most IIH patients were female.[18, 31] In contrast to weight and gender, the racial mix of patients reflects the population local to the treatment centres, suggesting that whilst being African American confers a worse prognosis, it does not affect the risk of disease.

The relationship between Frisén grade and CSF-OP has been previously reported in the IIHTT,[32] although there was no relationship between CSF-OP and baseline visual function in the IIHTT, which may be related to the exclusion of patients with severe visual loss from that population. The association between high CSF-OP and visual loss has not been previously reported except that cases series of patients with fulminant disease have reported high CSF-OP.[33] CSF-OP may affect visual function secondary to the association between Frisén grade and visual function, but does not appear to explain the observed UK-US differences and, with $R^2 < 0.1$, has a modest effect.

Conclusions

Visual loss at presentation was more severe in the US cohort, despite similar BMIs and similar LP pressures. The population differences in presenting visual function may relate to the higher proportion of patients of black race in the US population.

Conflicts

No authors have any conflict of interest with the published work.

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Country	Mean population BMI (kg/m2)	Year	Prevalence of IIH	Incidence of IIH	Mean BMI (kg/m2)
Australia[15]	27.4	‘17	7.9/100,000		
France[16]	25.6	‘88			33
India[17]	21.8	‘07			27.7
Israel[18, 19]	27.4	’01-‘16		0.94	32.2
Italy[14]	26.3	‘04		0.28	
Japan[20]	22.8	‘00	1/1000,000	0.03	only 2 cases
Libya[14]	27.9	‘93		2.2	
Portugal[18]	26.2	‘16			34.8
Spain[21]	26.6	‘15	1.2/100,000		73.77% obese
Sweden[22]	26.4	‘17	1/100,000	0.65	34.4
Switzerland[18]	25.7	‘16			36.4
Turkey[18]	27.9	‘16			31.2
UK[18, 23]	27.5	’91-‘11	10.9/100,000	0.51 - 1.57	39.7
US[14, 16, 24, 25, 26]	29.1	‘98-‘11	8.9/100,000	0.9	31.8-34

Table 1. Population and IIH rates of obesity. Population data from the World Health Organisation[27].

Parameter	UK	US	P value
Black race	7.10%	58.90%	n/a
Proportion with severe visual loss (%)	5	15.4	0.014
HVF mean deviation (dB)	-4.74±0.40	-6.52±0.35	<0.001
CSF Opening pressure (cmH20)	35.8±0.73	36.3±0.46	0.582
Visual acuity (logMAR)	0.085±0.02	0.152±0.01	<0.001
BMI (kg/cm2)	38.3±0.59	37.7±0.41	0.626
Proportion female (%)	95.9±1.8	94.0±1.27	0.284
Frisen grade	1 (IQR 1-2)	2 (IQR 1-3)	<0.001
Age (years)	31.7±0.51	32.8±0.58	0.17

Table 2. Summary of presenting features.

Symptoms	UK proportion (%)	US proportion (%)	p value (Chi squared)
Incidental papilledema	48.1	30.0	<0.001
Headache	85.4	65.0	<0.001
Diplopia	14.6	11.0	0.207
Nausea or vomiting	17.3	7.90	<0.001
Neck or back pain	4.86	2.86	0.208
Pulsatile tinnitus	43.2	17.2	<0.001
Transient visual obscurations	28.1	21.1	0.058
Other visual symptoms	40.0	35.0	.236

Table 3. Presenting symptoms in UK and US IIH patients.

Modelled Comparison	Effect	Effect size (95% CI)	P value
US white vs US black	Worse visual function in African American than white US patients	1.55 dB (0.27-2.83)	0.018
US white vs UK white	Non-significant difference with worse visual function in US white	0.76 dB (-0.38-1.89)	0.192
CSF opening pressure	Higher CSF pressure associated with worse visual function	0.123 dB/cmH_20 (0.05-0.20)	0.001
Race * Country Interaction	UK African Caribbean visual function is better than US white	3.05 dB (0.82-5.29)	0.007

Table 4. Model output for the comparison of race, nationality and CSF opening pressure.