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

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24 The authors declare no conflict of interest.

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33 Abstract

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

38 Methods

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

42 Results

43 US patients were more commonly of self-reported black race (58.9%vs7.1%) than UK patients, but
44 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
45 lower presenting Frisén grade (median 1 vs 2; $p<0.001$) and severe visual loss less frequently
46 (15.4%vs5%; $p=0.014$) but there was no difference in mean CSF-OP (35.8 ± 0.88 cmH₂O UK vs
47 36.3 ± 0.52 cmH₂O US; $p=0.582$). African-Americans had poorer visual outcomes compared with US-
48 whites (19.4% vs 10% severe visual loss; $p=0.011$). Visual function was weakly associated with CSF
49 opening pressure ($R^2=0.059$; $p=0.001$), which was similar between UK and US patients.

50 Conclusions

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

54

55

56 **Introduction**

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

60 Demographic factors that potentially influence the phenotype between IIH populations are body
61 mass index (BMI) and ethnicity. IIH is known to have a marked association with those who are
62 obese. In particular truncal fat mass and higher BMI has been associated with more severe visual
63 loss.^{4,5} Obesity affects 30.4% of British women and 38.2% of American women⁶ (Table 1). Previous
64 work has identified that those of African-American descent with IIH are more likely than white US IIH
65 patients to have severe visual loss,⁷ and 2.81% of the British population identified as black on the
66 latest census data, compared with 13.4% in the US.^{8,9}

67 IIH incidence is rising in England and worldwide^{10,11}, presumed to be related to the increasing global
68 prevalence of obesity (Table 1).^{11,12} The rise in CSF shunting procedures in the US between 1998 and
69 2002, paralleled the rise in obesity rates over that same period.¹³ The international prevalence of IIH
70 associates with the prevalence of obesity.^{11,14} However, the proportion of obesity in IIH cohorts
71 may vary independently of the overall population prevalence of obesity (Table 1). Given the
72 differences between the UK and US populations, we aimed to compare two large neuro-
73 ophthalmology IIH clinic cohorts from prospectively held databases in the two countries to assess for
74 differences in the presenting phenotype.

75

76 **Methods**

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

80 We included consecutive patients over the age of 16 with a diagnosis of IIH, seen in one US and one
81 UK tertiary referral centres. Only patients with a diagnosis of IIH according to the modified Dandy
82 criteria were included¹: specifically papilledema, normal neurologic examination except cranial
83 nerve palsies, normal neuroimaging, normal CSF constituents and elevated lumbar puncture opening
84 pressure (>25cm CSF). The US cohort was a retrospectively collected cohort of consecutive patients
85 evaluated in a standardised fashion by VB, NN and BB. The UHB cohort was prospectively collected
86 in consecutive patients with a diagnosis of IIH who consented to recruitment in the IIH: Life
87 database.

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

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

96 US patients' fundus images taken at or close to the time of initial presentation were Frisén-graded
97 by 3 different neuro-ophthalmologists, all masked to clinical details. For the UK dataset, 2 different
98 neuro-ophthalmologists performed Frisén-grading on slit lamp examination at presentation²⁸.

99 Disagreements were settled by referral to two additional observers. UK patients' disc appearance
100 was graded in clinic at the time of recruitment by two experienced neuro-ophthalmologists. Visual
101 fields were graded as severe visual loss when the Humphrey Visual Field Mean Deviation was <-15
102 dB or when Goldmann visual fields showed severe constriction.

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

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

119 **Results**

120 Presenting Demographics

121 Consecutive cohorts of 243 UK patients and 469 US patients presenting for evaluation of IIH after
122 2012 in two tertiary centers were included. One patient in the UK cohort was not included because
123 she did not consent to inclusion in IIH: Life.

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

127 There was no evidence that the UK and US patients differed in BMI ($38.3 \pm 0.63 \text{ kg/m}^2$ UK vs
128 $37.7 \pm 0.42 \text{ kg/m}^2$ US; $p=0.626$; 95% CI for the difference -0.8 to 2.1) or in the proportion of obese
129 patients (84.4% UK vs 79.7% US; $p=0.147$).

130 The gender proportions were similar between UK and US patients (6% males US vs 4.1% UK;
131 $p=0.284$).

132 Visual Function

133 Compared with US patients (Table 2), the UK cohort had better presenting VA (logMAR 0.09 ± 0.02 vs
134 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
135 also lower in UK patients (median 1 vs 2; $p<0.001$). Because of the potential for systematic
136 differences in how visual acuity and visual fields are assessed, we also looked at the proportion with
137 severe visual loss, defined as diffusely constricted Goldmann visual fields or a MD < -15 dB, as
138 previously described.¹⁶ The US patients were more likely to have severe VF loss at presentation
139 (15.4% vs 5%; $p=0.014$).

140 There was no evidence of a difference in mean CSF-OP between UK and US patients (35.8 ± 0.73
141 cmH_2O UK vs $36.3 \pm 0.46 \text{ cmH}_2\text{O}$ US; $p=0.582$).

142 History

143 Among symptomatic US patients, the mean reported duration of symptoms was 10.0 ± 0.64 weeks;
144 equivalent data on symptom duration were not available in the UK cohort. The prevalence of
145 headache as a presenting symptom was higher in UK than US patients (Table 3; 85 vs 65%; $p<0.001$).
146 Incidental finding of papilledema on routine examination was also more common in UK than US
147 patients (Table 3; 48 vs 30%; $p<0.001$). About half of the patients reported recent weight gain (54%
148 UK vs 46% US; $p=0.236$).

149 Variation in visual function at presentation

150 When the US and UK datasets were analysed together, Frisén grade and CSF opening pressure were
151 weakly associated ($R^2=0.109$, $p<0.001$). CSF opening pressure was available on 539/712 patients
152 (76%) and initial Frisén grade on 288/712 patients (40%). When Frisén grade, CSF opening pressure,
153 race, country, BMI and duration of symptoms were analysed together, CSF opening pressure and the
154 interaction between race and country were independently associated with visual function at
155 presentation (Table 4), assessed as mean deviation ($R^2=0.042$, $p<0.001$).

156

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

160 To assess the effect of missing data, multiple imputation of the missing values with pooled analysis
161 of the 10 imputed datasets yielded results consistent with the primary analysis: every $1\text{cmH}_2\text{O}$
162 increase in CSF opening pressure was associated with a 0.168dB reduction in MD ($p<0.001$) and
163 visual function was worse in African-American than white US patients by an average of 1.60dB
164 ($p=0.018$), whereas UK African Caribbean visual function was, on average, 3.15dB better than in US
165 white patients ($p=0.039$).

166 Race

167 Within the US cohort, African-American patients had a higher proportion of severe visual loss at
168 presentation (19.4% vs 10% ; $p=0.011$) and a worse mean deviation on visual field testing (-7.38 ± 0.52
169 vs $-5.58\pm 0.49\text{ dB}$; $p=0.003$). There was weak evidence of a difference in CSF opening pressure, which
170 was higher in African-American patients ($37.69\pm 0.720\text{ cmH}_2\text{O}$ vs $34.95\pm 0.794\text{ cmH}_2\text{O}$; $p=0.055$),
171 though minimal evidence of a difference in Frisén grade (median 3 African American vs 2 white;
172 $p=0.205$). There was no difference in presenting visual acuity (logMAR 0.14 ± 0.03 white vs logMAR
173 0.17 ± 0.03 African American; $p=0.857$). On average white patients had a longer duration of
174 symptoms before presentation (11.5 ± 1.13 weeks vs 9.02 ± 0.75 weeks; $p=0.042$), but no difference in
175 the proportion of patients with incidentally discovered papilloedema (24.1% African American vs
176 26.3% white; $p=0.624$).

177 There were 8 African Caribbean patients in the UK dataset, who had lower CSF opening pressures
178 (33.4 ± 1.81 vs $39.6\pm 2.11\text{ cmH}_2\text{O}$; $p=0.037$) and better mean deviations on Humphrey visual field
179 testing ($-2.02\text{ dB}\pm 0.63$ vs $-6.02\text{ dB}\pm 0.85$; $p=0.001$).

180 Discussion

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

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

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

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

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

209 The US has higher prevalences of both overweight and obesity than the UK (UK 68.6% male and
210 58.9% female overweight, 26.9% male and 28.6% female obese; US 72.7% male and 63.2% female
211 overweight, 35.5% male and 37% female obese). The similar weights and proportions of obesity
212 between US and UK IIH patients probably reflects that fact that only obese patients suffer from IIH
213 and we do not have data on the average BMI of obese patients in the UK and US. The equivalent
214 average BMI in our US and UK IIH cohorts excludes degree of obesity as an explanatory factor in the
215 more severe presentation of US patients.

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

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

226 **Conclusions**

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

230 **Conflicts**

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

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Country	Mean population BMI (kg/m ²)	Year	Prevalence of IIH	Incidence of IIH	Mean BMI (kg/m ²)
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 Organisation²⁷.

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 (cmH2O)	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 ₂ O (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.