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Idiopathic intracranial hypertension: A comparison between French and North-American white patients

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Abstract

Objective—To compare French and American white patients with idiopathic intracranial hypertension (IIH), and to determine prognostic factors associated with visual loss.

Methods—Medical records of all consecutive white patients with definite IIH seen between 2001 and 2006 in three French tertiary care medical centers and one American tertiary medical center were reviewed. Demographics, associated clinical features, and visual function at presentation and follow-up were collected. French white patients were compared to American white patients.

Results—One hundred and thirty-four patients (66 French, 68 American) were included. American patients were 8.7 times more likely than French patients to have visual acuity 20/60 or worse or visual field constriction (95% CI: 2.1–36.1, $p = 0.0001$). American patients were treated more aggressively than French patients. French patients were older (31 vs. 28 years, $p = 0.02$) and more likely to have anemia (20 vs. 2%, $p < 0.001$). American patients had a longer duration of symptoms prior to diagnosis (12 vs. 4 weeks, $p = 0.01$) and longer follow-up than French patients (26 vs. 11 months, $p = 0.001$). Multivariable analysis found that nationality was an independent risk factor for visual loss. French and American patients did not differ regarding gender proportion, frequency of obesity, sleep apnea, endocrine diseases, or systemic hypertension. Cerebrospinal fluid (CSF) opening pressures were similar in both groups.

Conclusion—American patients with IIH had worse visual outcomes than French patients despite more aggressive treatment. These differences are not explained by differences in previously known risk factors.

Keywords

Idiopathic intracranial; hypertension; Visual loss; Risk factors; Epidemiological studies

Conflicts of interest

S. Mrejen, C. Vignal, B.B. Bruce, R. Gineys, F. Audren, P. Preechawat, A. Gaudric, O. Gout, N.J. Newman, A. Vighetto, M.G. Bousser, and V. Biousse have no conflict of interest to declare.

1. Introduction

Idiopathic intracranial hypertension (IIH) is relatively common in young obese women regardless of ethnic background (Carta et al., 2004; Celebisoy et al., 2002; Craig et al., 2001; Deschamps et al., 2008; Durcan et al., 1988; Mezaal and Saadah, 2005; Radhakrishnan et al., 1993a; Radhakrishnan et al., 1986). Prognosis is variable, but severe visual loss occurs in 10 to 25% of patients (Corbett et al., 1982; Wall and George, 1991). Few studies of IIH have been performed in Europe (Carta et al., 2004; Craig et al., 2001), and no series has attempted to directly compare international differences in IIH. The purpose of the study was to compare the characteristics of white French and American IIH patients.

2. Patients and methods

This study included consecutive IIH patients from three academic French neuro-ophthalmology services seen between 2001 and 2006. Consecutive patients seen from a similar medical center in the United States during the same time period were also included. Only patients with definite IIH diagnosed according to the modified Dandy criteria were included (Friedman and Jacobson, 2002):

- signs and symptoms of increased intracranial pressure;
- no localizing signs except abducens nerve palsy;
- cerebrospinal fluid (CSF) opening pressure of at least 25 cmH₂O with normal CSF composition;
- normal neuroimaging (ruling out venous sinus thrombosis).

In addition, only patients with detailed clinical data and follow-up were included.

Although the study was retrospective, all patients had been evaluated in a standardized fashion by four experienced neuro-ophthalmologists (V.B. and N.N. in the United States, A.V. and C.V. in France), including documentation of body habitus, blood pressure, recording of factors associated with IIH, complete neuro-ophthalmic examination with ocular fundus examination, formal visual fields, and review of neuroimaging tests.

Demographic information regarding age, gender, and race were collected. Medication use (current and recent), the presence or absence of several associated factors (recent weight gain, known sleep apnea, iron deficiency anemia [hemoglobin below 12 g/dL], medical diagnosis of systemic hypertension, endocrine disorders, pregnancy, symptoms of raised intracranial pressure [headaches, tinnitus, diplopia, and transient visual obscurations], Snellen visual acuity, formal visual field [Humphrey automated perimetry, Metrovision automated perimetry, or Goldmann perimetry], and optic nerve appearance were recorded. Contributing medications included vitamin A preparations, cyclosporine, tetracycline, and recent discontinuation of steroids. The contributing medications were analyzed by their presence or absence for each patient. Degree of obesity was determined by the body mass index (BMI). Prediagnosis duration of symptoms, CSF opening pressure, height, weight, medical treatments, surgical treatments, follow-up duration, and visual outcome were also recorded.

Snellen visual acuity was converted to logMAR visual acuity for analysis. Formal visual fields were systematically reviewed for all patients. LogMAR visual acuity 0.5 or worse (equivalent to Snellen visual acuity 20/60 or worse) was considered impaired visual acuity. Automated visual field mean deviations were recorded. All visual field defects (both automated perimetry and Goldmann) were graded on a 0 to 3 scale as:

- 0: normal;
- 1: enlargement of the blind spot;
- 2: nasal or temporal defect (Fig. 1);
- 3: diffusely constricted (Fig. 2).

Papilledema was graded with the Frisen staging scheme (Frisen, 1982) in which stage 0 defines a normal optic nerve head and stage 5 a severe papilledema. Firstly, because of differences in visual field testing between France (primarily Goldmann type) and the United States (primarily Humphrey type) and, secondly, because these techniques may have different sensitivities for relative visual field defects, only the rates of severe visual field constriction were compared in statistical analysis. An average of each patient's eyes' LogMAR visual acuity, visual field grade, and papilledema stage were used for analysis.

Race was assessed by the judgment of the examiner based on patient appearance. Due to the underlying demographics of the local catchment areas 8.5% (6/70) of identified French patients were black while 47% (61/129) of American patients were black. Because American black patients have been shown to have a worse prognosis than American white patients with IIH (Bruce et al., 2008), we only compared white IIH patients in the present study.

All patients had definite IIH by the modified Dandy criteria, but two aspects of our population deserve further mention. Although all patients received a lumbar puncture with documented elevation of CSF opening pressure, the specific value was sometimes unavailable. Clinically appropriate neuroimaging was available or performed for all patients to rule out cerebral venous thrombosis. However, as the patient population is representative of an actual clinical practice, there were occasionally practical limitations to obtaining ideal imaging studies, such as body habitus preventing entry into imaging gantries and changes in the clinical usage of MRI and MR venography over the study period (Biousse et al., 1999). MRIs were all reviewed at the time of diagnosis and MR venography or CT venography were obtained when there was a doubt regarding possible cerebral venous thrombosis. The patients, who could not have a MRI, had a head CT with contrast, often associated with CT venography.

Statistical analysis was performed using Statview software (1998, SAS Institute Inc., USA). Continuous and ordinal variables were compared between groups using the Mann-Whitney *U*-test. Chi-square with Fisher's exact test was used to compare the frequency distribution of categorical variables between groups. These tests were two-tailed, and significance was set at 5%. Univariate analyses for country were undertaken. A multivariate logistic regression analysis was performed with the outcome of logMAR visual acuity 0.5 or worse or visual field grade of 3 or greater. Country, age, anemia, prediagnosis duration of symptoms, headache as first sign of IIH, tinnitus as first sign of IIH, and follow-up duration were included as predictors.

3. Results

One hundred and thirty-four consecutive white patients with definite IIH were included, 68 from the US at Emory University, and 66 from France (38 from Paris [16 from the Lariboisière Hospital and 22 from the Rothschild Ophthalmologic Foundation], and 28 from Lyon).

Table 1 compares the characteristics of French white patients versus American white patients. French white patients were older than American patients (median: 31 years vs 28

years, $p = 0.02$). Anemia was more common in the French patients (20% vs 2%, $p < 0.001$). There were no differences in the frequency of obesity, sleep apnea, hypertension, pre-disposing medications, endocrine disorders, pregnancy, symptoms other than headache, or CSF opening pressure.

Headaches were reported more frequently by American than French IIH patients (90% vs 71%, $p = 0.007$). Median prediagnosis duration was shorter for French patients (4 weeks vs 12 weeks, $p = 0.01$). Median follow-up was longer for American patients (26 months vs 11 months, $p = 0.001$).

At initial evaluation, 23% of American patients and 9% of French patients had visual acuity 20/60 or worse, nearly meeting our statistical significance threshold ($p = 0.051$). At last follow-up, American patients were significantly more likely to have visual acuity 20/60 or worse (18% vs 3%, $p = 0.009$). At initial visit, 23% of American patients versus 3% of French patients had diffuse visual field constriction ($p = 0.001$); this difference remained at last follow-up (15% vs 2%, $p = 0.009$). Median initial papilledema grade was worse in French than American patients at initial evaluation (3.5 vs 3.0, $p < 0.001$) and, although it improved in both groups, remained worse in French patients at last follow-up, although it was no longer significant (0.5 vs 0.0, $p = 0.08$). American patients were 8.7 times more likely than French patients to experience visual acuity 20/60 or worse or diffuse visual field constriction (95% CI: 2.1–36.1, $p = 0.0001$).

Regarding treatment, medication use (80% vs 94%, $p = 0.02$), and weight loss with dietary changes (21% vs 38%, $p = 0.01$) were less frequent in French than American patients. Repeat lumbar punctures (median: 1 vs 2, $p = 0.003$), and CSF shunting procedures (3% vs 25%, $p < 0.001$) were less frequent in French than American white patients. Repeat CSF shunting procedures (0% vs 9%, $p = 0.03$) and optic nerve sheath fenestration (0% vs 9%, $p = 0.03$) were only performed in American patients.

Nationality remained an independent risk factor for visual acuity 20/60 or worse or diffuse visual field constriction when adjusted for age, anemia, prediagnosis duration of symptoms, headache as first sign of IIH, tinnitus as first sign of IIH, and follow-up duration (adjusted odds ratio: 34.6, $p = 0.005$ vs unadjusted odds ratio: 11.5, $p = 0.001$); none of the other remaining factors were significant.

4. Discussion

Our study describes a large, international cohort, including 66 French and 68 American patients with IIH. This is the largest European series of IIH patients, and this study also provides evidence of important international differences in the presentation and prognosis of IIH.

Our most important finding was that American patients tended to have worse visual outcomes than French patients despite more aggressive treatment. American patients had more severe visual field defects at presentation. Although both the American and French populations improved with treatment, visual fields remained more severely affected in American patients at last follow-up. Visual acuity was also impaired more frequently in American than French patients. These worse visual outcomes occurred in American patients despite more aggressive treatments of all types: medication, weight management, lumbar puncture, nerve sheath fenestrations, and CSF shunting procedures. American patients had longer median follow-up than the French patients as would be expected given their more severe disease course and greater degree of intervention.

Since the outcomes did not appear to be related to management, we explored other factors that could account for outcome differences we observed between the French and American patients with IIH. We found that French patients were older and 10 times more likely to have anemia than American patients. This was surprising because prior studies have associated these two factors with worse visual outcomes in IIH (Biousse et al., 2003; Orcutt et al., 1984). However, our multivariable analysis did not find a significant influence of these factors on differences in visual outcomes between the countries. Other factors that have previously been associated with visual loss were not found to be different in our populations, including degree of obesity, hypertension, recent weight gain, race, CSF opening pressure, and sleep apnea (Bruce et al., 2008; Corbett et al., 1982; Digre and Corbett, 1988; Galvin and Van Stavern, 2004; Lee et al., 2002; Radhakrishnan et al., 1993b; Wall and George, 1991).

Regarding symptoms, American patients were more likely to report headache. Although one might expect that symptoms such as headache would lead to earlier diagnosis, instead, the prediagnosis duration of symptoms was significantly shorter in the French patients (4 weeks vs 12 weeks, $p = 0.01$). A possible conclusion, and major concern, is that ophthalmoscopic examinations may not be routinely performed on headache patients in the United States. In addition, lower degrees of papilledema could explain a longer prediagnosis duration in American IIH patients. The relationship between visual loss and delayed diagnosis in IIH is an important consideration because visual loss in IIH is typically insidious and patients may not be aware until a considerable amount of vision has already been lost. Thus, we could theorize that this difference might account for the significant visual impairment American patients had at presentation compared with French patients. However, pre-diagnosis duration of symptoms was not found to be significantly related to visual loss in the present or in previous studies (Bruce et al., 2008; Radhakrishnan et al., 1993b), and logistic regression analysis showed that prediagnosis duration of symptoms did not account for the differences in visual outcome between countries. Alternate explanations for the disparity in time to diagnosis from first symptom could include differences in health care access, referral, and delivery between the two countries.

Notably, French patients had more severe papilledema than American patients. This was a particularly surprising finding because papilledema is the presumed mechanism of visual loss in IIH and higher degrees of papilledema have been associated with worse visual outcomes in IIH (Mulholland et al., 1998; Wall and White, 1998). However, in chronic papilledema, when severe vision loss may have occurred, secondary optic atrophy may ironically reduce the amount of optic nerve swelling. Furthermore, due to the retrospective nature of the study, fundus photographs were not available on all patients to allow a single reviewer to rate both the French and American patients' degree of papilledema. Thus, this may not reflect a true difference, but interrater differences in papilledema grading. However, interrater differences could not explain everything because there were also different raters in France (between Lyon and Paris).

We acknowledge other limitations of our study. It is obviously impossible for us to precisely identify the patients' origin in this retrospective study. Patients' race was determined based on the patient's appearance at initial evaluation. Given the fact that all American patients were white (i.e., Caucasian), and therefore were originally mostly from Europe, it is possible that the main difference observed between the two populations may result from environmental factors rather than genetic background.

One concern that is particularly relevant is referral bias. Although this study only consisted of patients seen in similar tertiary, academic medical centers, differences exist that may have influenced study outcomes.

Nevertheless, it seems very unlikely that referral bias could fully account for the differences seen between French and American IIH patients. Therefore, American patients may have a more aggressive disease course than French patients. Furthermore, these differences do not appear to be accounted for by known risk factors, and suggest that other etiologic and prognostic factors likely remain yet undiscovered in IIH.

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Fig. 1.
Goldmann perimetry (B) right eye and (A) left eye: bilateral enlarged blind spot and nasal inferior defect (stage 2).

Fig. 2.
Humphrey automated perimetry (SITA standard 30-2) (B) right eye and (A) left eye: diffuse constriction more severe on the left than on the right eye (stage 3).

Table 1

Demographics, risk factors, cerebrospinal fluid (CSF) opening pressure, symptoms, visual function, and treatment of French and North-American white patients with idiopathic intracranial hypertension (IIH)

	France (<i>n</i> = 66)			United States (<i>n</i> = 68)		
	<i>n</i> or median	% or range		<i>n</i> or median	% or range	<i>p</i> value*
Demographics/risk factors						
Age (years)	31	(15–64)	28	(10–49)	0.02	
Gender (M/F)	7/59	(11%/89%)	6/62	(9%/91%)	0.73	
Contributing medications	6	(9%)	7	(10%)	0.81	
Sleep apnea	3	(5%)	4	(6%)	1.00	
Anemia	13	(20%)	1	(2%)	< 0.001	
Pregnancy	4	(6%)	2	(3%)	0.44	
Endocrine disorder	8	(12%)	7	(10%)	0.74	
Hypertension	13	(20%)	7	(10%)	0.13	
Predagnosis duration of symptoms (wks, <i>n</i> = 119)	4	(0–52)	12	(0–200)	0.01	
Follow-up duration (months, <i>n</i> = 134)	11	(1–77)	26	(2–216)	0.001	
CSF opening pressure (cm CSF, <i>n</i> = 117)	32	(25–61)	34	(25–60)	0.13	
Weight						
Body mass index (BMI), first visit	33	(22–57)	34	(19–61)	0.89	
Recent gain weight present	25	(38%)	19	(28%)	0.22	
Amount of recent weight gain weight ^a (<i>n</i> = 39)	26%	(5–83)	20%	(3–79)	0.82	
BMI, last visit (<i>n</i> = 121)	32	(22–57)	31	(19–55)	0.88	
Treatment						
Medication use	53	(80%)	64	(94%)	0.02	
Weight loss with diet modification	14	(21%)	26	(38%)	0.04	
Weight loss with surgery	2	(3%)	5	(7%)	0.44	
Number of lumbar punctures (<i>n</i> = 130)	1	(1–4)	2	(1–20)	0.003	
CSF shunt	2	(3%)	17	(25%)	< 0.001	
Repeat CSF shunt	0	(0%)	6	(9%)	0.03	
Optic nerve sheath fenestration	0	(0%)	6	(9%)	0.03	
Symptoms						

	France (<i>n</i> = 66)		United States (<i>n</i> = 68)		<i>p</i> value [*]
	<i>n</i> or median	% or range	<i>n</i> or median	% or range	
Headaches	47	(71%)	61	(90%)	0.007
Tinnitus	27	(41%)	36	(53%)	0.16
Transient visual obscurations	25	(38%)	20	(29%)	0.30
Diplopia	16	(24%)	15	(22%)	0.76
Examination					
Papilledema, first visit (<i>n</i> = 123)	3.5	(0.5–5)	3.0	(0–5)	< 0.001
Papilledema, last visit	0.5	(0–3.5)	0.0	(0–3)	0.08
Visual field constriction, first visit (<i>n</i> = 117)	2	(3%)	12	(23%)	0.001
Visual field constriction, last visit	1	(2%)	10	(15%)	0.009
VA 20/60 or worse, first visit (<i>n</i> = 127)	6	(9%)	14	(23%)	0.051
VA 20/60 or worse, last visit	2	(3%)	12	(18%)	0.009

Values set in bold are statistically significant.

^{*} *p*: statistical comparisons between French and North-American white patients.

^a In % of initial weight. *n* = 134 unless otherwise noted. M: male; F: female; wks: weeks; VA: visual acuity.