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Risk factors for idiopathic intracranial hypertension in men: A case–control study

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ABSTRACT

Objective: To identify risk factors for idiopathic intracranial hypertension (IIH) in men.
Design: Case–control study. A 96-item telephone questionnaire, answered retrospectively, with cases recalling at the age of their diagnosis and controls recalling at the age of their corresponding case's diagnosis.
Setting: Outpatient clinics in two US tertiary care centers.
Participants: The characteristics of 24 men with IIH were compared to those of 48 controls matched for sex, age, race, and World Health Organization body mass index (BMI) category.
Main outcome measures: Two previously validated questionnaires: the ADAM (Androgen Deficiency in Aging Males) questionnaire for testosterone deficiency and the Berlin questionnaire for obstructive sleep apnea (OSA), embedded within the telephone questionnaire. Analysis with Mantel–Haenszel odds ratios and mixed-effects logistic regression models accounted for matching.
Results: Cases and controls had similar enrollment matching characteristics. Although matching was successful by BMI category, there was a small difference between BMI values of cases and controls (cases: median 31.7, controls: median 29.9; $p=0.03$). After adjustment by BMI value, men with IIH were significantly more likely than controls to have a positive ADAM questionnaire for testosterone deficiency (OR: 17.4, 95% CI: 5.6–54.5; $p<0.001$) and significantly more likely to have either a positive Berlin questionnaire for OSA or history of diagnosed OSA (OR: 4.4, 95% CI: 1.5–12.9; $p=0.03$).
Conclusions: Men with IIH are more likely than controls to have symptoms associated with testosterone deficiency and OSA. These associations suggest a possible role for sex hormones and OSA in the pathogenesis of IIH in men.

1. Introduction

Idiopathic intracranial hypertension (IIH) predominantly occurs in young obese women [1–4], but about 9% of cases occur in men [5,6]. Although prognosis in IIH is variable, severe visual loss is more than twice as likely to occur in men as in women [6]. The pathophysiology of IIH remains unknown, but obesity, hormonal abnormalities, and obstructive sleep apnea (OSA) have been proposed as risk factors for the development of IIH in men [6–10]. The aim of our study was to identify risk factors for IIH in men through a case–control study.

The likely role of sex hormones in the pathogenesis of IIH is highlighted by the clear predilection of IIH for postpubertal, premenopausal women [11] and the absence of a gender preference before puberty [12–14]. Although female adulthood is characterized by high levels of estrogen and low levels of testosterone, women taking exogenous estrogens, such as oral contraceptives, and women who have high estrogen levels due to pregnancy seem not to be at higher risk for the development of IIH [11,15,16]. If, instead, low testosterone is implicated in IIH, it is possible that men with IIH may have lower testosterone levels than men in the general population, making them more similar hormonally to the young women usually affected by IIH.

The ADAM (Androgen Deficiency in Aging Males) questionnaire is a non-invasive, validated, 10-point survey used to screen for androgen (bioavailable testosterone) deficiency in aging males that can be administered by telephone [17]. A positive questionnaire defines a

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symptom complex associated with testosterone deficiency (hypogonadism) with a sensitivity of 88% and a specificity of 60%. Since the development of the ADAM questionnaire for testosterone deficiency in 2000, no other instruments have been superior in their correlation with biological confirmatory tests [18].

Similarly, the Berlin questionnaire for OSA was designed and validated as an easy-to-use instrument for identifying patients with OSA in the community setting [19]. A "high-risk" score on the Berlin questionnaire has a sensitivity of 86% and specificity of 77% for a sleep study diagnosis of OSA. For the purposes of this study, we used a positive Berlin questionnaire or known sleep study-diagnosed OSA (hereafter abbreviated as "BOSA") as a surrogate for the gold standard of a positive sleep study for use in estimating the prevalence of OSA among study subjects.

2. Methods

2.1. Cases

All consecutive charts for adult male patients (aged 18 or older) with a diagnosis of IIH seen by the neuro-ophthalmology services at Emory University between 1989 and 2008 and Rush University between 2005 and 2008 were reviewed. Only patients with definite IIH diagnosed according to the modified Dandy criteria were included: 1) signs and symptoms of increased intracranial pressure; 2) no localizing signs except abducens nerve palsy; 3) CSF opening pressure ≥25 cm of water with normal CSF composition; and 4) normal neuroimaging (ruling out venous sinus thrombosis) [20].

Twenty patients were enrolled from Emory University and four from Rush University. Fourteen of the twenty cases enrolled at Emory University were reported previously [6]. All patients were evaluated in the standardized fashion described in that report by experienced neuro-ophthalmologists [6]. Documentation included age, race, body habitus, blood pressure, and complete neuro-ophthalmic examination with formal visual fields, fundus photography, review of neuroimaging tests, and recording of factors associated with IIH. Of the 39 consecutive adult men found in our databases, 7 patients could not be located, and a search of the Social Security Administration's public Death Master File identified 4 additional patients who had died since their last clinic visit. Therefore, 28 patients were contacted by telephone for consent, and 4 refused to participate in the study. Informed telephone consent, as approved by our institutional review boards, was obtained from the remaining 24 cases. Demographic information regarding age, race, height, weight, and age at diagnosis of IIH was collected; in the few situations in which exact height and weight were not documented, cases were asked on the telephone to recollect their height and weight at their time of diagnosis. Degree of obesity was graded by body mass index (BMI) according to five categories corresponding to World Health Organization BMI cutoff points: underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9), obese (30.0–39.9), or morbidly obese (≥40.0). Race was assessed according to the judgment of the examiner based on patient appearance.

2.2. Controls

Each man with IIH was matched with two age-, race-, and BMI-matched control men. Control subjects were selected from male friends and family members accompanying adult non-IIH patients to the Emory Eye Center outpatient clinics and were enrolled if they were of the same race, age (within 5 years), and World Health Organization (WHO) BMI category as a corresponding case. Controls were excluded if they had a history of CNS disease or had ever consulted a neurologist or a neurosurgeon for intracranial disease. Informed written consent was obtained in the clinic, but the interview was conducted by telephone at a later date, similar to men with IIH.

2.3. Data collection

A 10–15 minute-long telephone-administered questionnaire, consisting of 96 items, was developed for use with both cases and controls (see Supplemental material). The questionnaire included questions about age, height, weight, past medical history, patterns of obesity, endocrine disorders (e.g. diabetes, thyroid dysfunction), sexual and reproductive health (e.g., difficulty achieving orgasm), fertility (e.g., number of biological children, history of difficulty having children), medication and substance use (e.g., tetracyclines, lithium, vitamin A preparations, spironolactone, marijuana). In addition, it incorporated the two previously validated question batteries described above: the ADAM questionnaire for testosterone deficiency [17] and the Berlin questionnaire for OSA [19].

Each subject was assigned an "index age". For cases, this index age was their age at the time of diagnosis with IIH; for controls, this index age was their age at the time of their corresponding case's diagnosis with IIH. Every subject was interviewed by telephone in a uniform fashion by the same examiner (J.A.F.) using a standardized script. All subjects were asked to answer the questionnaire retrospectively, thinking back to their health at their index age. To minimize recall bias, cases were not reminded that their index age was also their age of diagnosis with IIH. The questionnaire and study design were approved by the two participating universities' institutional review boards.

2.4. Statistical analysis

The ADAM questionnaire and BOSA status were decided *a priori* to be the primary outcome measures for the study. Bonferroni correction was applied to the statistical tests for the other 21 associations studied. Statistical analysis was performed with R: a language and environment for statistical computing (R Foundation for Statistical Computing, http://www.R-project.org). Univariate analysis was performed on data collected through summary measures, including medians and ranges for skewed data, and proportions for categorical variables. Mantel–Haenszel odds ratios were used as the measure of association, and between-group comparisons were performed using paired *t*-tests and Cochran–Mantel–Haenszel χ^2 tests as appropriate. Mixed-effects logistic regression models were used to examine associations of risk factors with case status, accounting for matching and adjusting for other variables.

3. Results

Twenty-four male patients with IIH and 48 age, race, and BMI category-matched control men were enrolled in the study (Table 1). There was no evidence of inexact matching between cases and controls based on the enrollment criteria. Age was not significantly different at enrollment, with a median case age of 37.5 years (range:

Table 1
Characteristics of the study subjects at index age.

Variable	Cases ($n=24$)		Controls ($n=48$)		*p*-value
	n or median	% or range	*n* or median	% or range	
Age, years	34.0	18–58	35.0	18–58	0.81
Black	7	29.2	14	29.2	1.00
BMI, kg/m^2	31.7	22.8–53.9	29.9	20.41–47.5	0.03
Positive ADAM	19	79.2	10	20.8	<0.001
Positive BOSA	18	75.0	20	41.7	0.002
Vitamin A use	2	8.3	4	8.3	1.00
Tetracycline use	3	12.5	5	10.4	1.00
Lithium use	1	4.2	1	2.1	1.00

ADAM = positive ADAM (Androgen Deficiency in Aging Males) questionnaire for testosterone deficiency.
BOSA = positive Berlin questionnaire for obstructive sleep apnea, or sleep study-diagnosed obstructive sleep apnea.