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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.

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Keywords

idiopathic intracranial hypertension; gender differences; androgen deficiency; sleep apnea; risk factors; neuro-ophthalmology

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 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.

Methods

Cases

All consecutive charts for adult male patients (age 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 ≥25cm 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.

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 Emory Eye Center outpatient clinics and were enrolled if they were 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, similarly to men with IIH.

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.

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.

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: 19-60 years) and a median control age of 39 years (range: 19-63 years) (p=0.42). BMI matching was successful by WHO category and numerical BMI values did not differ at enrollment between cases and controls (cases: median 32.9 [range: 23.7-53.5], controls: median 30.8 [range: 20.8-55.6]; p=0.21); however, there was a small difference between numerical BMI values of cases and controls at their index age (cases: median 31.7 [range: 22.8-53.9], controls: median 29.9 [range: 20.1-47.5]; p=0.03).

In univariate analysis, the Mantel-Haenszel odds ratio for a positive ADAM questionnaire was infinite (95% confidence interval: 5.685-infinity; p<0.001) for cases compared to controls. This value occurred because there were no case-control sets in which a control had a positive ADAM questionnaire and the corresponding case did not, resulting in division by zero in the Mantel-Haenzel odds ratio calculation. The Mantel-Haenszel odds ratio for a positive BOSA was 13.9 (95% confidence interval: 1.9-609; p=0.002) for cases compared to controls.

No past medical conditions, medications, or illicit substances were significantly associated with IIH in univariate analysis. The self-reported distributions of body fat (“belly” versus “thighs”) and body hair were not factors significantly associated with IIH in men. There was a trend toward difficulty achieving orgasm being significantly associated with IIH, with an odds ratio of 7.0 (95% confidence interval before Bonferroni correction: 1.33-69; after correction: 0.65-342; p=0.084).

Mixed-effects logistic regression was used to adjust for BMI at index age (Table 2). There was no significant interaction between positive ADAM questionnaire and positive BOSA. To assess for confounding between positive ADAM questionnaire and positive BOSA, a model including both of these predictors and adjusted for BMI was evaluated. Under this model, the adjusted odds ratio was 16.4 for a positive ADAM questionnaire (95% confidence interval: 5.0-52.5; p<0.001) and 4.0 for a positive BOSA (95% confidence interval: 0.90-5.1; p=0.087), suggesting there was no significant confounding between ADAM and BOSA status.

Discussion

Although our study is not the first case-control study to evaluate the risk factors for IIH in men, [5,21] it is the first study to compare men with IIH to a well-defined population of normal control subjects matched for sex, age, race, and BMI category – each of which independently modifies the risk of IIH.[1,11,22]

Our study found that a positive ADAM questionnaire and a positive BOSA were both strongly associated with IIH in men. Men with IIH had more than 17 times the odds of a positive ADAM questionnaire compared to controls, suggesting a possible association between testosterone

deficiency and IIH. Men with IIH were also found (with borderline significance) to be more likely to report difficulty achieving orgasm which, although not part of the ADAM questionnaire, is a recognized symptom of testosterone insufficiency.[23]

We recognize that the ADAM questionnaire, although useful as a screening questionnaire for testosterone deficiency, is not a substitute for biochemical measurement of testosterone levels; furthermore, it is unclear to what extent the symptoms of IIH could mimic symptoms of testosterone deficiency. It is also unclear to what extent the presence of a chronic illness like IIH, in itself, could lead to similar ADAM questionnaire responses, the ADAM questionnaire having been validated only in a presumably healthy population of 316 physicians. Nevertheless, no other clinical instrument has proven superior to the ADAM questionnaire in its correlation with biochemical evidence of hypogonadism,[18] and other non-invasive alternatives to serum measurements are lacking. One unpublished study did find low testosterone levels in seven of eight (87.5%) men with IIH; however, these men were not compared to controls matched by age and obesity, and because both of these factors influence testosterone levels, it could not be concluded that the testosterone deficiency was related to IIH.[24]

If the positive ADAM score in men with IIH truly represents hypogonadism, it is not known whether this is a cause, an effect, or a comorbidity of IIH. An association between hypogonadism and IIH may be mediated by the effect of low testosterone levels on body fat distribution in men. Testosterone has long been known to contribute to the sex-specific fat distribution differences seen between men and women, with men having twice as much visceral (intra-abdominal) adipose tissue accumulation as women.[25] Low testosterone levels in men are associated with increased visceral fat;26 accordingly, when hypogonadal men receive testosterone supplementation, they show a decreased amount of visceral fat.27,28 In women, the association seems to be reversed, and higher free testosterone levels are associated with increased visceral obesity.29,30 This association between high testosterone levels and increased visceral adiposity has been demonstrated in healthy pre- and post-menopausal women,30 female-to-male transsexuals receiving high-dose exogenous testosterone therapy,[31] and in women with polycystic ovarian syndrome (PCOS) who have elevated endogenous testosterone levels.[32,33]

An intra-abdominal, visceral, distribution of fat may be a common feature linking IIH both to PCOS (androgen excess) in women32,34 and to hypogonadism (androgen deficiency) in men. Fat distribution – and the hormonal influences that modify and accompany it – may be as important as total adiposity in the pathogenesis of IIH. Its influence is of emerging interest, particularly as adipose tissue is increasingly regarded as an endocrine organ, whose biological properties and hormonal secretions depend crucially on its regional distribution in the body.[35,36]

There also has been emerging interest in the role of obstructive sleep apnea (OSA) in the development of IIH, particularly in men.7-10 In a recent study of 721 patients with IIH, including 66 men, 24% of men had known OSA compared to 4% of women ($p<0.001$).6 Whether OSA is a causal or comorbid factor in IIH is not clear; however, CSF pressures of up to 750mm H_2O have been measured during nocturnal apneic events in patients with OSA, suggesting a link between OSA and raised intracranial pressure.[7,37]

We recognize that our choice of BOSA as a surrogate measure for sleep-study-proven OSA may have resulted in false-positive diagnoses of OSA. That is, some patients may have been misclassified as having OSA on the basis of a positive Berlin questionnaire when a sleep study, if it were done, would have shown normal sleep-related breathing. For the purposes of assessing the prevalence of OSA in our population, however, we believe BOSA is preferable to relying only on sleep-study-diagnosed OSA, since the sleep study is an underutilized tool in the general

population.[38] In fact, our BOSA measure improves upon the Berlin questionnaire for population screening, as it incorporates the result of the accepted gold standard, the sleep study, when available.

In our study, we found that men with IIH had about four times the odds of a positive BOSA compared with controls (p=0.03), independent of BMI. Although this effect was not significant (p=0.08) when a positive ADAM questionnaire was incorporated simultaneously in the model, the marginal difference in the odds ratios (4.4 when adjusted for BMI only; 4.0 when adjusted for BMI and ADAM status) suggests this was due to our small sample size rather than a significant degree of confounding between BOSA and ADAM status. Thus, we have primarily reported the odds ratios separately adjusted for BMI.

The major weakness of most retrospective case-control study designs, including our own, is the potential for recall bias. We attempted to reduce the effects of this bias by avoiding language that would invoke memories of their diagnosis of IIH, such as “at the time of your diagnosis” or “when you had symptoms,” instead using the more neutral phrase “at age X” where X was their age at the time of diagnosis. Also, we adhered to a standardized telephone script without placing undue emphasis on any particular portions of our telephone questionnaire. That we found only two significant associations in our small population despite a lengthy questionnaire, and that these two associations had been suspected *a priori*, argue that recall bias was likely minimized.

We have shown that men with IIH are different from control men in their responses to the ADAM questionnaire and in their BOSA status, after controlling for age, race, and BMI. Although the use of BMI was a strength of our study, BMI is a measure of total adiposity and does not reflect body fat *distribution*. Other anthropometric measures, such as waist circumference (WC), hip circumference (HC), WC-to-HC ratio, and WC-to-height ratio, are emerging as more helpful measures for categorizing obesity as visceral or subcutaneous.[39] Their use may ultimately prove more illuminating than BMI in understanding the relationships between adipose tissue, testosterone deficiency, OSA, and IIH. At present, the pathogenesis of IIH remains poorly understood; however, should hypogonadism or OSA emerge as a causal mechanism in the development of IIH in men, perhaps mediated through sex hormones and the distribution of body fat, then intervention in the form of exogenous testosterone or non-invasive nocturnal ventilation may prove therapeutically useful in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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

Legend:
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

Table 2

Results of mixed-effects logistic regression analyses for case status by predictor, individually adjusted for body mass index at index age

Predictor	Odds ratio	95% confidence Interval	p-value
ADAM	17.4	5.6-54.5	<0.001
BOSA	4.4	1.5-12.9	0.03

Number of IIH cases = 24, number of controls = 48.

Legend:
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