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Pediatric Idiopathic Intracranial Hypertension

Age, Gender, and Anthropometric Features at Diagnosis in a Large, Retrospective, Multisite Cohort

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Purpose: To examine anthropometric and maturational characteristics at diagnosis in pediatric idiopathic intracranial hypertension (IIH).

Design: Retrospective, international, multisite study.

Participants: Pediatric patients (2−18 years of age at diagnosis) with IIH.

Main Outcome Measures: Body mass index (BMI), height, and weight Z-scores; sexual maturation.

Methods: Cases of IIH were identified retrospectively based on diagnostic code, pediatric neuro-ophthalmologist databases, or both and updated diagnostic criteria (2013) were applied to confirm definite IIH. Anthropometric measurements were converted into age- and gender-specific height, weight, and BMI Z-scores CDC 2000 growth charts. When available, sexual maturation was noted.

Results: Two hundred thirty-three cases of definite IIH were identified across 8 sites. In boys, a moderate association between age and BMI Z-scores was noted (Pearson's correlation coefficient, 0.50; 95% confidence interval [CI], 0.30−0.66; $P < 0.001$; n = 72), and in girls, a weak association was noted (Pearson's correlation coefficient, 0.34; 95% CI, 0.20−0.47; $P < 0.001$; n = 161). The average patient was more likely to be overweight at diagnosis at age 6.7 years in girls and 8.7 years in boys, and obese at diagnosis at age 12.5 years in girls and 12.4 years in boys. Compared with age- and gender-matched reference values, early adolescent patients were taller for age ($P = 0.002$ in girls and $P = 0.02$ in boys). Data on Tanner staging, menarchal status, or both were available in 25% of cases (n = 57/233). Prepubertal participants (n = 12) had lower average BMI Z-scores (0.95±1.98) compared with pubertal participants (n = 45; 1.92±0.60), but this result did not reach statistical significance ($P = 0.09$).

Conclusions: With updated diagnostic criteria and pediatric-specific assessments, the present study identifies 3 subgroups of pediatric IIH: a young group that is not overweight, an early adolescent group that is either overweight or obese, and a late adolescent group that is mostly obese. Data also suggest that the early adolescent group with IIH may be taller than age- and gender-matched reference values. Understanding these features of pediatric IIH may help to illuminate the complex pathogenesis of this condition. *Ophthalmology 2016;■:1−8 © 2016 by the American Academy of Ophthalmology*

Pseudotumor cerebri syndrome encompasses the constellation of symptoms caused by elevated intracranial pressure of unclear cause with normal brain parenchyma and cerebrospinal fluid constituents.[1] When there is no identifiable secondary cause of pseudotumor cerebri syndrome, such as prior exposure to tetracyclines or vitamin A, the condition is termed *primary pseudotumor cerebri syndrome* or *idiopathic intracranial hypertension* (IIH).[1] Idiopathic intracranial hypertension can occur in both pediatric and adult populations. Pediatric IIH shares some, but not all, features of adult IIH. Previous studies have suggested an influence of age, gender, and pubertal status on the epidemiologic features of pediatric IIH.[2−6] Both female gender and obesity seem to be associated more strongly with IIH in older, but not younger, pediatric patients.[2,7] In addition, the clinical presentation of pediatric IIH also may vary with age, with a greater number of young children presenting after a routine encounter without symptoms as compared with adolescents.[2,5,8]

Previous studies examining the role of excess body weight in the presentation of pediatric IIH were limited by the lack of standardized, pediatric-appropriate measurements. For example, investigators have described the relationship between body weight and IIH by defining obesity based on percentage of ideal body weight.[2] The United States Centers for Disease Control and Prevention (CDC)

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defines pediatric obesity based on body mass index (BMI) and, more specifically, BMI percentiles or Z-scores.[9] Unlike adults, definitions of being overweight and obese in children are not defined by absolute BMI because this varies with age. Rather, the CDC uses BMI percentiles or Z-scores in the pediatric population: a BMI percentile of 85% or more (equivalent BMI Z-score, $\geq$1.04) is considered overweight, whereas a BMI percentile of 95% or more (equivalent BMI Z-score, $\geq$1.64) is considered obese.[9]

Pubertal status also may contribute to the presentation and prognosis of this condition. Indeed, it has been suggested that children diagnosed with IIH when they are within their pubertal years (estimated as 11−14 years of age) are less likely to obtain excellent visual outcomes.[6] Some previous studies examining the influence of pubertal status on the presentation of pediatric IIH also have assumed that all children younger than certain age threshold were prepubertal (e.g., patients younger than 11 years in one study).[5] Given the wide range of typical ages at pubertal onset in children, pubertal status should be measured explicitly when attempting to evaluate its role in pediatric IIH. Pubertal status is ascertained most accurately by the development of secondary sexual characteristics (i.e., breast development in girls and testicular enlargement in boys).[10,11]

The purposes of this study were (1) to identify and confirm cases of pediatric IIH through consistent and rigorous application of the recently revised diagnostic criteria[1] and (2) to examine the relationship between pediatric IIH, anthropometric features, and the development of secondary sexual characteristics. To address these issues, a multisite international study was undertaken to provide an adequate sample of pediatric patients with this relatively uncommon disorder.

Methods

This study was a retrospective chart review involving 8 international tertiary medical centers with expertise in pediatric IIH. Institutional review board/ethics committee approval was obtained by each site. The data coordinating center was located at The Children's Hospital of Philadelphia. This protocol was approved by the Institutional Review Board at The Children's Hospital of Philadelphia (no. 13-010158).

At each site, patient charts were identified via an electronic medical record search for International Classification of Diseases, Ninth Edition, code 348.2, physician patient databases, or both. For this pediatric study, only patients 2 to 18 years of age at diagnosis were included in the study because we considered the pathophysiologic features of this diagnosis in infancy to be distinct. Retrospective data were collected on patients seen between July 1993 and April 2013 for all sites except for the University of Arkansas, where data were collected between July 1993 and December 2014. Cases of definite IIH were verified through manual chart review according to the revised diagnostic criteria for IIH.[1] Cases that did not fulfill all of the criteria for definite IIH were not included in the study. Reasons for exclusion were (1) medical records lacking details of diagnostic studies (e.g., lumbar punctures not completed, cerebrospinal fluid results or opening pressure not recorded) or (2) magnetic resonance venography studies were not performed for atypical patients (i.e., boys, nonobese girls). Although venogram studies were necessary for many cases of IIH, so-called typical IIH patients (i.e., obese and female) did not require a magnetic resonance venography study for inclusion.[1] Cases were not included if there was a confirmed or suspected cause of secondary pseudotumor cerebri syndrome, aside from obesity, such as tetracycline use. Only patients fulfilling all diagnostic criteria for definite IIH were collected and included in subsequent analysis. Of note, patients fulfilling diagnostic criteria for probable IIH, that is, those patients who fulfilled all diagnostic criteria for definite IIH except for requirement of elevated opening pressure on lumbar puncture,[1] were not included in subsequent analysis.

In cases of definite IIH, age, gender, height measurements, and weight measurements at the time of diagnosis were collected. Pediatric obesity was defined using BMI Z-score. The BMI Z-scores were calculated from anthropometric data according to United States CDC 2000 growth standards.[9] According to the CDC, in children between 24 and 36 months of age, BMI Z-scores may be calculated based on stature, determined either by height or recumbent length. In our dataset, only 1 patient was younger than 36 months. In that patient, the method for determining stature is unknown. For all other patients, height was measured and documented. Overweight and obese were defined according to the CDC classifications of overweight (BMI Z-score, $\geq$1.04 and $<$1.64) and obese (BMI Z-score, $\geq$1.64) in children. Severe obesity was defined as the lower value of either BMI of 120% or more of the 95th percentile or more than 35 kg/m^2.[12] Study data were collected and managed using research electronic data capture tools[13] hosted at The Children's Hospital of Philadelphia.

Data on the development of secondary sexual characteristics were available in 57 patients with definite IIH. Data were collected on Tanner staging (breast, pubic hair, and testicular development, where appropriate[14]) as well as menarchal status, obtained within 3 months of diagnosis of IIH. Data were collected by patient self-report (menarchal status), after physical examination by a physician (Tanner stage), or both.[15] Pubertal status was defined as prepubertal if there was a documented Tanner staging of 1 for breast or testicular volume in girls and boys, respectively. Pubertal status was defined as pubertal if there was documented menarche, Tanner staging (breast) of 2 or more in girls, or both, or if testicular volume was 4 ml or more in boys.

Pearson's correlation analyses were used for examining the bivariate associations between normally distributed outcomes of interest. The relationships between anthropometric features and age were assessed using linear prediction models, with 95% confidence intervals (CIs). Analysis of the influence of gender on the anthropometric features of IIH was completed by linear regression analysis and chi-square testing. One-sample *t* tests were used to compare mean Z-scores against hypothesized mean Z-scores (e.g., of theoretical or actual age- and gender-matched reference values). Statistical significance was defined as a 2-sided *P* value of $<$0.05. Analyses were performed in Stata software version 13.1 (Stata Corp, College Station, TX).

Results

In total, 233 cases of definite IIH were identified from 8 international sites. Participants had a mean age $\pm$ standard deviation of 12.1$\pm$4.0 years and were predominately girls (69% girls; n = 161). Participants had a mean $\pm$ standard deviation BMI Z-score of 1.55$\pm$1.18, which indicated the average body habitus as overweight according to the CDC definition in the pediatric population. Compared with girls, boys were younger and had lower BMI Z-scores (see Table 1). Pubertal data were available in 57 patients with definite IIH (Table 2).