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Original Article

Predictors of Primary Intracranial Hypertension in Children Using a Newly Suggested Opening Pressure Cutoff of 280 mm H_2O

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ABSTRACT

OBJECTIVES: We assessed the clinical characteristics of primary intracranial hypertension (PIH) in children using a newly recommended threshold for cerebrospinal fluid opening pressure (280 mm H_2O).

METHOD: Cross-sectional study of patients age ≤21 years who had a lumbar puncture done for evaluation of PIH. Patients were excluded if lumbar puncture was done for a suspected infection, seizure, mental status changes, multiple sclerosis, or Guillain-Barre syndrome. Cases were identified using a text-search module followed by manual review. We performed $\chi 2$ analysis for categorical data and Mann-Whitney *U* test for continuous data, followed by a binary logistic regression.

RESULTS: We identified 374 patients of whom 67% were female, median age was 13 years interquartile range (11 to 16 years), and admission rate was 24%. Using an opening pressure cutoff of 250 mm H_2O, 127 patients (34%) were identified as having PIH, whereas using the new cutoff 105 patients (28%) met PIH criteria. Predictors for PIH included optic disc edema or sixth nerve palsy using both old, odds ratio (OR) 7.6 (4.3, 13.5), and new cutoffs, OR 9.7 (95% confidence interval 5.1, 18.5). Headache duration ≤61 days is predictive of PIH using the new cutoff OR 4.1 (95% confidence interval 1.3, 12.8). A model is presented which stratifies patients into groups with low (7%), medium (18%), and high (greater than 42%) risk of PIH.

CONCLUSIONS: A higher cerebrospinal fluid opening pressure threshold in the criteria of PIH is associated with PIH patients with a different symptom profile. Children with optic disc edema, bulging fontanel or sixth nerve palsy, are at increased risk for PIH.

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Introduction

Primary intracranial hypertension (PIH) has at various times been called "pseudotumor cerebri," "benign intracranial hypertension," and "idiopathic intracranial hypertension." Although the optimal terminology is still debated, PIH is not benign because vision loss may occur if treatment is delayed[1] and it is not always idiopathic as certain medications and medical conditions are associated with intracranial hypertension both in adults[2-4] and in children.[5-7] Patients with symptoms related to PIH may be referred to the emergency department (ED) for further assessment of headache and/or optic disc edema with consideration for a lumbar puncture (LP), advanced neuroimaging, and subspecialty consultation. Extrapolated from a registry of pediatric intracranial hypertension patients in Ohio, the incidence of pediatric PIH was been estimated to be 0.63 per 100,000.[8]

The diagnostic criteria for idiopathic intracranial hypertension have been recently revised to incorporate data from a prospective, single-center study which defined the threshold for elevated intracranial pressure (ICP) in pediatric patients.[9,10] Specifically, the proposed threshold for elevated ICP in pediatric patients undergoing a sedated LP in the lateral decubitus position is 280 mm H_2O and 250 mm H_2O for those patients undergoing a nonsedated LP or who are overweight at the time of LP.[10] Prior published data on the clinical presentation of patients diagnosed with PIH were based upon patients with a cerebrospinal fluid (CSF) opening pressure cutoff of 200 to 250 mm of H_2O. These data indicate that headache (up to 90%), transient visual complaints (70%), and a variety of other neurological complaints (more than 50%) are common.[11,12] Most patients with PIH have optic nerve head edema.[9,13-16] Little data exist in the literature regarding the clinical profile among children with a PIH diagnosis using the current criteria for opening pressure.

We sought to describe the clinical presentation of patients with PIH using the new diagnostic criteria which incorporates the new threshold for opening pressure. Additionally, we sought to determine whether there are clinical signs or symptoms which may be more readily predictive of PIH.

Methods

Study design

This is a retrospective cross-sectional study of consecutive patients who were evaluated at an urban tertiary care ED. The ED serves approximately 50,000 children per year. We reviewed ED electronic medical records of all patients that had a CSF opening pressure obtained as part of evaluation for PIH over a 16-year period.

Study population

We included children age one month to 21 years if they met the following criteria: (1) had an LP done as part of an evaluation for PIH; (2) were otherwise healthy; and (3) had normal neuro-imaging (computed tomography [CT] or magnetic resonance imaging) within 24 hours of the LP. Patients were excluded if the LP was done for evaluation of other conditions such as a suspected infection (all febrile children and those with infectious features), seizure, or mental status changes. We also excluded patients with a known history of PIH and those presenting for repeat LP. Patients with a broad differential diagnosis, such as multiple sclerosis and Guillain-Barre syndrome, were also excluded. Three authors (AD, AV, AAK) were assigned to perform the manual review to assure inter-reviewer agreement on included cases using the above criteria. Disagreements among the reviewers were resolved by consensus among the group.

Case identification

Case identification was conducted in two phases. First, for the initial screening, we created a computer-assisted screening tool similar to keyword search tools, but using regular expressions and a document classifier model. The technique of regular expression matching provides a more comprehensive and inclusive search than keyword searching by including possible misspelled and mistyped variations of the keyword(s) of interest.[17,18] The second step was running a document classifier[19] followed by a manual chart review of those patients identified by the screening tool, using the inclusion and exclusion criteria above.

If a trainee was involved in the patient care, both the trainee and the attending physician's notes were reviewed. Findings were considered present if they were documented either by the resident or the attending physician. All cases were reviewed to screen for a second ED visit or hospital admission within a week of the index visit. Three reviewers extracted the variables, and one person then reviewed all charts. A kappa score was calculated for inter-reviewer agreement.

Outcome measures

Our primary outcome was an elevated CSF opening pressure using two different cutoffs: 250 and 280 mm H_2O.

Statistical analysis

Data were analyzed using IBM SPSS for Windows Version 23 (Armon, NY, 2014). Univariate analyses were used followed by a binary logistic regression to determine independent clinical predictors of elevated CSF opening pressure.

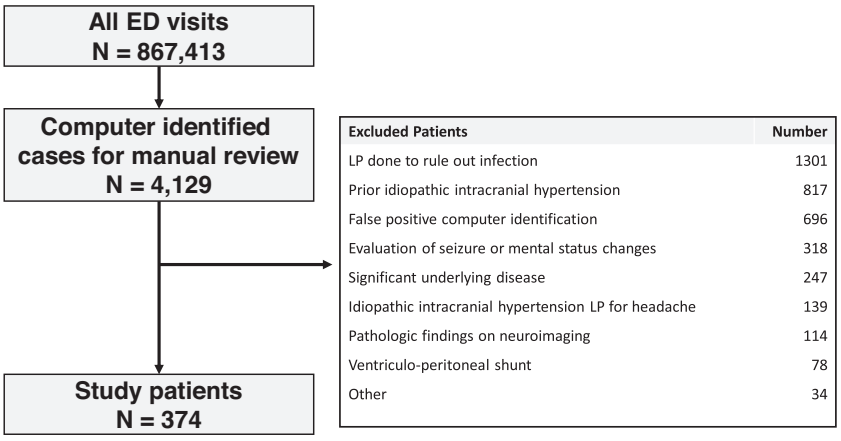
Results

Study group

During the study period there were 867,413 ED visits with electronic ED notes available for review. Three hundred seventy-four patients met the study criteria. See Fig 1 for case identification.

The median age was 13 years, interquartile range [11 to 16 years] and 67% (248/374) were female. The most common presenting symptom leading to an ED clinical evaluation was headache, described in 89% of the patients with a median duration of 14 days (interquartile range five to 30 days). Ninety-one patients (24%) were admitted for further management.

Information about the use of sedation was available in 360/ 374 (96.3%) patients. A total of 168 patients (45%) received local anesthesia only. Of the remaining 206 patients undergoing sedation, 67 (32.5%) received benzodiazepines alone, 13 (6.3%) received opioids alone (either fentanyl or morphine), 38 (18.4%) received fentanyl and midazolam, 59 (28.6%) received propofol, seven (3.4%) received nitrous oxide, and 20 (9.7%) needed



Excluded Patients	Number
LP done to rule out infection	1301
Prior idiopathic intracranial hypertension	817
False positive computer identification	696
Evaluation of seizure or mental status changes	318
Significant underlying disease	247
Idiopathic intracranial hypertension LP for headache	139
Pathologic findings on neuroimaging	114
Ventriculo-peritoneal shunt	78
Other	34

FIGURE 1. Case identification.

interventional radiology assistance where received general inhalation agent or a combination of three or more medications. One patient received chloral hydrate, and one patient received pentobarbital.

LP position was recorded in 298/374 patients (79.7%). In all but three, fluid was obtained in a lateral decubitus position, and the three patients who underwent he procedure in an upright position were then laid down for pressure measurements. The amount of fluid remove before change in position was not recorded.

Before the LP a head CT scan was obtained in 166 patients (46%), 126 (35%) had an MR/magnetic resonance imaging with venography (MRV), and 69 (19%) had both. Follow-up/complimentary imaging (including MR/MRV) was obtained in 111 patients, all of whom had undergone a prior CT alone (Table 1).

Figure 2 shows the distribution of opening pressure among our cohort. An elevated opening pressure was found in 194 patients (52%) using the cutoff of 20 mm H_2O, 127 patients (34%) using the cutoff of 25 mm H_2O and 105 patients (28%) using the newly offered cutoff of 280 mm H_2O.

Table 2 presents a univariate analysis of the predictors of PIH using a cutoff of 200 mm H_2O, the intermediate zone of 200 to 280 mm H_2O, and those with pressure greater than 280 mm H_2O side by side. Table 3 is presenting a multivariate analysis using similar cutoffs.

Overall, of the 105 patients with PIH using the newly suggested cutoff, 93% presented with a headache, visual complaints such as photophobia or visual field defects were reported in 61%, and 77% had optic disc edema on examination. Optic disc edema was recorded by an ED provider, a pediatric neurologist or an ophthalmologist, depending on availability of consulting services. Using a recursive partitioning model we were able to identify a low-risk group with PIH risk of 7%, the model is presented in Fig 3 ($R^2 = 0.31$).

Discussion

We present a large cohort of patients who underwent a LP to measure the CSF opening pressure as part of an evaluation for PIH. Using the newly published CSF opening pressure cutoff of 280 mm H_2O, patients are at greater risk of neurological complications. Furthermore, we identified a low-risk group in whom a LP can be deferred pending neurological evaluation, especially if procedural sedation is required.

Headache is the most common presenting symptom of PIH in children.[20] Published data suggest that the headache prevalence is age dependent, ranging from 40% in children younger than six years of age and up to 90% in children older than 12 years.[21] Other studies report a crude prevalence of 90% across all age groups. Bruce et al. described a lower prevalence of headache in males compared with women.[22] In our cohort we failed to show a gender difference.

Neck pain has been described in some patients with PIH, usually as a secondary complaint after headache,[23,24] but the frequency is not well described. In our cohort, data regarding neck pain was only available for a minority of patients (41%) but may deserve evaluation in future studies as this finding was found to be a significant predictor on univariate analysis.

TABLE 1. Revised Diagnostic Criteria for Pseudotumor Cerebri Syndrome*

1. Required for diagnosis of pseudotumor cerebri syndrome
   a. Optic disc edema
   b. Normal neurological exam except for cranial nerve abnormalities
   c. Neuroimaging: normal brain MRI with and without contrast; MRV indicated in atypical cases. CT should be performed if MRI contraindicated
   d. Normal CSF composition
   e. Elevated opening pressure (OP); ≥25 cm H2O in adults and ≥28 cm H2O in non-sedated, non-obese children
2. Diagnosis of pseudotumor cerebri syndrome without papilledema
No papilledema: Patient must meet criteria B-E above plus uni- or bilateral sixth nerve palsy
or
No papilledema, no sixth nerve palsy: at least three of the following neuroimaging criteria are satisfied:
   a. Empty sella
   b. Flattening of the posterior aspect of the globe
   c. Increased perioptic subarachnoid spaces, with or without optic nerve tortuosity
   d. Transverse sinus stenosis
Diagnosis of pseudotumor cerebri syndrome is considered definite if criteria A-E are fulfilled. Probable diagnosis is made if patient meets criteria A–D but CSF opening pressure is lower than specified.

Abbreviations:
CSF = cerebrospinal fluid
CT = computed tomography reprinted with permission from Friedman et al.[9]

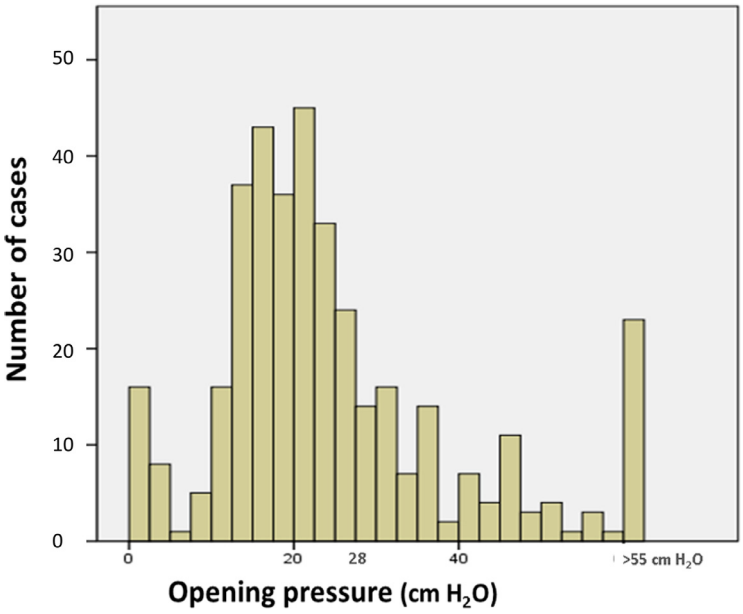


FIGURE 2. Distribution of opening pressure among cohort.

Visual complaints occur in up to 45% of patients.[5,25,26] While visual field abnormalities are described in 74% to 85%, visual acuity remains intact until relatively late in the disease, although brief episodes (up to 30 seconds) of vision loss or transient visual obscurations have been reported.[5,27] In our cohort visual complaints were highly predictive in a univariate model but failed to meet significance in a multivariate model. We do not know of data suggesting an age at which children can reliably articulate the presence of visual symptoms, a factor that may have played a role in this discrepancy.

Optic disc edema is reported in the majority of patients with PIH. The prevalence of reported optic disc edema varies significantly, ranging from a high of 80% to 90%,[28-30] to a low of 48%.[31] Reports vary depending on the clinical discipline performing the assessment (ophthalmologists versus neurologists, neurosurgeons or emergency medicine practitioners) and whether the pupils were dilated before the examination. In our cohort, optic disc edema was identified among 73% of patients with a CSF opening pressure of more than 250 mm H_2O and in 77% of those with a pressure of more than 280 mm H_2O, consistent with findings by Avery et al.[13] Recent diagnostic criteria accept VI nerve palsy as a substitute predictor from elevated ICP.[9] Finally, it is evident that a bulging fontanel can be a predictor among very young infants. Overall the positive predictive value of having any of these elevated ICP predictors (optic disc edema, VI nerve palsy, or a bulging fontanel) was 49%. Because optic disc edema is the most important predictor of vision loss (more than pressure values *per se*). We conclude that for this subset of patients,

TABLE 2. Side by Side Comparison of Patient Symptom Profile, Comparing Children with Normal Opening Pressure, Intermediate Opening Pressure and Those Above the Newly Defined Cutoff

	Opening P Pressure Less Than or Equal to 200 mm H_2O (N = 180)	Opening P Pressure 200-280 cm H_2O (N = 89)	Opening P Pressure More Than or Equal to 280 mm H_2O (N = 105)	*P* Value
Demographics				
Female gender	71%	53%	71%	0.09
Age (median IQR)	13.5 (11,13)	12 (10,15)	14 (12,16)	0.23
History				
Headache	90%	91%	89%	0.83
Headache duration less than or equal to 61 days	68%	70%	72%	0.82
Visual complaints*	43%	47%	67%	0.01
Medications†	9%	16%	24%	0.05
Neck pain	38%	22%	59%	0.03
Vomiting in the last 48 h	18%	23%	29%	0.11
Physical exam				
Papilledema	28%	42%	77%	< 0.001
Cranial nerve VI palsy	2%	5%	11%	0.04

Abbreviation:
IQR = interquartile range.
* Visual obscuration, blurred vision, double vision, flashes of light, completely blind.
† Minocycline/tetracycline/doxycycline, Growth hormone, Corticosteroids (especially withdrawal), Cyclosporine A, Retinoic acid, Vitamin A (excess or deficiency). Cases diagnosed with elevated ICP are considered SIH (secondary intracranial hypertension, rather than PIH).

TABLE 3. Multivariate Model for Children Evaluated for PIH

	Using OP Cutoff of 250 mm H_2O (N = 127) odds ratio (95% confidence interval)	Using OP Cutoff of 280 mm H_2O (N = 105) odds ratio (95% confidence interval)
Demographics		
Female gender	0.9 (0.6, 1.7)	1.4 (0.7, 2.6)
Age (median IQR)	1.03 (0.96, 1.14)	1.06 (0.97, 1.14)
History		
Headache	2.0 (0.9, 4.7)	1.7 (0.7, 4.2)
Headache duration less than or equal to 61 days	1.9 (0.8, 4.4)	4.1 (1.3, 12.8)
Visual complaints*	1.6 (0.9, 2.7)	1.4 (0.8, 2.4)
Medications*	0.4 (0.7, 2.8)	1.4 (0.7, 3.0)
Vomiting in the last 48 h	1.5 (0.8, 2.9)	1.6 (0.8, 3.1)
Physical exam		NS
Papilledema or VI nerve palsy	*7.6 (4.3, 13.5)*	*9.7 (5.1, 18.5)*

Abbreviations:
IQR = interquartile range
OP = opening pressure.
* Minocycline/tetracycline/doxycycline, growth hormone, corticosteroids (especially withdrawal), cyclosporine A, retinoic acid, vitamin A (excess or deficiency). Cases diagnosed with elevated ICP are considered SIH (secondary intracranial hypertension, rather than PIH).

the ED clinician should plan ahead to strategize the imaging technique, an LP and a single sedation period to cover both if necessary.

The evaluation of PIH involves neuroimaging and an LP. At times, imaging was obtained before the ED visit. Although less common, CT scans are performed to rule out a mass effect, confirming that an LP is "safe" to be performed even before advanced imaging. These images are typically obtained before the ED visit, or in a secondary center ruling out a mass before transferring to a pediatric center.

When the entire focused evaluation is done in the ED, special consideration should be given to the type of imaging ordered, ruling out not only a space occupying lesion, but also secondary causes of elevated intra-cranial hypertension. MRV is preferred, as evaluation of the venous sinuses may reveal venous sinus stenosis or thrombosis especially in prepubertal and very young children who may be at higher risk for cerebral venous sinus thrombosis in the setting of mastoiditis and complicated otitis media.[32] At times, findings associated with an elevated CSF opening pressure may confirm the diagnosis; these include flattening of the pituitary or an empty sella, Meckel's cave enlargement, and tonsillar ectopia. Orbital imaging with thin cuts may reveal flattening of the posterior pole of the ocular globe, optic nerve head protrusion, increased CSF signal surrounding the optic nerve sheaths, and tortuous optic nerves.[33] In pubertal children, scleral flattening, transverse sinus stenosis, and sella turcica changes were reported at higher frequency. Our cohort contained a large number of patients who were pre-imaged with a CT scan, some due to the nature of

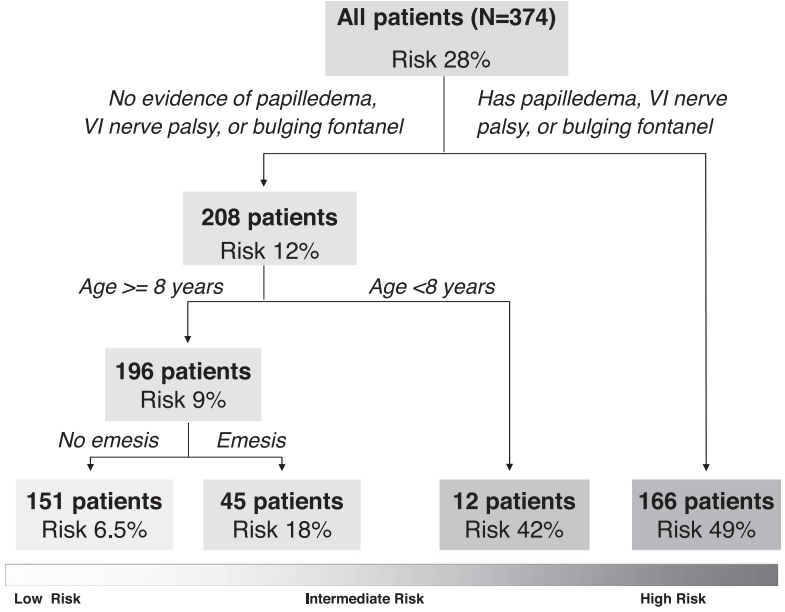


FIGURE 3. Recursive partitioning model.

this study spanning over 16 years, and many of the visits occurred before change in diagnostic criteria and the neuro-imaging breakthroughs. None of the patients who underwent advanced imaging after the LP exhibited any significant imaging findings.

We presented a large cohort of patients evaluated for intracranial hypertension in a pediatric ED. The authors, primarily pediatric emergency medicine (PEM) providers, feel that PEM providers should not be the sole providers assessing these children. Pediatric neurologists, ophthalmologists, or neuro-ophthalmologist provide level of expertise lacking in the ED. Ideally patients will be assessed by both expert disciplines and advanced imaging will be directed accordingly. Furthermore, the rate of optic disc edema may be proven to be different, and for some patients, diagnosis of drusen syndrome will be made and LP may be deferred altogether. Yet real life dictates other scenarios as suggested by the large cohort of the patients presented here. Patients present during all hours of the day and all days of the week, often referred by a primary care provider considering an ED referral to be a referral to "the hospital." Some patients travel hours to get to the ED, others are kept NPO anticipating a procedural sedation and an LP that is well within the PEM skillset. The PEM provider is therefore faced with a decision of whether to proceed or defer what might be a time-sensitive diagnosis. We provide a scheme to identify a cohort with a slightly lower likelihood of having intra-cranial hypertension (less than a quarter of the crude risk), in whom an LP can may be deferred for a short period of time, allowing expert disciplines to weigh in.

Limitations: (1) our data depend on the quality of the clinical documentation; (2) documentation was limited on other predictors of PIH described in the literature such as tinnitus,[34,35] anosmia,[28] or rhinorrhea as a manifestation of CSF leak.[36,37] For tinnitus in particular, a closed-ended question such as "do you hear whooshing noises?" instead of "ringing in your ears," to which children invariably answer in the negative. Children of young age may not have the insight to observe, let alone report these symptoms, and for children rhinorrhea is hardly a rare symptom. Visual complaints are not spontaneously stated by children; the interviewer should inquire about transient vision obscurations, difficultly seeing straight ahead or to the sides, double vision; and (3) the reporting of optic disc edema in our cohort has been done by clinicians with differing expertise and without consistent use of pupil dilation.

In summary, our study adds to the literature a different prevalence of symptom profile being associated with a newly suggested cut point of CSF opening pressure. Clinicians should be mindful of the need to coordinate the neuro imaging and LP when evaluating children with optic disc edema, a bulging fontanel, or a sixth nerve palsy.

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