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Original Article

Magnetic Resonance Imaging Findings in Pediatric Pseudotumor Cerebri Syndrome

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ABSTRACT

Background: Revised diagnostic criteria for pseudotumor cerebri syndrome require three of four neuroimaging findings in the absence of papilledema. We examined the sensitivity and specificity of three or more of four of these magnetic resonance imaging (MRI) findings for pseudotumor cerebri syndrome in children.

Methods: As part of clinical care, patients in whom there was suspicion for pseudotumor cerebri syndrome underwent neurological and fundoscopic examinations, lumbar puncture, MRI, or magnetic resonance venogram. For this retrospective study, we used this information to classify 119 subjects into definite (n = 66) or probable pseudotumor cerebri syndrome (n = 12), elevated opening pressure without papilledema (n = 23), or controls who had normal opening pressure without papilledema (n = 24). A neuroradiologist, unaware of the clinical findings or original MRI report, reviewed MRIs for pituitary gland flattening, flattening of the posterior sclera, optic nerve sheath distention, and transverse venous sinus stenosis.

Results: The presence of three or more MRI findings has a sensitivity of 62% (95% confidence interval: 47% to 75%) and a specificity of 95% (95% confidence interval: 77% to 100%), compared with controls. Two of

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three (transverse venous sinus stenosis, pituitary gland flattening, flattening of the posterior sclera) had a similar sensitivity and specificity. Transverse venous sinus stenosis alone had a slightly higher sensitivity (74%, 95% confidence interval: 60% to 85%) and specificity (100%, 95% confidence interval: 80% to 100%).
Conclusions: In children, three of four of the proposed neuroimaging criteria and transverse venous sinus stenosis alone have a moderate sensitivity and robust specificity for pseudotumor cerebri syndrome. MRIs should be reviewed for these criteria, and their presence should raise suspicion for pseudotumor cerebri syndrome in children, particularly if the presence of papilledema is uncertain.

Introduction

Pseudotumor cerebri syndrome (PTCS) may cause permanent vision loss in up to 33% and headaches in up to 98% children with the condition.[1–3] Accurate diagnosis and prompt treatment are critical. The syndrome is clinically heterogeneous and may occur with or without papilledema or other clinical signs of raised intracranial pressure (ICP). The headache associated with PTCS can be clinically indistinguishable from other headaches that commonly afflict adolescents and adults.[4,5]

In 2013, the diagnostic criteria for PTCS were revised, including clinical findings and imaging criteria, to facilitate making the diagnosis when papilledema and abducens nerve palsy are absent.[6] Definite PTCS is defined by papilledema, a normal neurological examination (except abducens nerve palsy), normal brain parenchyma on magnetic resonance imaging (MRI), normal cerebrospinal fluid (CSF) composition, and an elevated opening pressure (OP) on lumbar puncture (LP) (greater than 280 mm CSF in sedated children and more than 250 mm CSF in nonsedated or nonobese children).[7] Probable PTCS occurs when the above criteria are satisfied but the CSF OP is not elevated.[6] PTCS may also occur without papilledema, although an abducens nerve palsy and elevated OP must be present. Finally, PTCS may be suggested when papilledema and sixth nerve palsy are absent, OP is elevated, and three of four of the following MRI abnormalities are found: pituitary gland flattening (PGF), flattening of the posterior sclera (FPS), distension of the subarachnoid space within the optic nerve sheath (optic nerve sheath distension [ONSD]) with or without tortuosity, and transverse venous sinus stenosis (TSS).[6]

In patients with imaging findings suggestive of increased ICP without papilledema,[8] there is likely no impending risk of vision loss, but they often have refractory headaches. It is not known whether they represent a subset of PTCS and should be treated with medications to lower ICP or with medications directed toward their headache phenotype (usually chronic migraine)[9,10] and whether LP contributes to their care. This study was undertaken to establish the sensitivity and specificity of imaging criteria for PTCS in a pediatric cohort and to better understand the group of patients with suggested PTCS without papilledema.

Methods

This study was approved by the Institutional Review Board at our institution. Potential subjects were retrospectively collected from a PTCS database and from those given an International Classification of Disease Ninth Revision diagnosis of PTCS between July 1, 1993, and April 16, 2013 (included in the Pseudotumor Registry[11]). In addition, the electronic medical record of patients who had an LP performed to evaluate headaches or for PTCS, between 2009 (start of electronic medical record) and April 20, 2015, were also reviewed, yielding 237 potential subjects in total.

Using LP results and ophthalmologic examinations, which had been obtained as part of clinical care, subjects were categorized into study groups based on the revised criteria: definite PTCS, probable PTCS, elevated OP (elevated OP without papilledema, abducens nerve palsy, or three or more of four imaging criteria on clinical report), and control (LP performed for suspicion of elevated ICP but OP normal, no papilledema, abducens nerve palsy, or three or more of four imaging criteria on clinical report). Potential subjects with missing information necessary for classification or MRI were excluded. Those subjects with papilledema not confirmed by a neuro-ophthalmologist were excluded owing to concern for misdiagnosis[12] (see Fig 1).

The MRI studies were performed as part of routine clinical care on various Siemens MRI scanners (Siemens, Erlangen, Germany) over the course of 10 years. The MRI techniques were as follows. In T1-weighted images all patients imaged on a 3T scanner had a sagittal three-dimensional volumetric T1 MPRAGE image at $0.9 \times 0.9 \times 0.9$ mm, with reformats into other planes along with fat-suppressed postcontrast fast spin echo T1. The postcontrast T1-weighted images were similar with an added fat-suppressed T1-weighted fast spin echo sequence. Patients imaged on a 1.5T scanner had sagittal and axial T1-weighted images with 3 to 4 mm thickness. The postcontrast T1-weighted images were similar in technique, but with fat suppression and addition of coronal images. All magnetic resonance venogram (MRV) studies were done as a time-of-flight MRV in both axial and coronal planes, along with 3D maximum intensity projections. T2-weighted images were obtained as fast-spin echo T2-weighted images with slice thickness between 2 and 4 mm, with no interslice gap, in both axial and coronal planes.

One member of the research team (A.A.K.) compiled all eligible MRIs ($n = 119$) and MRVs ($n = 81$) into the radiology viewing software (PACS, Picture Archiving and Communication System), to prevent bias by the neuroradiologist. MRI and MRV closest to date of diagnosis were used, so as to decrease potential treatment effect, and imaging studies were presented in random order. A neuroradiologist (A.V.), unaware of the clinical findings or original MRI report, reviewed all imaging studies to assess for the presence or absence of the imaging features (Fig 2).[13] If an individual MRI feature was not assessed due to artifact from motion or from orthodontic hardware, the case was excluded from the analysis of that feature.

The following is the methodology for review of imaging criteria, based on Mallery et al.[14]:

1. PGF: Pituitary gland height was analyzed on midsagittal T1-weighted images as the maximal vertical distance to the upper surface of the pituitary gland measured perpendicular to the sellar floor (Fig 2), and was also assessed in the coronal plane to determine whether flattening was of the entire gland or only of the central median portion. PGF was also categorized as present (complete flattening or empty sella) or absent (central median flattening only on coronal imaging or not flattened in any plane).
2. FPS: FPS was judged subjectively as flattening of the globe at the site of insertion of the optic nerve (Fig 2).[15,16] FPS was

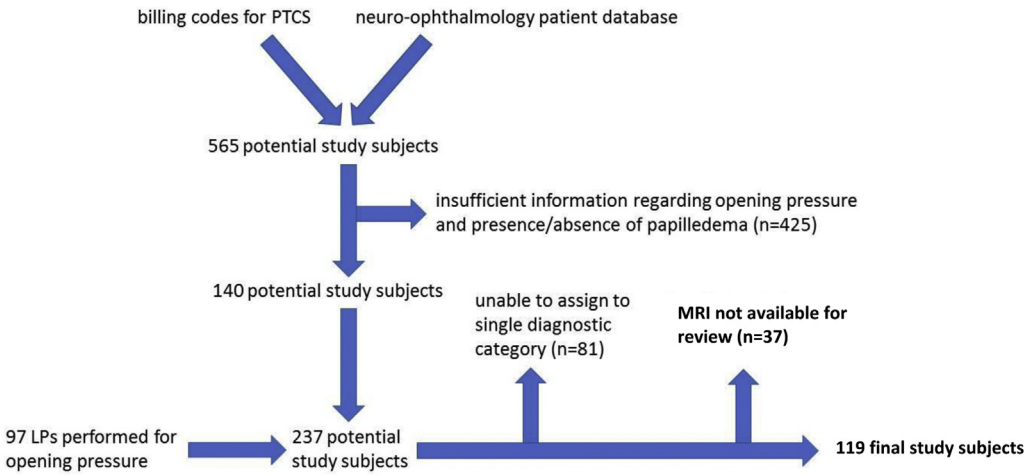

FIGURE 1. Flow diagram of study subjects. LP, lumbar puncture; MRI, magnetic resonance imaging; PTCS, pseudotumor cerebri syndrome. The color version of this figure is available in the online edition.

considered positive if present on one or both sides. The confidence of this flattening was also noted and was used in sensitivity analysis of FPS.

3. ONSD with or without a tortuous optic nerve: On T2-weighted axial images, ONSD was measured as the maximum optic nerve sheath diameter within the orbit (Fig 2). If both right and left measurements were available the mean was used. Hoffmann et al. defined a threshold value for ONSD[16] of 5.5 mm. This was used as the cut point when reporting the binary presence or absence of ONSD. Vertical tortuosity of the optic nerve was present if the optic nerve had an S-shaped trajectory on sagittal images.[17]
4. TSS: The presence of *focal* TSS and *diffuse* transverse sinus hypoplasia were assessed independently from the contrast-enhanced brain MRIs and MRVs. TSS was graded on a scale of 0 to 2 (0 = no stenosis, 1 = 25% to 50% stenosis; 2 = greater than 50% stenosis).[16,18,19] Any stenosis (1, 2, or above), whether unilateral or bilateral, was considered a positive finding. Transverse sinus hypoplasia was also graded on a scale of 0 to 2 (0 = no hypoplasia, 1 = 25% to 50% smaller than the contralateral side; 2 = greater than 50% diffuse narrowing compared with the contralateral side).

Statistical analysis

Data were collected and managed securely using Health Insurance Portability and Accountability Act-compliant REDCap (Research Electronic Data Capture[20]) tools. Analyses were performed with STATA 14.1. Fisher's exact test was used to compare counts in each group and calculate *P* values for categorical variables. Analysis of variance was used to compare the mean of continuous parametric variables, and Wilcoxon rank-sum test was used to compare the median of continuous nonparametric variables. Comparisons were considered significant when $P < 0.001$, after adjusting the standard *P* value of 0.05 for multiple comparisons (Šídák method). Receiver operating characteristic curve analysis was used to determine the best threshold value of ONSD to maximize the portion correctly classified, compared with the presence or absence of two of three other criteria in subjects with definite PTCS and controls. The sensitivity of each MRI feature and of the presence of at least three features was defined as the percentage of patients with definite PTCS who had that feature or group of features. The specificity of each feature was calculated from the number of subjects in the control group who did not have that finding out of the total number of subjects in the control group.

Univariate logistic regression was performed to test for associations between each individual variable and definite PTCS compared with control. Next, all variables with $P < 0.2$ were included in the initial multivariate model, and backward elimination was used. The variability explained by and area under the curve predicted by each model were noted, and the models were compared with chi-square test to determine the best fit model(s). Sensitivity analyses repeated univariate and multivariate regression analyses for PTCS (definite and probable) versus not PTCS (elevated OP and control) and elevated OP (definite and elevated OP) versus normal OP (probable and control).

Results

Patient characteristics

Of the 237 patients who were potentially eligible, 119 had a normal neurological examination, normal CSF constituents with documented OP, and normal imaging (except for those imaging findings reviewed here) and were included in this study. Of note, no subject had definite PTCS with an abducens palsy, in the absence of papilledema. No subject had suggested PTCS without papilledema based on original MRI reports. The median age of diagnosis was 12.7 years (interquartile [IQ] range: 9.1 to 15.5 years), and 60% were female. There was no significant difference in age, sex, race, or body mass index between all groups (Table 1). Secondary PTCS was uncommon (nine patients with definite PTCS, one with probable PTCS); associations included antibiotic use, withdrawal of chronic corticosteroids, renal failure, and trisomy 21. These patients were included in the analysis.

Pituitary gland flattening

Pituitary height, the maximal vertical distance to the upper surface of the pituitary gland measured perpendicular to the sellar floor on midsagittal T1-weighted images, was compared between each of the four groups (Fig 3). Pituitary height was significantly reduced in the definite PTCS group (median 3.6 mm, IQ 2.7 to 5.2) compared with the elevated OP (6.1 mm, IQ 5.2 to 6.9, $P < 0.001$) and control (5.9 mm, IQ 4.8 to 6.5, $P < 0.001$) groups, but was not

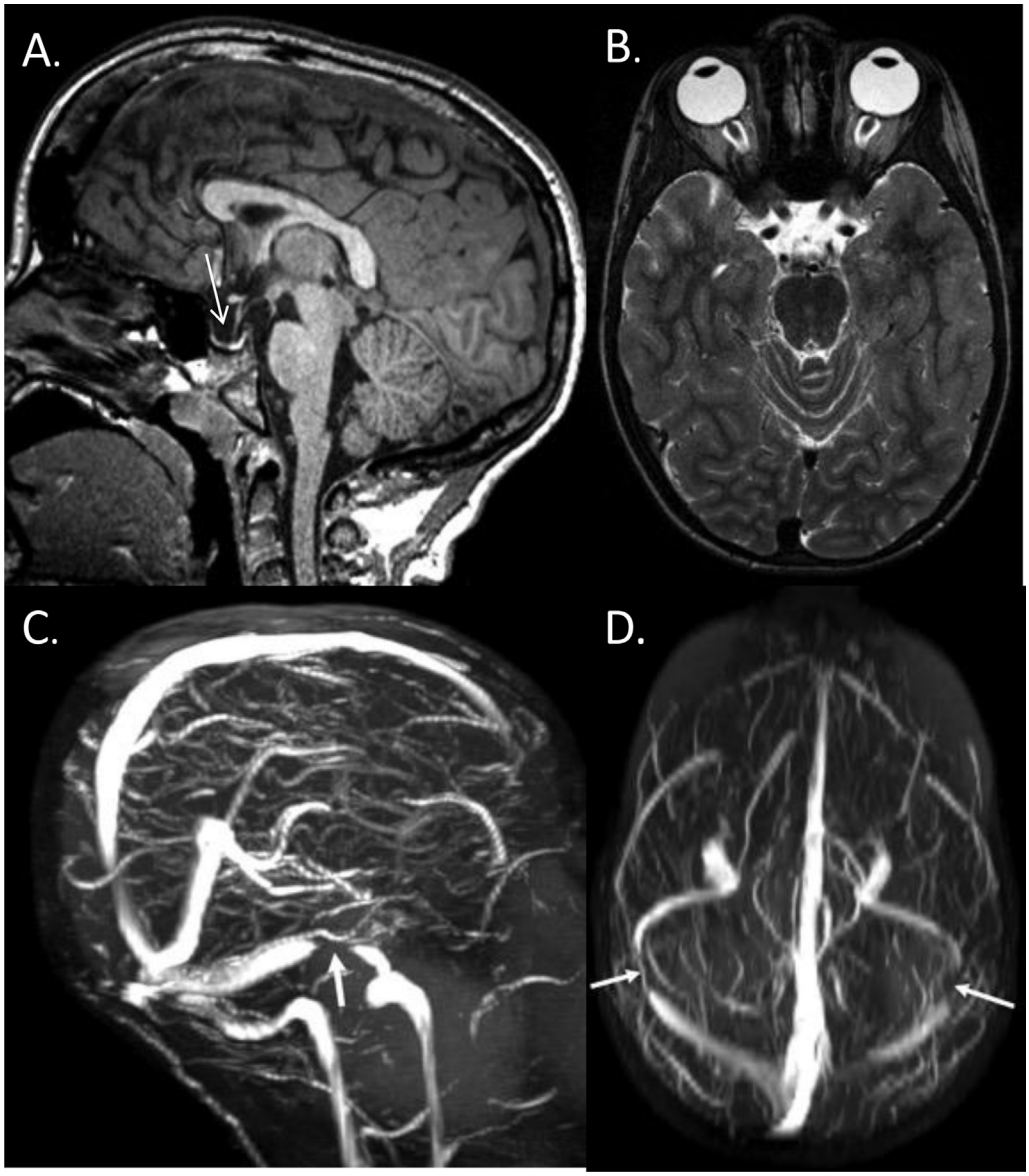

FIGURE 2. MRI features of raised intracranial pressure. (A) Sagittal T1-weighted MRI shows empty sella (arrow). (B) Axial T2-weighted MRI shows flattening of the posterior sclera, papilledema, and prominence of the perioptic subarachnoid space surrounding the optic nerve bilaterally. (C) Magnetic resonance venogram demonstrating stenosis of the right transverse sinus (arrow). (D) Magnetic resonance venogram in axial reconstruction demonstrating bilateral stenoses of the transverse sinuses (arrows). MRI, magnetic resonance imaging.

significantly different from the probable PTCS group (5.5 mm, IQ 3.4 to 6, $P = 0.125$). Flattening of the entire pituitary was present in 38% (n = 23) of those with definite PTCS, 8% (n = 1) with probable PTCS ($P = 0.079$ versus definite), 0% with elevated OP ($P < 0.001$ versus definite), and 4% (n = 1) of controls ($P = 0.002$ versus definite).

Flattening of posterior sclera

FPS, subjective flattening of the globe at the site of insertion of one or both optic nerves, was present in 41 of 60 subjects with definite PTCS (70.7%); in 30 of these cases the radiologist was confident of the flattening. FPS was present in four of 12 subjects with probable PTCS, with confidence in three and without confidence in one ($P = 0.067$ versus definite PTCS). FPS was present in eight of 23 subjects with elevated OP, none with confidence ($P < 0.001$ compared with definite). FPS was present in four of 24 subjects in the control group, half with confidence ($P < 0.001$ compared with definite).

Optic nerve sheath distention

Optic nerve sheath diameter, the maximum optic nerve sheath diameter measured within the orbit on T2-weighted axial images, was largest in the definite PTCS group (mean 6.98 mm, 95% confidence interval [CI]: 4.65 to 8.85 mm). However, there were no significant differences between groups (Table 1, online supplement). When distention was defined as greater than 5.5 mm, as suggested by Hoffman et al.,[16] 89% of subjects were positive for this finding across all groups, again with no significant difference between groups. To determine the best cutoff for our data, we compared ONSD with two of three other MRI findings. Receiver operating characteristic curve analysis demonstrated that a cutoff of 6.65 mm maximized sensitivity and specificity, but still, there

TABLE 1
Subject Characteristics: Number of Subjects With Each Demographic and Clinical Characteristic

Characteristic	Definite PTCS n = 60	Probable PTCS n = 12	Elevated OP n = 23	Control n = 24	*P* value
Characteristics defined by group classification					
Normal neurological examination and CSF constituents	60	12	23	24	NT
Papilledema	60	12	0	0	NT
Elevated opening pressure	60	0	23	0	NT
Opening pressure (mmHg): median (twenty-fifth to seventy-fifth percentile)	370 (353-445)	233 (203-250)	330 (312-365)	230 (181-250)	NT
Imaging characteristics based on clinical report					
Normal brain neuroimaging (MRI/HCT) by clinical review	60	12	23	24	NT
MRI suggested findings of PTCS on original clinical report	5	1	0	0	NT
MRV on original clinical report					
Normal	48	11	18	11	NT
Abnormal (attenuated transverse sinus)	1	0	0	0	
Not done	11	1	5	13	
Primary versus secondary PTCS					1.0
Primary	50	8	-	-	
Secondary	9	1	-	-	
Unsure	1	3	-	-	
Age: median (twenty-fifth to seventy-fifth percentile)	12.3 (8.3-15.5)	9.4 (6.9-13.3)	14.1 (10.6-16)	13.1 (9.7-14.9)	0.1473
Female: number (%)	37 (62)	7 (58)	14 (61)	13 (54)	0.935
Race					0.145
Asian	0	0	1	1	
Black or African American	12	0	4	2	
White	41	12	18	20	
Unknown/not reported	7	0	0	1	
BMI: median (twenty-fifth to seventy-fifth percentile)	23.8 (18-28.5)	21.7 (18.2-26.3)	23.6 (21.4-26.5)	19.2 (16.4-25.1)	0.2248
BMI *z* score: mean (95% CI)	1.1 (0.8-1.4)	1.1 (0.4-1.8)	1.3 (0.9-1.6)	0.46 (-0.1-1.0)	0.0943
BMI missing	3	2	4	3	

Abbreviations:
ANOVA = Analysis of variance
BMI = Body mass index
CI = Confidence interval
HCT = Head computed tomography
MRI = Magnetic resonance imaging
NT = Not tested because characteristics were used for classification per the revised criteria
OP = Opening pressure
PTCS = Pseudotumor cerebri syndrome
Median and interquartile range are presented for each continuous variable with a nonparametric distribution. Mean and 95% CI and presented for the continuous variable with parametric distribution. Comparisons were made across groups, and *P* values are presented (from Fisher's exact or chi-square test to compare counts in each group, from ANOVA to compare mean of continuous parametric variables, and from Wilcoxon rank-sum test to compare median of continuous, nonparametric variables).

was no significant difference between definite PTCS and control groups. The presence of tortuosity and ONSD did not result in a significant difference between groups.

Transverse venous sinus stenosis

TSS, defined as any area of focal stenosis on postcontrast MRI or MRV, was present in 74% (n = 37/50) of the definite PTCS group, 10% (n = 1/10) of the probable PTCS group ($P = 0.001$), 5% (n = 1/21) of the elevated OP group ($P < 0.001$), and 0% (n = 0/17) controls ($P < 0.001$). The sensitivity of TSS alone for the diagnosis of definite PTCS was 74% (95% CI: 60% to 85%), and the specificity was 100% (95% CI: 80% to 100%). To confirm that transverse sinus hypoplasia and stenosis were distinct, the two were examined separately. Stenosis and hypoplasia were poorly correlated, and hypoplasia was seen in a similar proportion of all groups.

Correlations between imaging characteristics

The correlation between the individual imaging characteristics was examined. There was moderate correlation between PGF and FPS (0.53), FPS and ONSD (0.54), TSS and PGF (0.55), and TSS and FPS (0.55). All other correlations between the four imaging criteria were between 0.4 and 0.5.

Analysis of overall imaging characteristics

Review of original clinical MRI reports for all 119 subjects indicated that only five in the definite PTCS group and one in the probable PTCS met three of four imaging criteria for diagnosis, and in none of these cases did the presence of imaging findings affect the diagnostic group. Research re-review confirmed the findings in these six subjects, and an additional 28 subjects (27 definite PTCS, one control) were found to have imaging signs of PTCS (Figure 4).

We examined the sensitivity and specificity of different combinations of imaging criteria. When using a threshold value of 5.5 mm for ONSD, the sensitivity of at least three of four MRI findings (PGF, ONSD, FPS, and TSS) was 62% (95% CI: 47% to 75%), and the specificity was 95% (95% CI: 77% to 100%). Using the calculated cut point of 6.65 mm for ONSD, the sensitivity of three of four criteria (PGF, ONSD, FPS, and TSS) fell to 53% (95% CI: 39% to 67%) and had no effect on specificity. If ONSD was excluded due to commonality, the presence of two of three criteria (FPS, PGF, and TSS) had a sensitivity of 65% (95% CI: 51% to 77%) for definite PTCS and a specificity of 95% (95% CI: 77% to 100%). As noted above, the sensitivity of TSS alone was 74%, and the specificity was 100%.

There were patients with zero of four imaging findings in all groups (five in definite, three in probable, six each in elevated OP and control), without significant differences among groups. The specificity of zero imaging findings for control (versus definite PTCS) was 90% (95% CI: 29% to 97%).

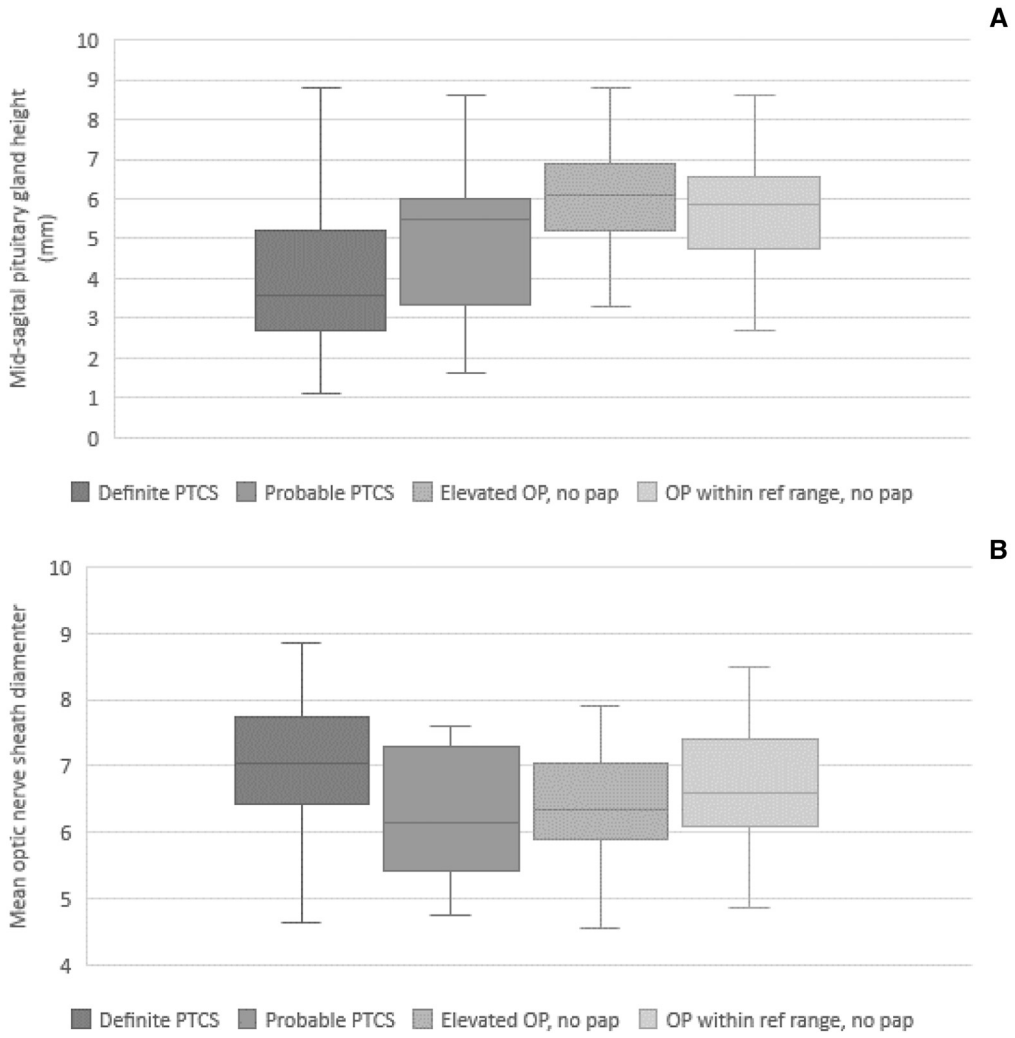

FIGURE 3. Comparison of pituitary gland height and optic nerve sheath diameter measurements between the study groups. (A) Box plot showing a significant reduction in median pituitary gland height for the definite PTCS group ($P < 0.001$ compared with elevated OP and control groups). (B) Box plot showing larger mean optic nerve sheath diameter for the definite PTCS group, but not significantly different from probable PTCS, elevated OP, or controls

Univariate and multivariate modeling

Univariate logistic regression models were created to examine the effects of imaging and patient variables on odds of PTCS (Table 2, online supplement). To compare the importance of the different imaging criteria and adjust for covariates, multivariable modeling was also performed. Because there were no control subjects with TSS, the models examined predictors of definite PTCS in subjects without TSS. Models that included any combination of FPS and PGF were statistically equivalent. The model using the composite variable FPS or PGF shows an odds ratio of 4.96 ($P = 0.042$) (Table 2).

Sensitivity analyses

Univariate analysis with the different comparison groups yielded similar results compared with the primary analysis (Table 2, online supplement). Multivariate modeling confirmed that transverse sinus stenosis was the most significant predictor of pseudotumor (Table 2). TSS was also the most significant predictor of having elevated CSF pressure. In alternate predictive models for these outcomes, either FPS or PGF were significant, consistent with their high degree of correlation. Therefore the simplest model that accounted for the presence of FPS or PGF was included. These

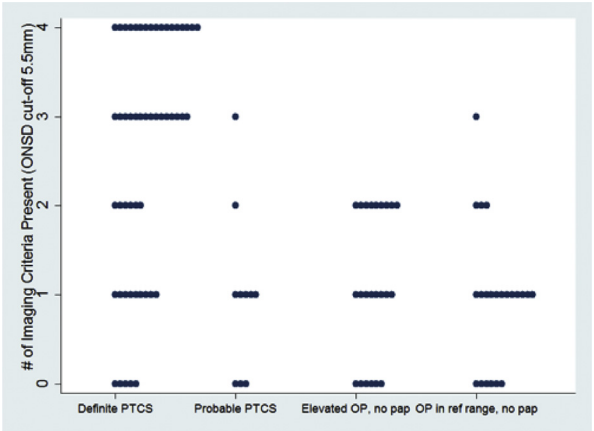

FIGURE 4. Count of subjects with specified number of imaging criteria present by group. OP, Opening pressure; PTCS, pseudotumor cerebri syndrome. The color version of this figure is available in the online edition.

models had similar area under the curve and were not statistically different from the models that included both variables. Of note, ONSD was not significant in any model, further demonstrating that two of three of the imaging criteria (excluding ONSD) have a moderate sensitivity and high specificity for PTCS.

Discussion

Summary of overall findings

The use of at least three of the MRI findings proposed by Friedman et al.[6] has not been previously validated for the diagnosis of PTCS in children. This study shows that at least three of four MRI characteristics were associated with a robust specificity (95%) but moderate sensitivity (62%) for definite PTCS. Thirty-four subjects (29%) had three of four imaging criteria based upon research review by the neuroradiologist. Research review of imaging did not result in reclassification of any subjects, and still no subjects met criteria for suggested PTCS without papilledema based on imaging findings. Interestingly, sensitivity and specificity were maximized by using either the presence of TSS alone (sensitivity 74% [95% CI: 60% to 85%] and specificity 100% [95% CI: 80% to 100%]) or the presence of two of three of TSS, FPS, and PGF (sensitivity 65% [95% CI: 51% to 77%] and specificity 95% [95% CI: 77% to 100%]). All four imaging criteria were seen in 33% of those with definite PTCS, but not in subjects in any other groups. Zero criteria were seen in subjects in all groups, so the absence of all imaging criteria does not rule out PTCS.

Pituitary Gland Flattening, Flattening of the Posterior Sclera, and Transverse Sinus Stenosis

We found that TSS, FPS, and PGF were independently specific for definite PTCS. In the overall comparison between definite PTCS and controls, all subjects with TSS had definite PTCS. In subjects without TSS, multivariate models with PGF, FPS, or either were similar, with an odds ratio of nearly 5 for definite PTCS.

Optic nerve sheath distention

ONSD had a lower specificity than the other three proposed criteria. ONSD measurements across all groups were larger than reported in previous studies,[21] which is most likely due to differences in MRI scanning technique. The magnetic resonance scanners at our institution are all 1.5- or 3-T magnets (slices 2 to 3 mm). This fact avoids volume averaging, allowing for more accurate measurements. Other explanations are possible. (1) *Axial versus coronal*: the 5.5-mm threshold was proposed based on maximal diameter measured via coronal images,[16] but in this study ONSD was measured as the maximum optic nerve sheath diameter within the orbit on axial images. We surmise that axial or coronal cross sections should not substantially affect ONSD measurements, particularly with thin-section imaging. (2) *Motion artifact*: One study proposed measuring ONSD at a standard location more posteriorly in the orbit, to decrease confounding from motion artifact.[21] Data confounded by motion artifact were not recorded, so this is an unlikely explanation. (3) *Age-related*: It is possible that the optic nerve sheath is more distensible in children, and the prior 5.5 mm cutoff was obtained in adults. However, there is evidence that optic nerve sheath diameter in children correlates with increasing age.[22] Overall, acknowledging the comparatively large measurements for ONSD, our data suggest that ONSD is not a robust predictor of PTCS in children. At least one prior study also found that there was overlap in the size of the optic nerve sheath between subjects with PTCS and controls with normal MRI.[23]

Comparison with prior studies

In 2006, one study of adults with PTCS found that the specificity of FPS was 100% for PTCS, although the cutoff for elevated CSF OP was defined as greater than 20 cm H_2O, which may have artificially elevated the specificity.[17] Görkem et al. evaluated the MRIs of 25 subjects with PTCS and 20 controls (who received MRI for "headache or irritability" and were read as normal), and found a slightly lower specificity of PGF, but higher specificity of ONSD and FPS.[24] The investigators did not evaluate transverse sinus stenosis. In a study of 11 children, 91% demonstrated ONSD (defined as more than 5 mm) and 46% had FPS on MRI, but this was confounded by the use of OP cutoffs dependent on age (elevated if greater than 180 mm H_2O if younger than 8 years and more than 250 mm H_2O if 8 years or older),[25] which may be inaccurate.[7] Before the proposition of the revised criteria for diagnosis of PTCS,[6] Lim et al. examined similar MRI characteristics to those in the present study, with the exclusion of TSS, and found lower proportions of patients with intracranial hypertension to have PGF, ONSD, or FPS.[26] Our results suggest that TSS is an important predictor of PTCS. Consistent with this, Maralani et al. also found that the specificity of TSS

TABLE 2
Multivariate Analyses

Model	For Definite PTCS versus Control	For Definite PTCS versus Not (Control + ElevOP)		For PTCS (Definite + Probable) versus Not (Control and ElevOP)		Elevated OP (Definite PTCS + ElevOP) versus OP in Reference Range (Probable PTCS + Control)			
PseudoR2	0.1383	0.4505		0.3254		0.3021			
AUC	0.8392	0.8770		0.8099		0.8366			
N	42 (*excluding those with TSS)*	85		95		95			
		OR	*P* value	OR	*P* value	OR	*P* value	OR	*P* value
Age, years		-		-		-		1.207	0.032
BMI *z* score		1.615	0.095	-		-		-	
Flattening of pituitary or posterior sclera		4.963	0.042	2.402	0.170	1.483	0.476	7.683	0.008
Transverse sinus stenosis (any, ref = none)		Excluded because no control had TSS		66.759	<0.001	48.639	<0.001	13.95	0.016

Abbreviations:
AUC = Area under the curve
BMI = Body mass index
ElevOP = Elevated opening pressure
OP = Opening pressure
OR = Odds ratio
PTCS = Pseudotumor cerebri syndrome
TSS = Transverse venous sinus stenosis

(using a combined stenosis score) was also 100%, and they highlighted the increased diagnostic yield when MRV was completed.[27]

A prior study from our group validating these imaging findings in adults[13] showed a similarly robust specificity of three of four imaging characteristics. Three of four MRI findings were found more often in the elevated OP group in adults. This finding may be explained by a potentially longer duration or recurrent episodes of increased ICP, producing these MRI findings over time. We found FPS to be the most specific imaging finding, but were unable to conclusively report the specificity of TSS, due to the low proportion of patients in the control group who had MRVs. In a comparison of an adult study[15] and a pediatric study[17] that used the same imaging criteria, the prevalence of empty sella was less in children, but there was no difference in the prevalence of the other imaging findings.[28] This suggests that the updated diagnostic criteria may be universally applicable.

Hartmann et al. also compared the prevalence of MRI findings in different aged children with that in adults and found that prepubescent children (less than 11 years old) did have similar MRI findings as adults, but at a lower incidence. The median age across groups in our study ranged from 9.4 to 14.1 years, and when compared with similarly aged patients in their study, PGF, TSS and FPS were found in higher percentages of patients.[23] This finding may be due to classification of patients based on modified Dandy criteria and the neuroradiologists' awareness of the diagnosis of PTCS in all patients.

Most recently, Inger et al. reviewed these same diagnostic criteria for PTCS in 50 pediatric patients and found a much higher rate of those with definite PTCS without any imaging findings (23 of 31), although the timing of the neuroimaging during the disease course is unclear.[29] Furthermore, no patient with definite PTCS had more than two of the four imaging characteristics, and none displayed transverse sinus stenosis, which we found to be the most specific imaging finding. Although these data provide support for the greater specificity of these imaging findings, it is unclear if the MRI or MRVs were re-read by neuroradiologists. The research re-review of the neuroimaging allowed for the identification of an additional 28 subjects with MRI findings in this study and possibly could have altered Inger et al.'s results.

Limitations

There are limitations to our study, as it was retrospective. There were significant motion and orthodontic hardware artifacts in some subjects, although not different among groups. An experienced neuroradiologist, who was unaware of the clinical diagnosis or original MRI report, re-reviewed all images using standard techniques, but establishing the presence of MRI features remains subjective; this would tend to increase variability and would have biased our results toward the null hypothesis, strengthening our positive results. The increased frequency of imaging criteria based on research review compared with initial clinical review limits the generalizability of our results. The control and elevated OP groups included subjects who had MRIs and LPs for clinical suspicion of PTCS. Therefore controls in this study could have had some imaging findings that relate to the presenting symptoms. If this were true, it would have also biased our results toward the null hypothesis and increases confidence in our positive findings.

Conclusions and future directions

The presence of three of four (or two of three, excluding ONSD) imaging criteria and TSS alone had a moderate sensitivity and robust specificity for definite PTCS. It may be appropriate to consider revision of the diagnostic criteria for PTCS in children to reflect that imaging abnormalities include either TSS alone or two of three of TSS, FPS, and PGF. Prospective studies could assess whether treatment for PTCS affects these imaging findings. Although Chang et al. demonstrated the persistence of imaging findings after resolution of papilledema in adults, the chronicity of these imaging findings in children remains unclear.[30]

Clinically, the presence of these imaging findings can assist in confirming the diagnosis of PTCS, especially in those cases wherein the presence of papilledema may be in question. The presence of TSS, especially in association with PGF or FPS, should significantly raise suspicion for PTCS. However, as the sensitivity of these criteria is moderate and there were cases in all four groups that had zero imaging criteria, the absence of these imaging criteria does not rule out the possibility of PTCS and funduscopic examination should still be performed. These data argue against the need for diagnostic evaluation for PTCS in children, unless papilledema, TSS, or three of four imaging criteria are present.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2019.04.010.

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