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Original Article

Presenting Symptomatology and Risk Factors in Pediatric Secondary Intracranial Hypertension due to Venous Sinus Thrombosis

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ABSTRACT

Background: There remains debate regarding the need for venous imaging in pediatric intracranial hypertension.
Methods: Records of patients aged 18 years or younger who were evaluated in the intracranial hypertension clinic at Nationwide Children's Hospital in Columbus, Ohio, were reviewed. Past medical history, diagnostic evaluation, and presenting symptoms were examined to evaluate differences in symptomatology presentation and risk factors in patients with pediatric intracranial hypertension with and without thrombosis.
Results: A total of 226 patients met inclusion criteria, 145 were diagnosed with primary intracranial hypertension, 81 with secondary intracranial hypertension, with 17 noted to have venous sinus thrombosis as the cause of their secondary intracranial hypertension. Of those with thrombosis, 41.2% did not have any thrombosis risk factors. Headache was the most prominent symptom, present in 73.8% (n = 107) of patients with primary intracranial hypertension, 87.5% (n = 56) of patients with secondary intracranial hypertension without thrombosis, and 82.4% (n = 14) with thrombosis.
Conclusions: The only clinically significant difference in presenting symptomatology between the thrombosis and the other groups was nausea or vomiting. Predisposing factors to develop thrombosis were absent in 41.2% of patients. Hence, the need for venous imaging in pediatric intracranial hypertension cannot be clearly determined by clinical presentation or risk factors alone. Patients with indwelling catheters should receive imaging in the region of their catheter to rule out catheter-associated thrombosis.

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Introduction

Primary intracranial hypertension (PIH), also known as pseudotumor cerebri and idiopathic intracranial hypertension, is associated with increased intracranial pressure with no apparent etiology. Laboratory investigations, including cerebrospinal fluid (CSF) studies, are normal and no structural abnormalities are detected on imaging studies. In contrast, increased intracranial pressure in secondary intracranial hypertension (SIH) is the direct result of another condition. Documented causes include head trauma, cerebral venous sinus thrombosis (CVST), meningitis, and certain medications including tetracyclines, steroids, and fat-soluble vitamins.[1] Laboratory and imaging studies may provide diagnostic clues to the underlying etiology, and appropriate treatment of the causative condition typically results in resolution of the intracranial hypertension.

Freidman et al.[2] suggest venous magnetic resonance imaging (MRV) is only needed for patients outside the prototypical patient demographic. One could argue that any pediatric patient would fall outside the normal for intracranial hypertension and thus warrant further imaging, but there are very few studies in this population.

Conflicts of interest: There are no conflicts of interest for any of the authors.

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Standridge et al.[3] retrospectively reviewed a cohort of pediatric patients with intracranial hypertension and found that 11% had evidence of thrombosis on MRV. They found no clinically significant differences in the demographics between the groups. Unfortunately, this study did not consider presenting symptomatology.

The aim of this study was to compare presenting symptomatology and risk factors in patients ultimately diagnosed with either PIH or SIH to those with SIH because of venous sinus thrombosis.

Materials and methods

The Institutional Review Board of Nationwide Children's Hospital approved the inclusion in the study database of patients seen in the subspecialty intracranial hypertension clinic from inception (May 2010) through December 2017. Inclusion criteria included patients who received a diagnosis of intracranial hypertension and follow-up at our institution, had cerebral venous imaging performed, and were aged 18 years or younger at the time of diagnosis. Cerebral venous imaging was performed via dedicated MRV or by traditional magnetic resonance imaging (MRI) with contrast that allowed the interpreting radiologist to adequately visualize the venous system.

Data on past medical history, evaluation, and presenting clinical features for each patient were collected along with basic demographic information. Among patients with SIH, data on the underlying cause of the patient's SIH were also collected. Opening CSF pressure was measured in the left lateral decubitus position, with legs extended. For dichotomous variables, Pearson's χ^2 tests for independence were conducted to examine potential differences between groups. Continuous variables were compared between groups using one-way analyses of variance. *Post hoc* probing (Tukey HSD Q statistic) was completed for all omnibus values reaching significance. For all analyses, a P value ≤ 0.05 was considered significant.

Results

A total of 256 records were reviewed, with 226 patients meeting inclusion criteria. Seventeen patients had thrombosis (Table 1), and an additional 64 patients had SIH related to other disorders (Table 2). The remaining 145 patients were diagnosed with PIH. There were no significant differences in age, gender, body mass index, or ethnicity across the three groups (Table 3). Headache was the most common presenting symptom in all three cohorts (73.8% to 87.5% of patients). The second most common presenting symptom was nausea or vomiting in the thrombosis cohort, photophobia in SIH, and blurred vision in PIH. In comparing groups, the proportion of patients presenting with symptoms of photophobia, nausea or vomiting, neck pain, or dizziness all reached clinical significance with P values of 0.03, <0.01, 0.02, and 0.04, respectively. Specifically, photophobia and neck pain were significantly more common in patients with SIH than either the thrombosis or PIH groups (P values 0.01 and <0.01, respectively). In addition, dizziness was more common in the thrombosis group than in individuals with PIH ($P = 0.01$). Nausea or vomiting was more common in the thrombosis group compared with both the SIH and PIH groups (P values <0.01, and 0.05, respectively) and more common in patients with SIH than those with PIH ($P < 0.001$; Table 4). The remainder of presenting symptoms did not reach significance. Because of zero values in the thrombosis cohort for patients with tinnitus or transient visual obscurations, χ^2 tests were not conducted for these presenting symptoms.

Opening CSF pressure measurements were not available for all patients, and the pressure differences between the groups did not reach significance. Specifically, two patients in the thrombosis cohort had opening CSF pressures that exceeded the measuring capability of the manometer, and six patients did not have an opening pressure recorded. In the SIH cohort, 11 patients had opening pressure values that exceeded the measuring capability of the manometer, and six patients had procedural errors resulting in an opening pressure not being recorded. The PIH cohort had 12 patients who exceeded the measuring capability of the manometer, nine patients with the measurement falling within the opaque adapter on the two-part manometer, and three patients had errors in opening pressure measurements.

Thrombosis was identified in four individuals on contrast computed tomography, and two others had intrathoracic thrombosis. In the remaining 11 thrombosis patients, five were diagnosed via dual MRI, three had suspicion but not clear evidence of thrombosis on dual MRI, and the thrombosis was missed in three patients using noncontrast MRI. In these 11 thrombosis patients, use of any MRI study had a sensitivity of 45.5% in documenting

TABLE 1.
Thrombosis Patients

Patient ID (Gender)	Presentation Risk Factor	Thrombosis Location
1 (F)	None	SSS, torcula, distal straight sinus, partial TS, superficial cortical veins at vertex
2 (F)	None	Bilateral TS
3 (F)	Lymphoma, indwelling catheter	SVC
4 (F)	None	Bilateral TS
5 (M)	Leukemia, indwelling catheter	Right IJ extending into braciocephalic, SVC
6 (F)	Nephrotic syndrome, concurrent illness, and dehydration	SSS, TS, straight sinus, SS
7 (F)	None	Bilateral distal TS
8 (F)	Mastoiditis	Left SS, TS, jugular
9 (M)	Mastoiditis	Right TS, sigmoid confluence
10 (M)	Leukemia	SSS, left TS
11 (M)	None	Left SS
12 (M)	Mastoiditis	Right TS, SS
13 (F)	None	SSS
14 (M)	Poorly controlled nephrotic syndrome	SSS, right TS
15 (F)	Mastoiditis	Right jugular, TS, SS
16 (F)	None	Right TS
17 (M)	Mastoiditis	Right TS, left TS, SS, jugular into bulb

Abbreviations:
IJ = internal jugular
SS = sigmoid sinus
SSS = superior sagittal sinus
SVC = superior vena cava
TS = transverse sinus

TABLE 2.
Causes of Secondary Intracranial Hypertension

Cause	Number of Patients
Meningitis/encephalitis*	18
Leukemia	10
Minocycline	8
Chiari 1 malformation*	4
Shunt-dependent shunted cyst*	4
Ventriculomegaly/hydrocephalus*	3
Doxycycline*	3
Juvenile inflammatory arthritis*	3
Venous malformation/stenosis	2
Behcet disease	2
Crohn disease*	2
Growth hormone	1
Muckle-Wells/cryopyrin-associated disease	1
Lymphoma	1
Lithium	1
Steroid withdrawal	1
Rocky Mountain spotted fever*	1
Small vessel vasculitis*	1
Kawasaki disease	1
Poststrep*tococcal* glomerulonephritis	1
Membranoproliferative glomerulonephritis type 2*	1
Meningeal sarcoma/radiation	1

* Denotes categories with patients that had multiple diagnoses for their intracranial hypertension.

thrombosis; the sensitivity increased to 62.5% if dual MRI was used.

In the thrombosis cohort, 41.2% (n = 7) did not have any identifiable risk factor for thrombosis at the time of presentation (Table 1). The patient with nephrotic syndrome (Patient 6) who presented with a concurrent illness had low antithrombin III and protein S that were attributed to the nephrotic syndrome. This patient was also later found to have a heterozygous factor V mutation. Patient 7 did not have any outward risk factors at initial presentation, but was subsequently found to have a protein S deficiency. Patient 17 was also found to have a heterozygous factor V mutation.

Discussion

CVST has an annual incidence of seven per one million children.[4] The clinical presentation is variable and more than 80% of patients have a favorable outcome. Occlusion of the smaller cerebral veins can lead to edema and infarction, but it is the occlusion of the major venous sinuses that is believed to lead to intracranial hypertension via increased venous pressure resulting in impaired absorption of cerebrospinal fluid.[4]

An increase in intracranial pressure may be the only presenting clinical symptom in up to one fifth of patients with CVST.[4] Standridge et al.[3] found 11% of those who received venous imaging had evidence of thrombosis. In our cohorts, there were clinically significant differences in the proportion of symptoms of photophobia, nausea or vomiting, neck pain, and dizziness between the groups. However, *post hoc* analyses inferred that significant differences in the proportion of presenting symptoms for photophobia, neck pain, and dizziness were because of significant differences between the PIH and SIH groups and not the thrombosis group. Although the proportion of presenting nausea or vomiting symptoms was significantly different in the thrombosis cohort compared with those with PIH and SIH, this finding is nonspecific and should not be used as the sole factor in the decision whether to obtain imaging.

Possible risk factors for CVST include infections (otitis and mastoiditis), traumatic head injuries, pregnancy (especially last trimester), immediate postpartum period, medications (growth hormone and L-asparaginase), and iatrogenic causes (venous catheterization, neurosurgical intervention).[4-6] Other conditions associated with CVST include diabetic ketoacidosis, inflammatory

TABLE 3.
Patient Demographics

	Thrombosis (n = 17)	SIH (n = 64)	PIH (n = 145)	*P* value
Mean age (years)	14.77 (2.3-16.7)	12.7 (2.8-18.4)	11.9 (2.1-18.6)	0.10
Female (%, (n))	53 (9)	64.1 (41)	63.4 (92)	0.92
Ethnicity (%, (n))				0.61
Caucasian	70.6 (12)	75 (48)	75.2 (109)	
African American	11.8 (2)	12.5 (8)	13.1 (19)	
Biracial	6.3 (1)	3.1 (2)	3.4 (5)	
Other	11.8 (2)	9.4 (6)	8.3 (12)	
BMI (M, (range))	28.2 (15.5-61.8)	28.5 (14.4-56.5)	27.5 (12.5-53.6)	0.81
Weight designation (%, (n))				0.64
Normal weight	47 (8)	34.4 (22)	31 (45)	
Overweight	5.9 (1)	12.5 (8)	15.9 (23)	
Obese	47 (8)	53.1 (34)	51.7 (75)	
Opening pressure (cm H_20, M, (range))	40.7 (n = 7) (16-70)	37.4 (n = 47) (15-67)	34.7 (n = 121) (17-65)	0.15
Presenting symptoms (%, (n))				
Papilledema	76.5 (13)	33 (51.5)	67.6 (98)	0.08
Headache	82.4 (14)	87.5 (56)	73.8 (107)	0.08
Photophobia	52.9 (9)	57.8 (37)	38.6 (56)	**0.03**
Phonophobia	23.5 (4)	40.6 (26)	25.5 (37)	0.07
Nausea/vomiting	82.4 (14)	56.3 (36)	31 (45)	**<0.01**
Tinnitus	0	25 (16)	21.4 (31)	n/a
Neck pain	29.4 (5)	31.3 (20)	15.2 (22)	**0.02**
Dizziness	41.2 (7)	23.4 (15)	16.6 (24)	**0.04**
Blurry vision	23.5 (4)	26.6 (17)	40 (58)	0.10
Diplopia	23.5 (4)	31.3 (20)	22.1 (32)	0.36
Transient visual obscurations	0	9.4 (6)	6.2 (9)	n/a

Abbreviations:
BMI = body mass index
PIH = primary intracranial hypertension
SIH = secondary intracranial hypertension
P values reaching significance are indicated in bold.

TABLE 4.
Post hoc χ^2 Comparison *P* Values

Presenting Symptom	Thrombosis versus SIH	Thrombosis versus PIH	SIH versus PIH
Photophobia	0.72	0.25	**0.01**
Dizziness	0.14	0.15	0.24
Nausea/vomiting	**0.05**	**<0.01**	**<0.001**
Neck pain	0.88	0.14	**<0.01**

Abbreviations:
PIH = primary intracranial hypertension
SIH = secondary intracranial hypertension
P values reaching significance are indicated in bold.

bowel disease, systemic lupus erythematosus, thyrotoxicosis, nephrotic syndrome, gastroenteritis, chronic hemolytic anemia, B-thalassemia major.[7-12] A genetic predisposition should also be considered. Prothrombotic risk factors exist in one third to two thirds of patients with CVST. DeVeber et al. noted that 32% of children tested for a prothrombotic disorder had an abnormality. Anticardiolipin antibody and factor V Leiden were the most common acquired and genetic disorders, respectively.[13] The remaining prothrombotic disorders were attributed to the underlying disease. It is unclear whether acquired prothrombotic disorders cause CVST or represent mere associations. No CVST risk factors were identified in 41.2% of our thrombosis patients. Standridge et al.[3] documented a factor V Leiden mutation in two of five (40%) thrombosis patients. In our thrombosis cohort, three patients (17.6%) were subsequently found to have prothrombotic diagnoses. Patient 6 had low antithrombin III and protein S levels following an exacerbation of her nephrotic syndrome associated with a concurrent illness, but she had a heterozygous factor V mutation. Patient 7 had protein S deficiency, and patient 17 had a heterozygous factor V mutation; neither of these individuals had any outward risk factors at the time of presentation.

Adequate imaging to exclude CVST requires a high index of suspicion. Studies recommend a multisequence approach to reduce the risk of missed thrombosis.[14,15] MRV is the most sensitive, and gradient echo T2-weighted sequences are the most specific.[15] In our thrombosis cohort, the sensitivity of MRI alone was 45.5%. This sensitivity was increased to 62.5% with the use of contrast. This finding supports the need for dedicated venous imaging if the initial MRI is negative.

Interestingly, 29.4% of the patients (n = 5) in the thrombosis cohort had extracranial thrombosis. Of these, three extracranial thromboses were associated with mastoiditis and were found on routine imaging. The other two patients had thrombosis involving the superior vena cava associated with indwelling catheters placed for treatment of leukemia and lymphoma. The likely etiology is a combination of the hypercoagulable state related to their cancer and the nidus of the catheter, which when combined placed these patients at high risk to develop thrombosis. These two patients highlight the need for imaging of the neck and chest to assess for extracranial thrombosis in at-risk individuals.

Conclusions

In our cohort, the only clinically significant difference in presenting symptoms of patients with PIH, SIH, or those with SIH due to thrombosis was the percentage of patients presenting with nausea or vomiting. However, given the relatively nonspecific nature of this symptom, it is difficult to use this symptom as a marker for determining the need for venous imaging. Hence, we recommend that all patients with suspected intracranial hypertension receive neuroimaging (MRI/MRV) to rule out thrombosis as the cause for their intracranial hypertension. Furthermore, patients with indwelling venous catheters imaging in the region of their catheter to rule out catheter-associated thrombosis should be considered.

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