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Elevated Cerebrospinal Fluid Opening Pressure in a Pediatric Demyelinating Disease Cohort

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Abstract

BACKGROUND—Cerebrospinal fluid opening pressure is elevated with central nervous system infection and vasculitis, but has not been studied in inflammatory demyelinating disease. This retrospective study sought to determine whether children with demyelinating disease demonstrate elevated cerebrospinal fluid opening pressure, and to explore possible clinical and radiologic correlates.

METHODS—Pediatric patients with acute disseminated encephalomyelitis, multiple sclerosis, or a clinically isolated syndrome (including optic neuritis and transverse myelitis) who had a lumbar puncture within 1 month of presentation were eligible for inclusion, and were compared with a reference cohort of healthy children from the same institution. Regression analyses were used to determine the association of variables collected with opening pressure.

RESULTS—Opening pressure was elevated in 15 of 53 (28%) children, which was significantly higher than the reference cohort ($P = 0.001$). There was no relationship between elevated opening pressure and any of the clinical or radiologic variables collected.

CONCLUSION—Although almost one third of children with inflammatory demyelinating disease have an elevated cerebrospinal fluid opening pressure, the clinical and radiologic variables evaluated in this study did not explain this finding, and further understanding may require assessment of cerebrospinal fluid flow dynamics.

Keywords

pediatric; demyelinating disease; opening pressure; intracranial pressure; lumbar puncture; multiple sclerosis; acute disseminated encephalomyelitis

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Introduction

The standard evaluation for a child with a suspected demyelinating disease includes a lumbar puncture. Routine measurements include cell counts, protein, glucose, oligoclonal bands, and an evaluation of cerebrospinal fluid opening pressure. Although increased intracranial pressure has been previously reported in a 15-year-old girl with multiple sclerosis,¹ a systematic investigation to determine whether the cerebrospinal fluid opening pressure is routinely elevated with acute demyelination has not yet been described. The purpose of this study was to determine whether children with inflammatory demyelinating disease have elevated cerebrospinal fluid opening pressure and to explore the possible clinical and radiological correlates.

Methods

We performed a retrospective analysis of all patients presenting with an initial demyelinating event at the Children's Hospital of Philadelphia between January 2007 and December 2011. Patients were included if they met consensus criteria for acute disseminated encephalomyelitis, multiple sclerosis, or a clinically isolated syndrome (including optic neuritis and transverse myelitis), were between ages 1 and 18 years, and had a lumbar puncture within 1 month of their initial clinical presentation.

Age, gender, body mass index (BMI), opening pressure, cerebrospinal fluid cell count and protein, prior corticosteroid use, clinical presentation (including presence of headache), presence of optic disc edema, and use of sedation at the time of the lumbar puncture were collected for each patient. Brain magnetic resonance imaging obtained at the time of lumbar puncture was also evaluated using a scoring tool² to determine lesion distribution, which served as a marker for the degree of white matter involvement. The presence of lesions or leptomeningeal enhancement was also recorded.

The percentage of patients with an elevated opening pressure (>28 cm of water)^{3,4} was then calculated and linear and logistic regression analyses (including multivariable analyses) were used to determine the association of variables collected with opening pressure. Using a test of proportions, the proportion of demyelinating patients with an elevated pressure was compared with the proportion of patients with increased pressure in a reference cohort previously collected at our institution. This reference cohort consisted of children undergoing diagnostic lumbar puncture as clinically indicated, with exclusion of all patients who had evidence of a disease process that might potentially elevate their opening pressure (e.g., meningitis, Chiari malformation) or who were treated with medications known to affect opening pressure.³ Of note, of the 197 patients in this reference cohort, 21 patients had a diagnosis of demyelinating or white matter disease. All of these patients were removed from the reference group before making any comparisons with the demyelinating cohort under current study.

Standard protocol approval

The study was approved by the Children's Hospital of Philadelphia's Institutional Review Board. A waiver of informed consent was granted as this study was a retrospective chart review.

Results

One hundred and seventeen patients with demyelinating disease met inclusion criteria and 53 of them had a documented opening pressure. Records indicate that all patients were in the lateral recumbent position for the procedure and a standard manometer was used in all cases.

To exclude selection bias, the demographics and clinical characteristics of the demyelinating cohort for whom opening pressure was recorded were compared with those of the patients without opening pressure recorded. There were no significant differences between the two groups (Figure). The rationale for measurement of opening pressure was not clearly documented by the ordering providers for the patients in this cohort.

For the demyelinating group with opening pressure recorded, 53% were female and the mean age was 10.6 years (Table 1). Notably, the mean BMI was 20.1 and only 16% of the cohort had a BMI ≥ 25 . Eighty-two percent of the cohort were sedated for the procedure, with the majority of patients receiving midazolam and/or fentanyl. Mean time from symptom onset to lumbar puncture was 9 days (range 0-30 days), whereas mean time from hospital presentation to lumbar puncture was 2.6 days (range 0-10 days).

Opening pressure ranged from 5 cm to 41 cm of water, with a mean of 23 cm of water (Table 2). Opening pressure was elevated in 15 of 53 (28%) children. Of the 15 patients, seven had monophasic acute disseminated encephalomyelitis, four were diagnosed with multiple sclerosis (two presented with optic neuritis), three had monophasic optic neuritis, and one had monophasic transverse myelitis. Optic disc edema was noted in eight patients (four with acute disseminated encephalomyelitis, three with monophasic optic neuritis, and one multiple sclerosis patient with an initial optic neuritis presentation). There was no relationship between elevated opening pressure and clinical diagnosis, complaint of headache, cerebrospinal fluid cell count, cerebrospinal fluid protein, BMI, or the use of sedation (Table 3). Additionally, there was no relationship between elevated opening pressure and the radiologic variables that were evaluated (Table 4). When compared with the proportion of patients with an elevated pressure in our reference cohort (10%), we found that the proportion of patients with increased opening pressure in our demyelinating cohort was significantly higher ($P = 0.001$).

Discussion

Almost a third of children in our demyelinating disease cohort had an elevated cerebrospinal fluid opening pressure, which is significant when compared with the 10% of children with elevated pressure in our reference cohort. The pathophysiology of elevated cerebrospinal fluid pressure in these children is not fully understood but does not appear to relate to

variables associated with central nervous system inflammation (cerebrospinal fluid cell count, protein) or to extensive central nervous system white matter involvement.

Though unmeasured in our study, we suspect that cerebrospinal fluid flow dynamics may be dysregulated with acute central nervous system demyelination and may ultimately result in elevated pressure in some patients. Another theory is that inflammation within the central nervous system may prevent adequate cerebrospinal fluid absorption, which would also result in increased pressure during an acute demyelinating attack.

Surprisingly, cerebrospinal fluid opening pressure elevation was not associated with BMI, although this relationship may have been masked by sample size as only a few of the patients in this cohort had an elevated BMI. As was seen in prior studies, age was not associated with cerebrospinal fluid opening pressure in this cohort.^{3,5}

Headache is a nonspecific symptom that occurred in this cohort independently of the opening pressure. Although many of the patients in this cohort experienced resolution of their headaches over time, we were unable to determine whether this was a result of treatment of their underlying inflammation, resolution of stressors, time, or other factors. Individuals in our cohort with elevated opening pressure were not treated with pressure-lowering medications such as acetazolamide and did not have repeat lumbar punctures to follow their pressures.

Our results highlight that opening pressure can be elevated in acute central nervous system demyelination and should be interpreted using the clinical context. For example, although pseudotumor cerebri may be suspected in a patient with bilateral acute vision loss and optic disc edema, bilateral optic neuritis should also be on the differential. In this scenario, clinical features suggestive of optic neuritis, such as pain with eye movement and loss of color vision, should be evaluated and may help to distinguish the two diagnoses.

We acknowledge that the rationale for obtaining an opening pressure could not be confirmed using a retrospective study design. Opening pressure may have been routinely ordered by some physicians or may have been prompted by clinical symptoms. To address this, we compared the demographics and disease processes of the group without opening pressure recorded to the group with opening pressure recorded to show that the children were not demonstrably different. We also reviewed the medical records of patients for whom an opening pressure was recorded, and we did not find a difference in symptoms (such as headache) that may have influenced the decision to obtain an opening pressure.

Although this study was limited by its retrospective nature and limited sample size, our data confirm that elevated cerebrospinal fluid opening pressure does occur in pediatric patients with acute demyelinating disease; investigations for additional causes of elevated opening pressure in these patients may be unnecessary. As clinical and visible radiologic variables do not explain this finding in our pediatric demyelinating cohort, further understanding may require assessment of cerebrospinal fluid flow dynamics.

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FIGURE.

Diagnostic breakdown of demyelinating disease patients with a recorded opening pressure versus those without an opening pressure recorded. There were no significant differences between the two groups. ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; MS, multiple sclerosis; ON, optic neuritis; TM, transverse myelitis. (The color version of this figure is available in the online edition.)

TABLE 1

Demographics of Demyelinating Patients With a Documented Opening Pressure as Compared to Those Without an Opening Pressure Recorded

Variable	Demyelinating Patients With Opening Pressure Recorded	Demyelinating Patients Without Opening Pressure Recorded	<i>P</i> Value
Age (years)	10.6	10.2	0.66
Gender (% female)	52.7	64.3	0.83
Body mass index (kg/m ²)	20.1	21.2	0.40
Sedation (% sedated)	82	72	0.99

TABLE 2

Summary of Opening Pressure Data by Diagnosis

Diagnosis	Mean Opening Pressure $\pm$ SD (cm of water)	Range of Opening Pressure (cm of water)	Percentage With Opening Pressure >28 cm of water (n)
ADEM	24.2 $\pm$ 9.6	5-39	38.8 (7)
MS	24.4 $\pm$ 8.5	8-38	28.5 (4)
ON	22.3 $\pm$ 9.4	6-41	23 (3)
TM	18.4 $\pm$ 9.1	8-36.5	14.2 (1)
All diagnoses	22.8 $\pm$ 9.0	5-41	28.3 (15)

Abbreviations:

ADEM = Acute disseminated encephalomyelitis

MS = Multiple sclerosis

ON = Optic neuritis

TM = Transverse myelitis

TABLE 3

Relationship of Clinical and Demographic Variables and Opening Pressure

Variable	<i>P</i> Value (Opening Pressure >28 cm of water) *	<i>P</i> Value (Opening Pressure Continuous Variable) †
Age	0.29	0.16
Body mass index	0.66	0.98
Use of sedation	0.52	0.44
Cerebrospinal fluid cell count (>8 cells)	0.83	0.93
Cerebrospinal fluid protein (>45 mg/dL)	0.15	0.10
Diagnosis	0.48	0.67
Pretreatment with corticosteroids	0.98	0.92
Complaint of headache	0.06	0.15

* Logistic

† linear regression analyses showed that there was no significant relationship between any clinical or demographic variable collected and elevated opening pressure.

TABLE 4**Relationship of Radiologic Variables and Opening Pressure**

Variable	<i>P</i> Value (Opening Pressure >28 cm of water) *	<i>P</i> Value (Opening Pressure Continuous Variable) †
Presence of T2 hyperintense lesions	0.18	0.11
Lesion distribution (total number of locations where lesions were present)	0.50	0.67
Lesion contrast enhancement	0.83	0.50
Leptomeningeal contrast enhancement	0.86	0.17

* Logistic

† linear regression analyses showed that there was no significant relationship between any radiologic variable collected and elevated opening pressure.