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Clinical and Prognostic Significance of Cerebrospinal Fluid Opening and Closing Pressures in Pediatric Pseudotumor Cerebri Syndrome

Shannon J. Beres^{a,b,*}, Claire A. Sheldon^{b,c}, Chantal J. Boisvert^{d,e}, Christina L. Szperka^f, Grace L. Paley^{a,g}, Evanette K. Burrows^h, Marianne R. Chilutti^h, Geraldine W. Liu^f, Shana E. McCormack^{g,i}, Grant T. Liu^{a,b,g}

^aDepartments of Neurology and Ophthalmology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

^bDivision of Ophthalmology, Neuro-ophthalmology Service, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

^cDepartment of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, British Columbia, Canada

^dDivision of Ophthalmology, Rady Children's Hospital San Diego, San Diego, California

^eDepartment of Ophthalmology, Gavin Herbert Eye Institute, University of California Irvine, Irvine, California

^fDivision of Neurology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

^gPerelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

^hCenter for Biomedical Informatics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

ⁱDivision of Endocrinology and Diabetes, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Abstract

Background: The purpose of this study was to determine the prognostic utility of closing pressure and volume of cerebrospinal fluid removed with respect to papilledema resolution and headache improvement in pediatric pseudotumor cerebri syndrome.

Methods: This is a retrospective observational study of 93 children with definite pseudotumor cerebri syndrome. The primary outcome measure was time to resolution of papilledema, and the secondary outcome measure was time to resolution of headache.

*Corresponding author. sberes@stanford.edu (S.J. Beres).

Shannon J. Beres, MD, provided the retrospective data abstraction for additional elements, data collection, electronic chart review, and original paper writing. Shana E. McCormack, MD, performed the data analysis. Grace L. Paley, MD, PhD, Claire A. Sheldon, MD, PhD, Evanette K. Burrows, BS, Marianne R. Chilutti, MS, and Geraldine W. Liu, ALM, provided the original data abstraction of the cohort into the electronic database. All authors provided proofreading.

Results: There were no significant differences in gender, age, or body mass index *z* score observed between subjects with (*N* = 35) and without (*N* = 58) documented closing pressure. The median time to resolution of papilledema was not statistically different between children above or equal to and those below the median closing pressure (170 mm of cerebrospinal fluid, *n* = 31, *P* = 0.391) or the volume of median cerebrospinal fluid removed (16 mL, *n* = 19, *P* = 0.155). There was no statistically significant difference detected in days of headache between the children with opening pressure above and equal to the median (400 mm of cerebrospinal fluid) and the children with opening pressure below the median (*n* = 44, *P* = 0.634).

Conclusions: No significant association between closing pressure, amount of cerebrospinal fluid removed, and time to resolution of papilledema due to pseudotumor cerebri syndrome was detected. The diagnostic and therapeutic purposes of either measuring the closing pressure or maximizing the volume of cerebrospinal fluid removed were not evident in these analyses.

Keywords

Pseudotumor cerebri; Idiopathic intracranial hypertension; Opening pressure; Closing pressure; Headache; Children; Papilledema

Introduction

Pseudotumor cerebri syndrome (PTCS) refers to the constellation of primary and secondary disorders that cause elevated intracranial pressure in patients with normal brain parenchyma and normal spinal fluid constituents; papilledema is typically present. Idiopathic intracranial hypertension (IIH) is the primary form of PTCS that occurs most commonly in obese adolescent and young adult women. However, in prepubertal children, the prevalence of IIH is similar in girls and boys, and they are more often of thin habitus.¹ Headaches are the most common symptom in pediatric IIH, occurring in 75%,² and are often both severe and debilitating. The mechanisms that cause primary or secondary PTCS and the associated headache are unknown.³

During diagnostic lumbar puncture, it is common to document the opening pressure, the total volume of cerebrospinal fluid (CSF) removed, and the closing pressure measured after the removal of CSF.^{4,5} The opening pressure during the lumbar puncture is integral to making the PTCS diagnosis¹; however, there is limited information about the clinical significance of the volume of CSF removed or the closing pressure measurements. Before widespread use of neuroimaging with modern volumetric analytic technology,⁶ the opening and closing pressures were used to estimate the volume of the CSF reservoir, known as the Ayala index (Ayala index = $(10 \times \text{closing pressure}) / \text{initial pressure}$) calculated after 10 mL of CSF was removed. A value of <5 suggested a small CSF reservoir as seen in the spinal block and a value of >7 indicated a large CSF reservoir similar to that of hydrocephalus.⁴ This diagnostic purpose is obsolete today, yet anecdotal experience with improved or worsened headache or papilledema with draining too much or too little fluid suggests a therapeutic value to recording such data. Without supporting data, some PTCS experts recommend attaining a low closing pressure by removing a high volume of CSF to improve symptoms, but short- and long-term outcomes have not been rigorously studied in adults or in children.

One study from 1974 documented these particular intracranial pressure dynamics in 20 patients with IIH using continuous monitoring from a ventricular catheter.⁷ In the 16 patients who exhibited unprovoked “plateau waves” with raised intracranial pressure of 300 to 800 mm of CSF for five to 20 minutes, there were no associated complaints of acute headache in this pressure range. Simultaneous ventricular catheter and lumbar drain were placed in five of the patients with a mean opening pressure of 300 mm of CSF and the mean closing pressure was 70 mm of CSF after removal of 15 to 25 mL. Predrainage pressures returned to baseline after an average of 82 minutes, and the authors did not mention the effect on headache. An evaluation of papilledema was not performed. There is a paucity of studies that report these lumbar puncture measurements and their relationship to resolution time of papilledema or headache in children or in adults with PTCS.

Our study investigates the relationship between opening pressure, closing pressure, and volume of CSF removed during diagnostic lumbar puncture for PTCS, and time to resolution of papilledema and headache in children.

Methods

This is a retrospective observational series using an electronic research database collected under an existing protocol approved by the Institutional Review Board at the Children’s Hospital of Philadelphia (IRB no. 12-010158), which includes waivers of consent, in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

Subjects

All children between ages two and 18 years diagnosed with PTCS between July 1, 1993, and April 16, 2013, were identified, and clinical data were abstracted into an electronic research database as described in detail in the paper by Paley et al.² A total of 427 patients were identified from two sites (Children’s Hospital of Philadelphia and Rady Children’s Hospital San Diego), and 93 patients were found to have definite primary or secondary PTCS by the revised criteria from 2013.¹ An elevated opening pressure was defined as ≥ 250 mm of CSF and ≥ 280 mm of CSF if the child was obese or given moderate sedation during the procedure.⁸

Clinical characteristics

In the electronic database, age, gender, body mass index z score (BMI-Z, with overweight denoted by BMI-Z ≥ 1.04), date of lumbar puncture, and opening pressure at the time of diagnosis (defined as within three months of the date of initial diagnosis) were extracted. Further medical chart review of the 93 patients included notation of the opening pressure, the closing pressure, the volume of CSF removed, the beginning and the end dates of headache and acetazolamide treatment. Information about headache was interpreted as present or absent based on patient recall as documented in the medical chart during each appointment. A “large volume tap” was defined by more than 30 mL of CSF removed.

Clinical outcomes

The primary outcome measure was the time to resolution of papilledema by ophthalmoscopy. The time to resolution was calculated by the amount of days between the first and the last dates of observed papilledema by a neuro-ophthalmologist at scheduled clinical visits. One key secondary outcome measure was the time to resolution of headache, calculated as the difference between the first date of headache and the last date of headache as recalled by the patient and documented in the clinic notes. Headache resolution within 10 days after the lumbar puncture was defined as “early headache resolution.”

Statistical analysis

Anthropometric BMI-Z was calculated according to the US Centers for Disease Control growth reference values.⁹ Summary statistics are presented as means $\pm$ standard deviations (SDs) or medians $\pm$ interquartile intervals were calculated, as appropriate. The associations between primary outcomes and the clinical characteristics of interest were explored using Pearson correlation analyses. A two-sample *t* test with equal variances was performed to determine whether there was a difference in age, BMI-Z, and gender between those with and those without closing pressures documented. Additionally, Kaplan-Meier survival analysis was used to estimate the time to resolution of papilledema from the opening pressure, the closing pressure, and the change in pressure (delta pressure), as well as the time to resolution of headache from the opening pressure. A two-sided *P* value of 0.05 was considered statistically significant. Statistical analyses were performed using STATA (version 13; College Station, TX) and R (version 3.3.2).

Results

Demographics

A total of 93 patients had adequate chart documentation to establish a diagnosis of definite PTCS and were thus included in this analysis. There were 24 male patients (26%) and 69 female patients (74%). Primary PTCS was diagnosed in 77 patients (i.e., IIH), secondary PTCS was diagnosed in 15 patients, and there was one patient for whom medical record documentation was not sufficient to distinguish primary versus secondary PTCS. The causes of secondary PTCS included antibiotics (*n* = 11), chronic kidney disease (*n* = 3), and withdrawal from chronic glucocorticoids (*n* = 1). Closing pressure was documented in 35 of 93 patients (female = 26, 74%), of which 28 patients had primary PTCS. Table 1 summarizes the demographics and the BMI-Z. We did not detect a statistically significant difference in age, BMI-Z, or gender between the two groups, that is, patients who had closing pressures documented and those who did not.

Treatment

Acetazolamide was begun in eight patients before and 64 patients after the lumbar puncture. There were three patients who never started acetazolamide (one had symptom resolution after stopping tetracycline and two had mild symptoms with no treatment given), and acetazolamide status was unknown in 18 patients because some parts of the medical record were not available for review (archived paper records). Of the patients who started

acetazolamide before the lumbar puncture, the average length of time was 21 days (SD 21 days, range one to 65 days). The treatment start and end dates were recorded in 59 patients (57/59 had days of papilledema documented) with an average of 240 days of treatment (SD ± 186 , range seven to 985 days, excluding one patient, an outlier who was on acetazolamide for 2073 days and who had other family members with PTCS). The reason for modifying the dose or stopping acetazolamide was not uniformly recorded. In this retrospective study, in general, we found that typical pediatric doses were used, and acetazolamide was weaned before being discontinued. Other treatments such as furosemide, topiramate, amitriptyline, or cyproheptadine were not recorded in the present study but were used very infrequently.

Opening and closing pressure

Table 1 details the opening and the closing pressure data collected. The opening pressure was not statistically different ($P = 0.661$ by two-sample t test) between the children with closing pressure documented ($N = 35$) and the children without closing pressure documented ($N = 58$). The opening pressure was positively associated with both BMI-Z ($n = 35$, $r = 0.51$, $P = 0.002$) and age ($n = 35$, $r = 0.38$, $P = 0.021$) at diagnosis.

CSF volume

The CSF volume removed was recorded in 23 patients, of which 19 patients had time to resolution of papilledema and 21 patients had closing pressure also documented (Table 1). The range of volume removed in these 21 patients was seven to 35 mL (50th percentile of volume removed = 16 mL; 25th percentile to 75th percentile, 11.5 to 25.5 mL) and the two patients without the closing pressure documented had 4 and 18 mL of CSF removed.

Papilledema

In the overall cohort, the first and the last days of observation of papilledema was documented in 72 patients (primary PTCS $n = 57$, secondary PTCS $n = 15$, not recorded or unavailable = 21) and resolution of papilledema took a median of 145 days (25th percentile to 75th percentile, 70 to 291 days) with a range of 18 to 994 days. This result was similar to that in the subgroup with documented closing pressures ($n = 31$, four patients lost to follow-up before papilledema resolution) with a median of 119 days (25th percentile to 75th percentile, 70 to 283 days).

In addition, the days of papilledema in the children who took acetazolamide were similar to those who had undetermined or no treatment, and both groups had similar opening pressures. Of the children who had documented days of acetazolamide treatment and days of papilledema ($n = 57$; median opening pressure 370 mm of CSF; 25th percentile to 75th percentile, 330 to 480 mm of CSF; range 250 to 620 mm of CSF), the resolution of papilledema took a median of 139 days (25th percentile to 75th percentile, 70 to 270 days; range 25 to 994 days). These children had on average 241 days of acetazolamide (SD ± 188 , range 7 to 985 days). Those excluded in the subanalysis for not having clear documentation of ($n = 12$) or for never taking acetazolamide ($n = 3$) took a median of 169 days ($n = 15$; 25th percentile to 75th percentile, 94 to 358 days; range 37 to 648 days). The opening pressure median for this subgroup ($n = 15$) was 410 mm of CSF (25th percentile to 75th

percentile, 365 to 450 mm of CSF; range 290 to 650 mm of CSF). The three children who did not take acetazolamide had resolution of papilledema in 37, 252, and 457 days.

Thus in comparing the two groups of subjects, those with and those without documented closing pressure measurements, no statistically significant differences with respect to demographics, opening pressure, treatment patterns, or timing of resolution of papilledema were detected (Table 1).

Next, to evaluate if higher or lower opening and closing pressures or volume of CSF removed had an association with longer or shorter duration of papilledema, the cohort was dichotomized to compare those above the median parameter of interest (i.e., opening pressure, closing pressure, or volume of CSF removed) with those below the median using Kaplan-Meier survival analysis. Because acetazolamide treatment can affect opening pressure, the same analysis was then performed on specific subgroups: (1) patients with primary PTCS and (2) patients with primary PTCS who were on acetazolamide treatment that was started on or after the date of the lumbar puncture. Table 2 shows the data for the cohort stratified by opening pressure, closing pressure, delta pressure, and the primary PTCS on acetazolamide subgroup for each. CSF volume is also included in this table.

Opening pressure and days of papilledema

In the 72 children of the overall cohort, the median time to resolution of papilledema was significantly lower ($P = 0.004$, Table 2) in the children with opening pressure above or equal to the median opening pressure compared with those below the median. A trend to more rapid resolution of papilledema was noted even in sensitivity analyses performed when the cohort was restricted to only the patients with primary PTCS (not represented in Table 2; $P = 0.011$; above median cohort: 50th percentile resolution time = 62 days, 25th percentile to 75th percentile, 62 to 227 days; and the below median cohort: 50th percentile resolution time = 119 days, 25th percentile to 75th percentile, 199 to 379 days). However, when restricted to patients with primary PTCS and acetazolamide treatment started after the lumbar puncture, there was a similar direction of effect, but it was no longer statistically significant (Table 2).

Closing pressure and days of papilledema

In the children ($n = 31$) who had closing pressure and start and end dates of papilledema documented, the time to resolution of papilledema was not statistically different ($P = 0.391$, Table 2) between the two groups. There was no difference observed when we evaluated the children who had acetazolamide treatment.

Additionally, we used the same groups and subgroups in the closing pressure cohort and analyzed the change in pressure (delta pressure) and the days of papilledema. The median time to resolution of papilledema was not statistically different between the two groups ($P = 0.167$, Table 2) either.

CSF volume and days of papilledema

The median time to resolution of papilledema was also not significantly different ($P = 0.155$, Table 2) in the children ($n = 19$) with both CSF volume removed and days of papilledema calculated. There were too few children to analyze when restricting the subgroup to those with documented CSF volume removed, primary PTCS, and acetazolamide treatment.

Headache

Headache information was available for 76 of the 93 patients. At presentation, 83% of the patients ($n = 63$) reported headache. Complete headache information with a start date and an end date was found in 49 patients with headache lasting on average 120 days ($SD = 152$, range one to 580 days). The Figure depicts the patients who had persistent headache after the lumbar puncture and does not include five of the 49 patients who had resolution of headache before the lumbar puncture.

To identify if higher or lower opening and closing pressures had an association with the duration of headache, the cohort was dichotomized to compare those above the median parameter of interest (i.e., opening pressure, closing pressure, or volume of CSF removed) with those below the median using Kaplan-Meier survival analysis. Because acetazolamide treatment can affect opening pressure, the same analysis was then performed on specific subgroups: (1) patients with primary PTCS and (2) patients with primary PTCS who were on acetazolamide treatment that was started on or after the date of the lumbar puncture. Table 3 shows the data for the cohort stratified by opening pressure, closing pressure, delta pressure, and the primary PTCS on acetazolamide subgroup for each. There were not enough patients with volume of CSF recorded and length of time of headache to analyze.

Opening pressure and days of headache

In the analysis of the patients with headache present after the lumbar puncture, there was no statistically significant difference detected ($P = 0.634$, Table 3) in days of headache between those with opening pressure above and equal to the median opening pressure and those below the median opening pressure. Subgroup analyses also did not detect a statistically significant difference in only patients documented with acetazolamide treatment.

Closing pressure and days of headache

There were few patients with documented closing pressures and days of headache; however, there was a statistically significant ($P = 0.037$) trend showing those with higher closing pressures ($n = 4$, Table 3) had faster resolution of headache in the subset of patients treated with acetazolamide, although this was a small cohort. This analysis was repeated using the delta pressure, and there was a trend similar to that of the closing pressure cohort.

Periprocedural headache changes

Early resolution of the headache within 10 days postlumbar puncture was found in 16 of 44 patients (36%) who had a headache on or after the lumbar puncture. Two of the 16 patients had headache resolution on the day of the procedure. Acetazolamide treatment for the early resolution cohort includes one patient on acetazolamide three weeks before the lumbar

puncture, 13 patients started on acetazolamide between the interval of the lumbar puncture and the date of the headache resolution, and two patients were not treated. There were no large volume taps in the five patients with early headache resolution who also had the volume of CSF removed documented.

Seven patients had a postlumbar puncture headache recorded, two of which had closing pressure or volume removed available. One patient had 35 mL of CSF removed with a change in pressure of 230 mm of CSF (opening pressure = 390 mm of CSF, closing pressure = 160 mm of CSF), and the other patient had a change in pressure of 300 mm of CSF (opening pressure = 450 mm of CSF, closing pressure = 150 mm of CSF) but with no volume removed recorded. A blood patch was needed in one of the seven patients.

Discussion

An association between lumbar puncture measurements and headache and papilledema outcomes has not been well described in the pediatric PTCS population. The present study provides insight into the clinical course of PTCS after lumbar puncture.

In our study, the average child with definite primary or secondary PTCS had papilledema for about seven to eight months and was treated with acetazolamide for a similar duration. The duration of papilledema ranged from three weeks to 3.5 years with ongoing treatment, highlighting heterogeneity in this group with respect to etiology, anatomy, or treatment compliance. The difference between opening pressure and closing pressure in the children with definite primary or secondary PTCS was positively associated with both BMI-Z and age, likely driven by higher opening pressures related to both BMI-Z and age.¹⁰

The present study identified a relationship between opening pressure and clinical features. The higher opening pressure in the children with definite primary or secondary PTCS was associated with faster resolution of papilledema. This effect was not seen when considering children with primary PTCS who were treated with acetazolamide. Thus this is unlikely a treatment effect but, rather, reflects sampling time bias, given that children who never took acetazolamide and those who had missing information had longer duration of papilledema. The children with higher opening pressures may have more frequent office visits, and the more frequent sampling would identify resolution of papilledema closer to the day of true resolution. A larger, prospective cohort study would be needed to further investigate this possibility.

The frequency of headache in our PTCS population was similar to that in previous reports. There was a trend toward faster overall headache resolution in those with higher closing pressures, but this result is difficult to generalize given our very small sample size.

There were no statistically significant differences detected between the opening pressure, age, gender, and BMI-Z of the children who had closing pressure documented and those who did not, suggesting that the decision to document a closing pressure is based on physician preference and not on patient characteristics. The closing pressure or the change in pressure measured during the diagnostic lumbar puncture showed no significant relationship to the timing of resolution of papilledema in our cohort, which is likely related to the rapid

CSF replacement and only temporary change in CSF volume with a one-time lumbar puncture. Indeed, with the typical rate of CSF production of 15 to 20 mL/h,⁴ CSF removed during lumbar puncture is likely to be replenished within one to two hours. Measurement of the closing pressure takes little procedural time and is with little risk to the patient; however, the significance of this measurement cannot be determined.

Often physicians choose an arbitrary volume of CSF to remove or to stop CSF removal after an arbitrary closing pressure is reached for acute headache management. We had limited available data on acute postprocedural headache improvement related to closing pressures and volume of CSF removed; however, one third of our patients did have early resolution of headache, including two patients with resolution of headache on the day of the procedure. The limited number of patients also prevents analysis of risk of postlumbar puncture headache as related to closing pressures and volume of CSF removed. A prospective study on patients without acetazolamide treatment during and around the time of the lumbar puncture is needed to better understand the effect of the opening pressure, closing pressure, and volume removed on headache.

The retrospective nature and the small sample size are the largest study limitations. Although the overwhelming majority of the patients were scheduled at similar intervals based on one practitioner's practices (GTL), the visits to the neuro-ophthalmologist naturally do vary, introducing the possibility of sampling bias. The days calculated for papilledema and headache reflect the interval between examinations, and we could not ascertain the exact duration of these clinical and examination features. In addition, the gradations of papilledema and headache, as well as other causes of headache, such as migraine or variables (dose of acetazolamide and other medications aside from acetazolamide), were not uniformly documented; in a prospective study, including these additional covariates may modify results. Further prospective studies to control for consistent lumbar puncture measurements, headache presence, and ophthalmoscopy examinations are needed. Additional visual outcomes associated with these measurements would also be helpful.

Despite these important limitations, our findings call into question the utility of routine measurement of closing pressures and high volumes of CSF removal. The diagnostic lumbar puncture for children with pseudotumor cerebri many times requires sedation or anesthesia. With possible prolongation of sedation or anesthesia time for removing a large volume of CSF or measuring closing pressure to see how much more CSF needs to be removed to attain a target closing pressure, it is important to understand further how these measurements affect outcomes of signs and symptoms of PTCS. It is possible that the diagnostic and therapeutic purposes of the closing pressure are unnecessary and can be eliminated from the lumbar puncture protocol for PTCS, shortening the time under anesthesia for children. Prospective studies can build on these initial findings to investigate this further.

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FIGURE.

Depiction of the number of days of headache in each of the patients who had persistent headache after the lumbar puncture. PTCS, pseudotumor cerebri syndrome.

TABLE 1.

Patient Demographics and Lumbar Puncture Pressures and Volume

Characteristics	Without Closing Pressure Documented (N = 58)	With Closing Pressure Documented (N = 35)	P Value
Gender, n (%)	Female Male	26 (74) 9 (26)	0.987 [*]
Age, mean $\pm$ SD	12.8 $\pm$ 4.9	12.5 $\pm$ 3.7	0.848 [†]
BMI-Z, mean (SD)	1.37 (1.08) [†]	1.46 (1.10)	0.744 [†]
Opening pressure (mm of CSF)	Mean $\pm$ SD Range	421 $\pm$ 98 250-650	0.664 [†]
Closing pressure (mm of CSF)	Mean $\pm$ SD Range	173 $\pm$ 60 60-360	
Delta pressure (mm of CSF (median)) [§]		60-485 (230)	
Volume (mL) of CSF removed	Number of patients documented Median Range	2 11 4-18	21 16 7-35

Abbreviations:

BMI-Z = Body mass index z score

CSF = Cerebrospinal fluid

SD = Standard deviation

^{*} Pearson chi-squared.[†] Forty-four patients with documented BMI-Z.[‡] Two-sample t test.[§] Delta pressure = opening pressure – closing pressure.

TABLE 2.

Time to Resolution of Papilledema

Parameter	Cohort	Median	n	Median	25th Percentile	75th Percentile	P Value
Opening pressure	All patients	<400 mm of CSF	39	199	87	379	0.004 [*]
		400 mm of CSF	33	113	55	205	
	Primary PTCS on acetazolamide [‡]	<400 mm of CSF	24	146	73	272	0.142
Closing pressure	All patients	400 mm of CSF	20	139	55	205	
		<170 mm of CSF	14	80	54	139	0.391
	Primary PTCS on acetazolamide [‡]	170 mm of CSF	17	196	104	293	
		<170 mm of CSF	9	87	46	139	0.779
Delta pressure [‡]	All patients	170 mm of CSF	10	157	119	209	
		<230 mm of CSF	15	119	80	293	0.167
	Primary PTCS on acetazolamide [‡]	230 mm of CSF	16	113	54	169	
		<230 mm of CSF	9	119	70	209	0.648
Volume of CSF removed	All patients	<230 mm of CSF	10	139	55	196	
		<16 mL	10	104	70	209	0.155
		16 mL	9	80	55	139	
	Primary PTCS on acetazolamide ^{§§}	<16 mL	2	–	–	–	
		16 mL	6	–	–	–	

Abbreviations:

CSF = Cerebrospinal fluid

PTCS = Pseudotumor cerebri syndrome

^{*}Two-sided *P* value of 0.05 is considered statistically significant.[‡]Delta pressure = opening pressure – closing pressure.[‡]Includes only the patients who had acetazolamide begun on the day of or after the lumbar puncture.[§]Too few to analyze.

TABLE 3.

Time to Resolution of Headache

Parameter	Cohort	Median	n	Time to Resolution of Headache (d)		P Value
				Median	25th Percentile	75th Percentile
Opening pressure	All patients	<400 mm of CSF	18	52	17	273
		400 mm of CSF	26	52	29	133
	Primary PTCS on acetazolamide [‡]	<400 mm of CSF	14	21	14	206
Closing pressure		400 mm of CSF	22	48	29	153
	All patients	<170 mm of CSF	6	119	29	211
		170 mm of CSF	13	45	21	69
Delta pressure [‡]	Primary PTCS on acetazolamide [‡]	<170 mm of CSF	4	153	29	211
		<170 mm of CSF	10	26	21	52
	All patients	<230 mm of CSF	8	21	16	69
Primary PTCS on acetazolamide [‡]		230 mm of CSF	11	52	29	165
		<230 mm of CSF	5	21	16	21
		230 mm of CSF	9	52	31	165

Abbreviations:

CSF = Cerebrospinal fluid

PTCS = Pseudotumor cerebri syndrome

* Two-sided *P* value of 0.05 is considered statistically significant.[‡] Delta pressure = opening pressure – closing pressure.[‡] Includes only the patients who had acetazolamide begun on the day of or after the lumbar puncture.