

Acetazolamide to treat symptomatic ruptured arachnoid cysts: illustrative cases

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BACKGROUND Arachnoid cysts are benign, often asymptomatic intracranial mass lesions that, when ruptured, may cause seizures, raised intracranial pressure, hemorrhage, and/or loss of consciousness. There is no widely agreed upon treatment, and there is debate as to whether a nonoperative or surgical approach is the best course of action. The carbonic anhydrase inhibitor acetazolamide may be an effective nonoperative approach in treating ruptured arachnoid cysts.

OBSERVATIONS The Pediatric Neurosurgery Clinical Database at BC Children's Hospital from 2000 to 2020 was queried, and four pediatric patients who were treated with acetazolamide after presentation with a ruptured middle cranial fossa arachnoid cyst were identified. All patients showed some degree of symptom improvement. Three of the patients showed complete reabsorption of their subdural collections in the ensuing 6 months. One patient had an inadequate response to acetazolamide and required surgical management.

LESSONS Acetazolamide is a safe and reasonable primary treatment option in pediatric patients with ruptured middle cranial fossa arachnoid cysts, and it may help avoid the need for surgery.

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KEYWORDS ruptured arachnoid cyst; acetazolamide; intracranial pressure; pediatrics

Arachnoid cysts (ACs) are typically benign, fluid-filled sacs with a prevalence between 1.3% and 2.6% in children.^{1–3} Most ACs are found incidentally through computed tomography (CT) or magnetic resonance imaging (MRI), with cysts in the middle cranial fossa being the most common.⁴ Most ACs (60%–80%) are diagnosed in the pediatric population and have been found to have a higher prevalence in boys.^{1,5–7}

Most ACs are asymptomatic and do not require intervention, but in selected cases, such as large ACs with mass effect, progressively enlarging ACs, or ruptured ACs, intervention may be needed.⁵ Particularly in the case of an AC rupture, there is a risk of intracystic hemorrhage, subdural hematoma, or subdural hygroma, which can cause raised intracranial pressure (ICP) and lead to adverse neurological symptoms.⁵ The optimal treatment for a ruptured AC remains controversial, and a consensus has yet to be

reached on whether a conservative, nonoperative, or surgical approach is most effective.

Because ruptured ACs are relatively uncommon, there is limited literature on treatment options and treatment effectiveness. One possible nonoperative intervention that has been reported or mentioned in the literature is use of the drug acetazolamide.^{8–11} In general, acetazolamide is believed to reduce ICP by decreasing cerebrospinal fluid (CSF) production, allowing it to act as a potential noninvasive method to treat raised ICP in a variety of circumstances.¹² Although there are two case reports of this treatment being attempted, to our knowledge, this is the first case series of pediatric patients with ruptured middle cranial fossa AC who were all treated with acetazolamide as the initial treatment option.^{9,10} This small case series suggests that acetazolamide is a safe and effective option to treat ruptured middle fossa ACs, potentially avoiding invasive surgery.

ABBREVIATIONS AC = arachnoid cyst; CSF = cerebrospinal fluid; CT = computed tomography; ICP = intracranial pressure; MRI = magnetic resonance imaging.

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TABLE 1. Case summaries

Case No.	Age (yrs)	Sex	Cyst Location, CNS Changes	Symptoms/Signs	Treatment & Outcome	Follow-Up
1	7	F	Lt middle cranial fossa, 3.5 × 3.0 × 4.7 cm (AP, TR, CC), bilat cerebral subdural collections extending to sylvian fissures	Diplopia, increased frequency of headaches, photophobia, phonophobia, vomiting, papilledema	Acetazolamide: symptom improvement, papilledema resolution	1 yr
2	12	F	Lt middle cranial fossa, 5.4 × 4.9 × 3.7 cm (AP, TR, CC), 7-mm subdural collection, midline shift, enlarged rt ventricle	Worsening headaches, nausea, vomiting, increased ICP, papilledema	Acetazolamide: initial symptom improvement; cyst fenestration after 3 mos; symptoms & papilledema resolution	3.5 yrs
3	13	M	Lt middle cranial fossa, 4 × 3 × 3 cm (AP, TR, CC), 14-mm subdural collection, midline shift	Headaches, vomiting, lethargy, papilledema	Acetazolamide: symptom improvement, papilledema resolution	7 mos (ongoing)
4	15	M	Lt middle cranial fossa, 6.7 × 5.5 × 7.6 cm (AP, TR, CC), 5-mm bilat cerebral subdural collections, AC partly decompressed w/ a defined defect consistent w/ a tear; mass effect	Progressive headaches & nausea, photophobia, vomiting	Acetazolamide: symptom improvement	7 mos (ongoing)

AP = anteroposterior; CC = craniocaudal; TR = transverse.

Illustrative Cases

Methods

The pediatric neurosurgery database at BC Children's Hospital from 2000 to 2020 was queried to identify all patients with AC. One hundred thirty-nine patients with AC were identified, eight of whom presented with evidence of rupture. Four of these children were treated initially with acetazolamide, and the remaining four were treated with surgery. The patients who received surgery were managed operatively either because they showed increasing mass effect and/or neurological deterioration or, when all the options were discussed, the parents elected surgery. The four patients treated with acetazolamide were admitted to the pediatric neurosurgery service at BC Children's Hospital with ruptured left middle cranial fossa ACs. The medical records of these four patients were reviewed in detail. A summary of each case can be found in Table 1.

Case 1

A 7-year-old girl presented with diplopia, headaches, and vomiting with no history of head injury. Diplopia began 3 weeks before admission, and headaches were progressively increasing in frequency over the past few weeks prior to presentation. Headaches lasted from 1 hour to a few hours and were biparietal. They occasionally caused nocturnal awakening and were associated with phonophobia, photophobia, and vomiting. Bilateral papilledema was found on examination. CT and MRI showed a Galassi type 1 left middle fossa AC with bilateral mild-to-moderate subdural collections extending into the sylvian fissure, consistent with a ruptured AC (Fig. 1).¹³ There was some mass effect, with mild flattening of the left temporal and inferior frontal lobe. A lumbar puncture revealed an elevated opening pressure of 39 cm H₂O with a normal CSF profile (white blood cells, protein, glucose, lactate). Treatment with 62.5 mg of acetazolamide twice daily (4.8 mg/kg per day) was initiated with no further symptoms while in hospital.

At 3-month follow-up, the patient continued to show significant symptom improvement, with no subjective diplopia and only occasional headaches. Repeat CT scans showed that the cyst size was unchanged but the extraaxial fluid collection was more extensive, causing some flattening of the cerebral hemispheres. On ophthalmological examination, her papilledema was improved but not fully resolved.

At 6-month follow-up, the patient was symptom-free, with no academic or social difficulties. Acetazolamide treatment was stopped at that time. Repeat CT scans showed a slight increase in AC size with resolution of the right hemispheric subdural collection but persistence of the left-sided collection. Minor blurring of her disc margins was observed, but it was improved from her previous visit.

At 1-year follow-up, she had no symptoms, and all clinical examinations were normal. She had only minor blurring of disc margins in her right eye. The CT showed that the bilateral subdural collections had resolved and mass effect had improved, with cyst size remaining stable.

Case 2

A 12-year-old girl presented with progressively worsening headaches that began after she dove into a pool during a swim meet 3 weeks before admission. Three days prior to admission, she had progressive nausea and vomiting. MRI showed a Galassi type 3 ruptured AC in the left middle fossa resulting in a subdural hygroma that caused mass effect and 3 mm of midline shift (Fig. 2).¹³ There was a 7-mm subdural collection overlying the left frontal and temporal lobes causing some flattening of the left cerebral hemisphere. She also had an enlarged right ventricle. Neurological examination was normal other than minor papilledema of the left eye. Upon admission, the patient was started on acetazolamide, 250 mg twice daily. Although cyst fenestration was contemplated, the patient's symptoms improved after initiation of acetazolamide therapy. She was discharged on 250 mg of acetazolamide twice daily (9.0 mg/kg per day).

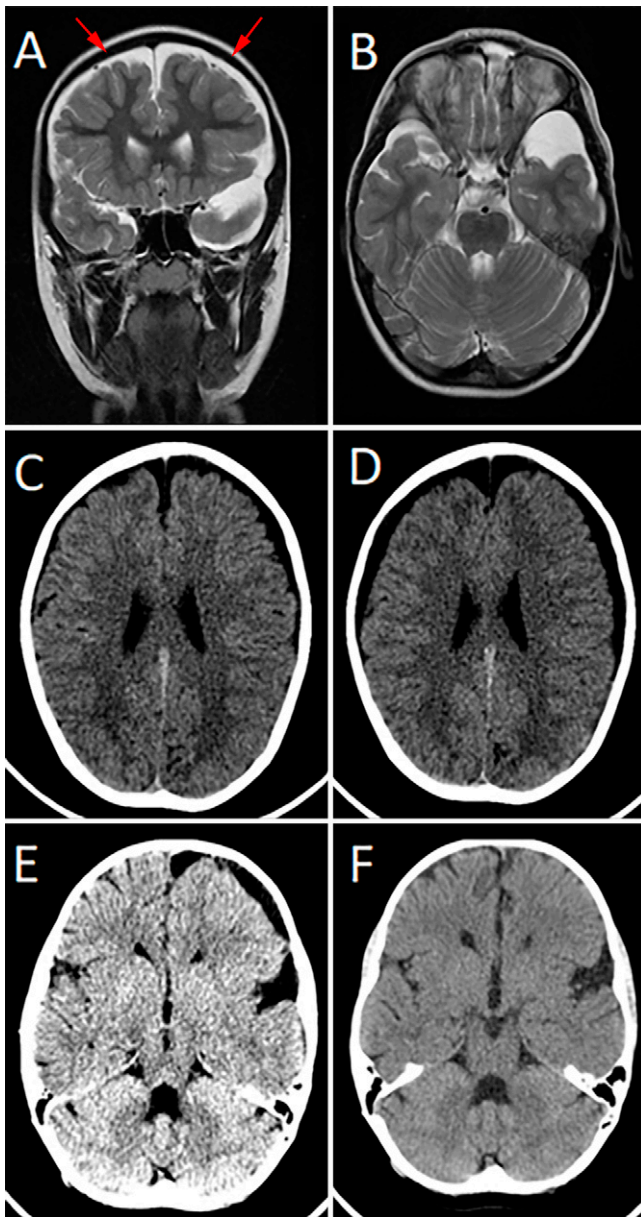


FIG. 1. Patient 1 neuroimaging. **A:** Coronal T2 MRI upon admission before acetazolamide treatment shows an arachnoid cyst and bilateral extraaxial subdural fluid collections (*red arrows*) causing mild flattening of both hemispheres. **B:** Axial T2 MRI upon admission, before acetazolamide treatment, again shows the left middle cranial fossa arachnoid cyst. **C:** Axial CT scan before acetazolamide treatment shows bilateral fluid collections. **D:** Three months after acetazolamide treatment, axial CT scan shows more extensive extraaxial fluid collections overlying both hemispheres, leading to some bilateral flattening of the hemispheres. **E:** Six months after acetazolamide treatment, axial CT scan shows resorption of right subdural collection and static left subdural collection. **F:** Eleven months after acetazolamide treatment, axial CT scan shows complete resorption of both left and right subdural collections.

For the following 3 weeks, the patient reported improved symptoms, but thereafter, she had resurgence of headaches and nausea. Upon physical examination, all test results were normal except for minor bilateral papilledema. Repeat MRI showed that the subdural

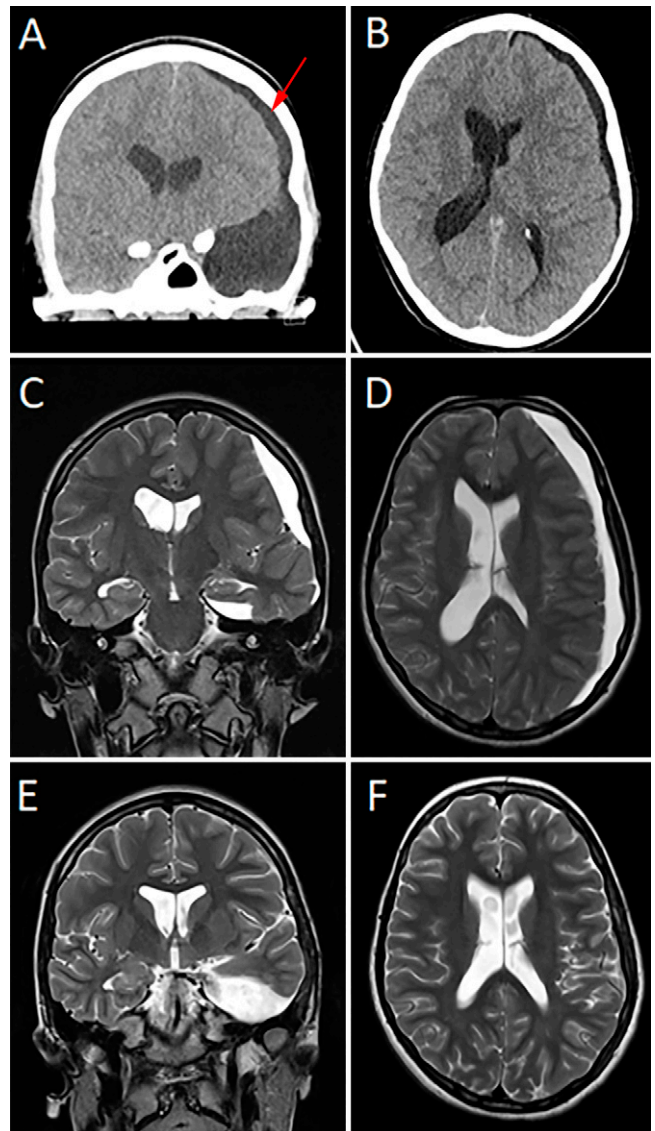


FIG. 2. Patient 2 neuroimaging. **A:** Coronal CT scan upon admission before acetazolamide treatment shows a left middle cranial fossa arachnoid cyst and an associated left-sided subdural collection (*red arrow*). **B:** Axial CT scan before acetazolamide treatment shows a compressed left lateral ventricle and a slightly dilated right lateral ventricle as well as a left subdural collection. Also present is 3 mm of midline shift. **C:** Three months after acetazolamide treatment, coronal T2 MRI shows an increase in subdural collection size and flattening of the left frontal and temporal lobes. **D:** Axial T2 MRI at the same time point shows persistent midline shift and an enlarged right ventricle as well as a larger subdural collection. **E:** Three months postoperatively (6 months after initial admission), coronal T2 MRI shows resorption of fluid collection and resolved mass effect. **F:** Concurrent axial T2 MRI shows symmetric lateral ventricles and no fluid collections.

collection had enlarged to 10 mm, with greater flattening of the cerebral hemispheres and persistent dilation of the right ventricle. The dose of acetazolamide was increased to 500 mg twice daily (18.0 mg/kg per day).

Two months after initial admission, the patient was responding well to acetazolamide, with headache improvement and resolution of vomiting. MRI showed that the cyst size was unchanged but the subdural collection had increased further to 14 mm, causing increased flattening of the left frontal and parietal lobes.

At the 3-month follow-up, the patient reported improved headaches and nausea, but she had paresthesia and loss of appetite, thought to be side effects from acetazolamide. A week after the follow-up, her headaches began to increase again. MRI was performed and showed no change since the last follow-up. Given the imaging and persistent symptoms, surgery was recommended, and a craniotomy with cyst fenestration and hygroma drainage was performed. It was noted at surgery that the subdural collection was not in communication with the AC.

Postoperatively, symptoms resolved. CT scan showed a reduction in the subdural collection and a small reduction of the AC leading to reduced mass effect. The patient had no neurological deficits and her papilledema improved. The acetazolamide dose was reduced gradually and ultimately stopped over the course of 6 weeks.

Six weeks postoperatively, she had less frequent headaches but presented to the emergency department with numbness and tingling of her right arm, loss of the ability to speak, and a severe headache, thought to be due to focal seizures. A CT scan showed resolution of the subdural collection and no change in the AC, but there was a new left parietal extraaxial hematoma, remote from the craniotomy site. The patient was placed on antiseizure medication that successfully stopped her seizures. In all subsequent follow-ups, most recently 3.5 years after diagnosis, imaging showed a stable cyst and no evidence of a recurrent collection or hematoma. The patient had reduced frequency and severity of headaches and no papilledema.

Case 3

A 13-year-old boy presented with increasing intermittent headaches associated with nausea and vomiting. On admission, he was lethargic and had bilateral papilledema. MRI showed a Galassi type 3 left middle cranial fossa AC causing mass effect on the left temporal lobe (Fig. 3).¹³ The cyst was associated with a 14-mm left-hemispheric convexity crescentic subdural fluid collection, consistent with AC rupture. The extraaxial fluid collection caused partial effacement of the left lateral ventricle, with 5 mm of midline shift and flattening of the optic nerve sheath indicating raised ICP. A small amount of subarachnoid blood was also seen. He was given 250 mg of acetazolamide twice daily (7.2 mg/kg per day) and showed significant clinical improvement within 12 hours. He was discharged 3 days after admission with complete resolution of symptoms.

After 2 weeks, repeat MRI showed a reduction in the subdural fluid collection overlying the left hemisphere and reduced midline shift with mild compression of the left lateral ventricle. Cyst size remained stable. Clinically, the patient had occasional mild headaches that were significantly less severe than at presentation. The patient was weaned off acetazolamide over the course of 4 weeks.

At 2-month follow-up, the patient remained symptom-free, and repeat MRI showed further reduction of the extraaxial fluid collection and a stable AC.

Seven months after admission, the patient remained asymptomatic with no papilledema. The MRI showed complete resolution of the subdural collection and a slight increase in AC size thought to be due to reduced compression from the subdural fluid.

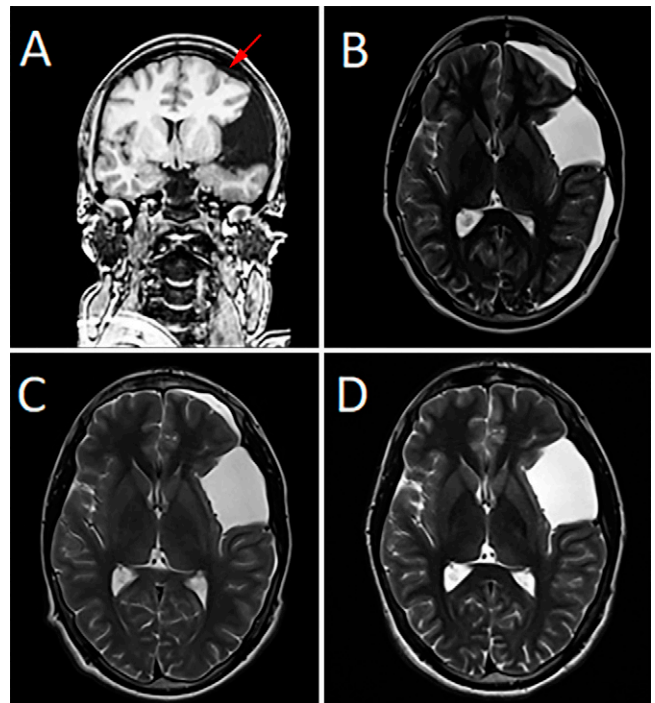


FIG. 3. Patient 3 neuroimaging. **A:** Coronal T1 MRI before acetazolamide treatment shows a left middle cranial fossa arachnoid cyst with associated extraaxial fluid collection (red arrow) causing a 5-mm midline shift. **B:** Axial T2 MRI before acetazolamide treatment shows a large left crescentic subdural fluid collection and suggestion of some internal blood products. **C:** Axial T2 MRI 2 weeks after acetazolamide treatment shows a reduction in size of the subdural fluid collection and a subsequent improvement of midline shift. Cyst size is unchanged. **D:** Axial T2 MRI 2 months after acetazolamide treatment shows a static cyst and a near complete resolution of the subdural fluid collection.

Case 4

A 15-year-old boy presented with progressively worsening headaches and nausea after repeatedly heading the ball at soccer practice 16 days before admission. Five days before he was admitted, his headaches acutely worsened and he developed photophobia and vomiting. His family doctor prescribed ondansetron, but the patient experienced no improvement. Upon admission, neuroimaging showed a Galassi type 3 left middle cranial fossa AC extending to the sylvian fissure with bilateral subdural fluid collections causing partial effacement of the left lateral ventricle consistent with a ruptured AC (Fig. 4).¹³ The patient did not have any evidence of papilledema. He was treated in the emergency department according to the hospital's migraine protocol (intravenous saline, ketorolac, metoprolamide) with some symptom improvement. He was subsequently treated with acetazolamide, and his symptoms rapidly improved thereafter. He was discharged on 250 mg of acetazolamide four times a day (14.4 mg/kg per day) for 2 weeks.

At 3-week follow-up, the patient was symptom-free with no papilledema or focal neurological deficits. However, MRI showed that his left subdural collection was larger (previously 6 mm, now 8 mm) than previously but the right subdural collection had completely resolved.

At 6-week follow-up, repeat MRI showed interval hemorrhage into the left convexity subdural collection consistent with a chronic subdural hematoma, causing it to increase to 18 mm and producing

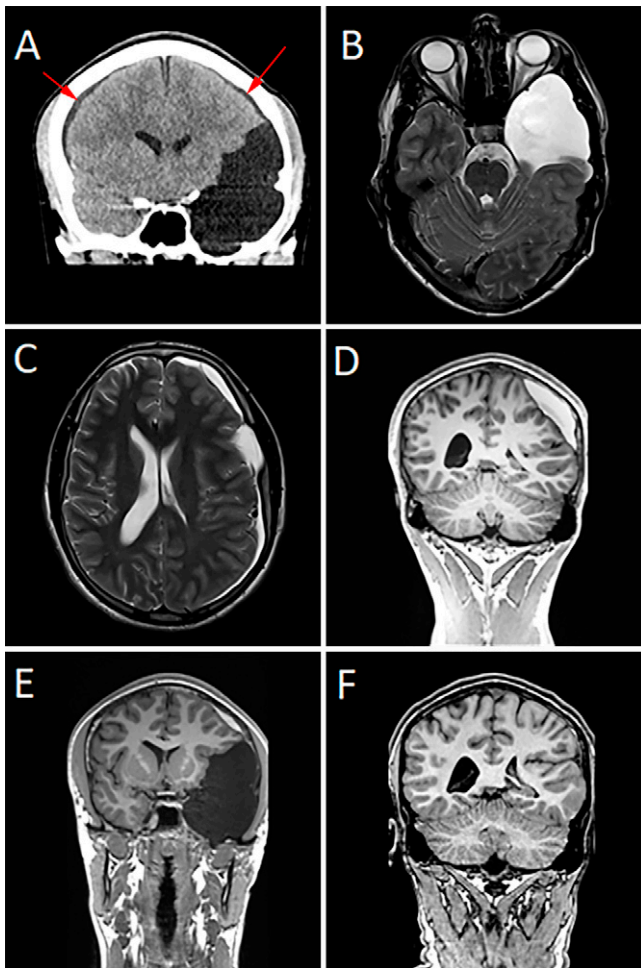


FIG. 4. Patient 4 neuroimaging. **A:** Coronal CT scan for patient 4 at presentation shows a large left middle cranial fossa arachnoid cyst with small bilateral subdural collections (red arrows). **B:** Axial T2 MRI at the time of 3-week follow-up shows the AC with internal CSF signal intensity. **C:** A second image from the same study at the level of the lateral ventricles shows that the right subdural collection has resolved whereas the left has enlarged slightly, and there is mass effect on the body of the left lateral ventricle. **D:** Coronal T1 MRI at 6-week follow-up shows hemorrhage into the left subdural collection, which has enlarged and shows bright, hyperintense T1 signal due to internal blood products. **E:** The AC itself remains similar in signal to CSF (i.e., T1 dark) without evidence of internal hemorrhage. **F:** Coronal T1 MRI at just over 4 months after presentation shows essentially complete resolution of the hemorrhagic left subdural collection with no reaccumulation of the right collection. The AC was unchanged in size.

mass effect on the left parietal lobe. However, the anterior part of the subdural collection was reduced, and the AC remained unchanged in size. Surgery to drain the left-sided collection was offered, but because the patient remains clinically significantly improved with a normal physical examination, the patient and parents opted for continued conservative management.

Three months after admission, the patient remained symptom-free, except for what he described as a vague mental fog. On examination, he was neurologically intact with a normal ophthalmological

examination. He reported having two headaches that resolved on their own and some irritability. MRI showed a reduction in size of the left parietal subdural collection.

By 4 months after admission, the left subdural collection had completely resolved and the cyst remained stable in size. The patient remained asymptomatic for both his 4- and 7-month follow-up visits.

Discussion

A traumatic or spontaneous rupture of an AC can cause mass effect leading to compression of structures and intracranial hypertension.¹⁴ Raised ICP may present clinically as headaches, nausea, vomiting, and seizures, with or without focal neurological deficits and often with papilledema.¹⁴ These progressive symptoms may also be due to cyst expansion, obstructive hydrocephalus, or intracystic hemorrhage, and as such, CT or MRI is required to make the diagnosis of AC rupture.¹⁵ Both cyst structure and intracystic pressure may be contributing factors to the development of subdural fluid collections.¹⁶

In the case of asymptomatic ACs in general, nonsurgical management is preferred, but if symptoms develop or there are signs of cyst growth or rupture, surgical intervention is often favored.^{17–19} Endoscopic cyst fenestration, shunting, and open cyst fenestration via craniotomy are the procedures most commonly undertaken.^{19,20} Balestrino et al. found that of the 57 ruptured AC cases reported in the literature, 83.6% were treated surgically and the remaining were treated conservatively (observation alone or with medical therapy, either acetazolamide or steroids).⁵ Additionally, the single-institution retrospective report by Hall et al. found that 78.6% of AC ruptures had been treated surgically, with only three patients (21.4%) treated conservatively with observation only.²¹ Among the conservatively treated cases of ruptured ACs reported in the literature, all showed complete or partial recovery of symptoms; however, symptomatic resolution was not immediate and occurred between 2 weeks and 2 months after symptom onset.^{5,21,22} Although surgical intervention can provide rapid improvement of symptoms, using a nonoperative approach avoids the possible complications that accompany these more invasive surgical methods, such as infection, CSF leak, and shunt dependence.^{4,20} Based on the reports in the literature, 17%–33% of surgeries for ACs (not just ruptured ACs) are associated with a surgical complication and 39%–42% require reoperation.^{20,23–25}

When symptomatic ACs are managed nonsurgically, the management has predominantly been observational.^{5,21} However, there have been some accounts in the literature of acetazolamide administration being attempted as a conservative treatment option as well.^{8–11}

Acetazolamide is a carbonic anhydrase inhibitor that was first approved for treating altitude sickness and glaucoma but now has many off-label applications as well.²⁶ This drug causes a reduction in hydrogen ion excretion, which, in turn, decreases CSF and aqueous humor production, causing a reduction in ICP and intraocular pressure.²⁶ As a result, it has also been used to treat benign intracranial hypertension, CSF leaks, and increased ICP, allowing patients to avoid invasive procedures.^{26–28} Acetazolamide has been shown to be safe and effective in the pediatric population as well.^{29,30}

Observations

The presented cases show that in neurologically stable patients demonstrating symptoms of raised ICP, acetazolamide is a promising, often fast-acting alternative to surgical treatment options for AC

ruptures. Typically, these cases would have been treated with surgery upon admission, but with the administration of acetazolamide, all four cases showed significant clinical improvement within 24 hours of drug administration. Additionally, with continuous acetazolamide administration, three patients showed complete resolution of their subdural collections and were able to avoid surgery altogether. Only one patient had a recurrence of headaches after a month on acetazolamide and later required surgery. This could be because the patient had a larger cyst than the other cases and there was no communication between the cyst and the subarachnoid space. A noncommunicating cyst is an indicator that surgery is more likely to be required and may explain why patient 2 did not have a persistent response to medical management.^{25,31} It has been suggested that using CT or MR cisternography to determine flow between cyst and subarachnoid space can help to establish if surgery is necessary; however, this approach was not carried out in any of our patients.^{31,32} In addition to cyst communication, cyst size and age at presentation are the two other significant predictors for cyst rupture and surgery.^{20,33} Therefore, the larger cyst and older age at presentation in combination with the cyst being noncommunicating may have played a role in patient 2's lack of response to the drug.

Acetazolamide dose was determined at the attending physician's discretion. The dose of acetazolamide did not predict responsiveness because patient 2 received the highest relative dose of acetazolamide and did not improve whereas patients 1 and 3 showed improvement and received lower relative dosages by weight. This may suggest that cyst pathology and anatomy are the primary factors involved in the response to acetazolamide treatment and that increasing the dose will not have an effect.

Lessons

Three patients were able to avoid surgery solely with medical management with acetazolamide. Clinically, it was fast acting and symptoms improved over the time of hospital admission. Radiologically, improvements were seen by 3 months, 2 weeks, and 3 weeks after acetazolamide administration in patients 1, 3, and 4, respectively. There was no reduction of cyst size on follow-up imaging on any of the patients, only resolution of the subdural fluid collections. Symptoms remained resolved after acetazolamide administration was stopped in the three patients who did not receive surgery. It may well be that acetazolamide mitigates an initial relatively acute increase in ICP sufficiently to avoid operative intervention for ICP symptoms/signs, whereas the underlying natural history of the subdural fluid collections tends toward spontaneous resolution.

Given the small numbers in this case series and the fact that these patients were not selected or treated in a controlled manner, one cannot make substantial claims about the effectiveness and mechanism of action of acetazolamide. The changes observed in the patients may not be a result of acetazolamide administration and instead may be due to a placebo effect or the natural history of ruptured ACs without surgical intervention.

Despite these limitations, acetazolamide may be a promising, nonoperative, primary treatment option for ruptured ACs. Based on the findings in this study and the published literature, it rivals surgical intervention as an effective treatment for ruptured ACs.⁸⁻¹⁰ Furthermore, if medical management with acetazolamide fails, surgical management remains an option. A randomized, controlled study on acetazolamide as a treatment for ruptured ACs has not been conducted and is likely not feasible given the rarity of the condition.

However, further investigation could elucidate the criteria for a successful response to acetazolamide treatment and establish a guide to intervention.

In this series of four patients with ruptured ACs, initial treatment with oral acetazolamide resulted in symptom improvement in all patients, and three of the four patients were able to avoid surgery. This suggests that acetazolamide may be a safe, appropriate, and effective treatment that acts quickly to reduce ICP symptoms, potentially allowing patients to avoid unnecessary surgery and complications.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Singhal, Watson, McDonald, Steinbok. Acquisition of data: Singhal, Watson, McDonald. Analysis and interpretation of data: Singhal, Watson, McDonald, Graeber. Drafting the article: Watson, Steinbok, Graeber. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Singhal. Administrative/technical/material support: McDonald. Study supervision: Singhal.

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