Idiopathic intracranial hypertension following spinal deformity surgery in children

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Idiopathic intracranial hypertension (IIH) after pediatric spinal deformity surgery has not been previously reported. The authors conducted a retrospective analysis of more than 1500 pediatric spinal surgeries performed between 1992 and 2011. From their analysis, they report on 3 adolescent patients who underwent uncomplicated segmental spinal instrumentation for pediatric spinal deformity correction and subsequently developed features of IIH. The common variables in these 3 patients were adolescent age, spinal deformity, being overweight, symptom onset within 2 weeks postoperatively, significant estimated blood loss, and intraoperative use of $\epsilon$-aminocaproic acid (antifibrinolytic) injection. The authors postulate that the development of IIH could be the result of venous outflow obstruction due to derangement of the epidural venous plexus during surgery. The use of $\epsilon$-aminocaproic acid could potentially have the risk of causing IIH, probably mediated through hyperfibrinogenemia, although there have not been published cases in the neurosurgical, orthopedic, cardiac, or general surgical literature. Idiopathic intracranial hypertension after spinal deformity correction is a condition that should be recognized by neurosurgeons and orthopedic surgeons, because appropriate intervention with early medical therapy can lead to a satisfactory clinical outcome. (DOI: 10.3171/2011.7.FOCUS11160)

Key Words • idiopathic intracranial hypertension • idiopathic scoliosis • posterior spinal fusion • segmental spinal instrumentation • antifibrinolytic therapy • hyperfibrinogenemia

Idiopathic intracranial hypertension is an uncommon but potentially devastating disorder in the pediatric population.1,2,5,9,15 First described by Heinrich Irenaeus Quincke33 in 1893 as “serous meningitis,” this poorly understood disease process has changed names multiple times, alternately referred to as pseudotumor cerebri, otitic hydrocephalus, and benign intracranial hypertension. However, the term “idiopathic intracranial hypertension” has been maintained since Corbett and Thompson’s description in 1989,9 as the exact etiology and pathophysiology remains uncertain.7,8,24,41–43 Among the implicated causes are the following agents: vitamin A, tetracycline, oral contraceptive pills, lithium carbonate, recombinant human growth hormone, cimetidine, and amiodarone. Endocrinological causes that have been postulated are obesity, pregnancy, menarche, adrenal steroid withdrawal, and hyperadrenalism.22,23 There are some hematological and connective tissue disorders associated with development of IIH such as iron-deficiency anemia, infectious mononucleosis, lupus, hypothyroidism, hypoparathyroidism, Cushing disease, adrenal insufficiency, and Wiskott-Aldrich syndrome.7,22,23 Neurological causes for venous outflow obstruction such as transverse sinus thrombosis, mastoiditis, head trauma, marantic sinus thrombosis, and hyperfibrinogenemia have also been implicated.23

Patients with IIH often present with headache or dizziness and visual disturbances including blurred vision and diplopia.15 The incidence of IIH was reported in a study from the Mayo Clinic (Rochester, MN) as 0.9 case per 100,000 population (1.6 cases per 100,000 women, 3.3 cases per 100,000 female patients 15–44 years of age, and 7.9 cases per 100,000 obese female patients 15–44 years of age).54 Diagnostic criteria for IIH were set forth by Friedman and Jacobson18 in 2002. It is a syndrome of elevated ICP without hydrocephalus or mass lesion, with normal CSF composition.4,18,21 Before lumbar puncture can safely be performed, MR images or CT studies should be obtained to identify any mass lesions that could result in brain shift or uncal herniation.4 The cutoff limit for abnormal ICP has been considered to be greater than 250 mm H2O; pressure in cases of IIH has sometimes
been reported at 2 or 3 times that number.\textsuperscript{38} Permanent severe visual disturbance occurs in cases of undiagnosed IIH in up to 24\% of cases that have been monitored for 5–41 years.\textsuperscript{43}

We present 3 cases of IIH in a previously unreported setting of pediatric spinal deformity correction surgery (Table 1). The aim of the current report is to alert neurological and orthopedic surgeons that visual disturbances and headaches in the early postoperative period can represent a serious, but treatable, condition. In addition, we propose a possible explanation for these cases based on the current literature.

Case Reports

Case 1

This 13-year-old girl presented in 2009 with esotropia, diplopia, tinnitus, and headache. Her symptoms had started 2 weeks after PSF with segmental spinal instrumentation from T-3 to L-4 for idiopathic scoliosis (T2–6 left apex 26°, T6–11 right apex 42°, and T11–L4 left apex 49°). The intraoperative blood loss was 1 L, and the patient received 1 U of autologous blood. Epsilon–aminocaproic acid was administered intraoperatively. Hospitalization medications included morphine, Dilaudid, piperacillin-tazobactam, and ondansetron. She was discharged home on postoperative Day 5 and was given acetaminophen with codeine for pain.

The patient’s medical history was significant for systemic hypertension and prior myringotomy tubes as an infant for recurrent otitis media. Physical examination showed bilateral papilledema and left esotropia with no visual acuity changes. Findings from cranial MR imaging, MR venography, and contrast-enhanced CT scanning of the head were found to be unremarkable. Lumbar puncture showed an opening pressure of 390 mm H$_2$O. The CSF glucose was 57 mg/dl and protein was 29 mg/dl, and cultures never grew any organisms. The patient was placed on a regimen of acetazolamide 250 mg twice daily, and her headache and diplopia resolved in a period of 6 weeks.

Case 2

This 13-year-old girl presented to the emergency department in 1999 with a 4-day history of constant left parietal headache, episodic diplopia, and blurred vision in the right eye. Her symptoms developed 2 weeks following a PSF and a hybrid segmental spinal instrumentation from T-5 to L-3 for a progressive thoracolumbar scoliosis with a T10–L3 curve of 57° (Fig. 1). The perioperative blood loss was 1500 ml. The patient underwent a blood transfusion using cell saver blood and received 1 U of autologous packed red blood cells along with intraoperative EACA. The patient’s medical history was significant for a sacral teratoma removed at 3 days of age. She had developed precocious puberty at 5 years. Examination in the emergency department showed a visual acuity of 20/70 vision (right eye) and 20/20 (left eye). She was afebrile and had no signs of infection. She was sent home from the emergency department with a prescription for ergotamine and caffeine, and it was advised that she follow up with the ophthalmology and neurology services in the next few days. On the 13th postoperative day, the patient remained normal neurologically. However, her eye examination showed bilateral papilledema, and visual testing demonstrated 20/100 vision (right eye) and 20/20 (left eye). There was a central scotoma in the right eye with an afferent pupillary defect, and a right sixth cranial nerve palsy was noted.

Magnetic resonance imaging findings of the head and entire spine were unremarkable (Fig. 2). Lumbar puncture showed an opening pressure of 400 mm H$_2$O, and the patient was placed on a regimen of acetazolamide 500 mg initially, which increased to 1 g per day with resolution of her headache. Her visual field defects improved over the course of the next 3 months. At 2 years postoperatively, her visual acuity was 20/40 (left eye) and 20/20 (right eye).

Case 3

This 16-year-old boy presented in 2008 on postoperative Day 18 with a progressive worsening severe headache along with vomiting, photophobia, and blurry vision that lasted for 3 days. He had undergone anterior discectomy and fusion from T-6 to T-10 for T-8 to T-9 disc herniation and deformity correction by PSF and from T-2 to L-3 for Scheuermann kyphosis with a progressive 84° curve of thoracic kyphosis (Fig. 3).

The patient’s medical history was significant for Asperger syndrome, systemic hypertension, obesity, and dysthyemic disorder. He also had a history of recurrent otitis media as a child, requiring myringotomy tubes. Active medications on admission included sertraline, iron, and amiodipine. He had an intraoperative blood loss of 1150 ml

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**TABLE 1: Summary of characteristics in 3 patients with IIH after spinal instrumentation**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Medical History</th>
<th>Diagnosis</th>
<th>Levels of Spinal Fusion</th>
<th>EBL (ml)</th>
<th>EACA Given</th>
<th>BMI (kg/m$^2$)</th>
<th>Treatment, Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13, F</td>
<td>hypertension, recurrent otitis media</td>
<td>scoliosis</td>
<td>T3–L4</td>
<td>7 hrs, 30 min</td>
<td>1000</td>
<td>yes</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>13, F</td>
<td>sacral teratoma, precocious puberty</td>
<td>scoliosis</td>
<td>T5–L3</td>
<td>6 hrs</td>
<td>1500</td>
<td>yes</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>16, M</td>
<td>Asperger syndrome, dysthyemic disorder, obesity, hypertension</td>
<td>Scheuermann kyphosis</td>
<td>T2–L3</td>
<td>8 hrs, 50 min</td>
<td>1150</td>
<td>yes</td>
<td>31.4</td>
</tr>
</tbody>
</table>

* BMI = body mass index; EBL = estimated blood loss.
and received EACA during surgery for blood conservation. Postoperatively, he was started on duloxetine and pregabalin for back pain, along with home medication. Other medications included morphine and hydromorphone for pain.

Examination in the emergency department showed bilateral papilledema and normal visual acuity in both eyes, but later during the admission there was an abnormal enlargement of the blind spot in the left eye noted on formal visual field testing.

Findings from cranial CT and MR imaging including MR venography were normal (Fig. 4). A lumbar puncture showed an increased opening pressure of 330 mm H2O. The diagnosis of IIH was made, and the patient was treated with acetazolamide 500 mg twice daily with an additional 250 mg at noon (total 1250 mg/day) and pregabalin 150 mg twice daily. Topiramate 25 mg daily and oxycodone 30 mg twice daily were also prescribed for pain control, while he was maintained on his home doses of sertraline and amlodipine. Hematology workup indicated that he was homozygous for methylenetetrahydrofolate reductase (MTHFR) enzyme deficiency, resulting in elevated levels of homocysteine; he was started on a regimen of folic acid. His headache resolved, and visual acuity and fields returned to normal. However, the papilledema persisted for about 2 years postoperatively.

Discussion

Idiopathic intracranial hypertension is a condition characterized by increased ICP in the absence of clinical, laboratory, or radiographic evidence of CNS infection, vascular malformation, intracranial space-occupying lesion, or ventricular dilation. The exact nature and pathogenesis of the disorder has yet to be elucidated; however, the natural history leads to persistent headache and ensuing visual acuity loss. Idiopathic intracranial hypertension among young children has been associated with several new etiologies, including recombinant growth hormone and all-trans retinoic acid.6,12,15,49 The diagnosis of optic nerve involvement is made using automated perimetry and more recently, optical coherence tomography, laser scanning tomography, and spectral Doppler blood flow analysis of the optic nerve head. More modern neuroimaging techniques such as MR imaging, MR venography, and auto-triggered-elliptic-centric-ordered (ATECO) 3D MR venography are being used to evaluate intracranial processes such as venous sinus thrombosis.4 In cases of IIH in which there is a high suspicion of sinus thrombosis, procedures such as conventional cerebral angiography, direct retrograde cerebral venography, and manometry are performed to characterize their morphological features and venous pressures, to perform a therapeutic balloon venoplasty or endoluminal venous sinus stenting if necessary.4,16,30–32 Although most children with IIH improve with medical treatment, those who have had visual progression despite medical treatment have undergone optic nerve sheath fenestration and lumboperitoneal shunting or even ventriculoperitoneal shunting in certain cases.38

All patients reported on in our series were of similar age and body habitus, and all had a preexisting spinal deformity. Their IIH symptoms developed approximately 2
weeks after elective uncomplicated spinal deformity surgery with a moderate amount of intraoperative blood loss that required transfusion with cell saver and autologous blood in each case. Each patient presented with clearly definable IIH based on the criteria set forth by Friedman and Jacobson.\textsuperscript{18} There are no previously reported cases of this intracranial condition occurring in spinal deformity surgery. In 1995, a similar presentation was reported by Daftari et al.\textsuperscript{10} in the setting of occipitocervical arthrodesis for persistent nonunion of an odontoid fracture following multiple operations to treat a trauma-related injury. The patient in that report was a thin young woman in her 20s with neck pain and upper-extremity myopathy and sensory neuropathy, which is in contrast to the typical IIH presentation in obese women of childbearing-age presenting with vision-threatening headache.\textsuperscript{12,45}

The final common mechanism for IIH has been suggested as an elevation in intracranial venous pressure in a retrospective analysis of 10 patients (children and young adults) with IIH symptoms who required surgical intervention.\textsuperscript{26} Measurements were made of central venous pressure as well as ICP, and it was observed that 5 patients had dural venous outflow obstruction and 5 patients had normal venous anatomy with elevated right atrial pressure and venous sinus pressure. The authors suggested that the elevated intracranial venous pressure is the universal common pathway to explain IIH due to “various etiologies.” To further illustrate this concept, the same mechanism has been shown to work in the progression of certain types of hydrocephalus.\textsuperscript{36,37}

Significant debate continues about the etiopathogenesis of IIH.\textsuperscript{29} Dandy\textsuperscript{11} postulated that the volume of either CSF or blood might be increased in pseudotumor cerebri. Foley\textsuperscript{14} also hypothesized an increase in cerebral blood flow in these cases. Sahs and Joynt\textsuperscript{41} demonstrated microscopic evidence of intracellular and extracellular edema in pseudotumor cases. Johnston et al.\textsuperscript{25} suggested a defective CSF absorption from increased sagittal sinus pressure as a cause for IIH. Malm et al.\textsuperscript{28} postulated that the high CSF pressure in IIH resulted from an increase in sagittal sinus pressure or a decreased CSF conductance. The concepts of venous outflow impairment and cerebral venous hyperemia have been implicated. There is also a suggestion that these patients can be divided on the basis of body habitus; thin patients are more likely to demonstrate venous hyperemia and obese patients have venous outflow impairment given a subtle underlying increase in right atrial pressure.\textsuperscript{2,3,30,36,37,45} There are several theories proposed to have a direct link between obesity and IIH, through a specific fat distribution in the body or through production of lipokines, while some others have suggested a converse causation with raised ICP actually causing obesity.\textsuperscript{3,5,6,12,45}

Over the years, venous obstruction has been reported by authors to cause hydrocephalus in babies. These authors include Shulman and Ransohoff,\textsuperscript{44} Rosman and Shands,\textsuperscript{39} and Bateman et al.\textsuperscript{3} Likewise, venous outflow obstruction has been implicated in IIH by Karahalios et al.,\textsuperscript{28} King et al.,\textsuperscript{27} Owler et al.,\textsuperscript{32} and Bateman et al.\textsuperscript{3} With the advent of direct retrograde cerebral venography and venous sinus manometry, as well as studies with simultaneous measurement of CSF pressures, it has been re-

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**Fig. 3.** Case 3. Radiographs (anteroposterior and lateral full-length scoliosis images) obtained before (left panels) and after (right panels) segmental stabilization surgery.

**Fig. 4.** Case 3. Sagittal MR imaging section (left) with corresponding MR venography image (right) showing no evidence of cerebral venous sinus thrombosis.
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Ported that CSF pressure can be reduced by relieving a venous sinus obstruction causing venous hypertension of the superior sagittal sinus.\textsuperscript{32} Given the fact that 80\% of the intracranial vascular compliance is provided by the venous system, we believe that the alterations in venous return due to distortion or displacement of vertebral venous plexus during extensive spinal surgery could have a contributory effect for developing IIH in our patients. The reduction of high ICP and the favorable clinical response seen in IIH with acetazolamide would be explained by an increase in venous compliance.\textsuperscript{32}

It is unclear whether the use of EACA as a blood conservation agent may play an indirect role in the development of IIH. Epsilon–aminocaproic acid is a 6-aminoheptanoic acid belonging to the lysine class of antifibrinolytic agents. This agent can bind the lysine site on plasminogen and plasmin, preventing plasmin from binding to fibrin. Antifibrinolytic drugs are widely used, particularly in cardiac and orthopedic surgery, and previous reviews have found them to be effective in reducing blood loss, the need for transfusion, and even the number of reoperations for continued or recurrent bleeding.\textsuperscript{47} The use of EACA in our institution has also shown a statistically lower intraoperative estimated blood loss, a total perioperative blood loss (including through the chest tube and Hemovac), and transfusion requirements. However, EACA has a manufacturer-reported risk of causing intracranial hypertension, although this has never been published in neurosurgical, cardiac, orthopedic, or general surgical literature after the intraoperative use of EACA.

All 3 patients in our current case series had been given EACA after anesthesia induction at 100 mg/kg over a period of 15 minutes (not to exceed 5 g), and then a maintenance dose of 10 mg/kg/hr was given until wound closure.\textsuperscript{46–49} Our institution has extensive experience with EACA, as more than 1500 spinal deformity cases have been surgically treated since 1998, but there have been no neurological or other complications directly related to its use. Our experience includes a prospective preliminary study, a randomized double-blinded study, a fibrinogen study, and anterior and posterior spinal fusion studies, as well as a study on neuromuscular disorders.\textsuperscript{13,47} However, the serum fibrinogen levels were found to be significantly elevated above normal in the initial 2 weeks after administration of aminocaproic acid.\textsuperscript{46,47} Thompson et al.\textsuperscript{46} had reported that the postoperative fibrinogen levels in the serum of 57 consecutive patients with idiopathic scoliosis increased gradually and substantially from Day 1 to Day 5 after surgery, despite stopping EACA at the end of surgery.

Notably, there is a reported case of intracranial hypertension in an infant with vertebral osteomelitis with spinal canal stenosis and kyphosis, where the fibrinogen levels were remarkably elevated.\textsuperscript{48} Considering the aforementioned reports, the underlying hyperfibrinogenemia cannot be disregarded as a probable mechanism for development of intracranial hypertension in patients with spinal deformity after surgical correction in which antifibrinolytic therapy has been used.

It is important that spine surgeons treating deformities be aware of the phenomenon of IIH as a cause of postoperative headache. The recommended medical treatment of IIH comprises acetazolamide 500 mg at bedtime for 3 days and then 500 mg twice daily up to 2–4 g per day if there are no contraindications.\textsuperscript{40} Topiramate is another alternative in patients who are acetazolamide-intolerant. Lasix has been tried in some cases, but it has no proven benefit; steroids are generally avoided, except in acute visual loss.\textsuperscript{3} This clinical disorder is distinct from the postoperative spinal headache that develops from intraoperative dural tear and resultant CSF leak, where the patient exhibits postural variation of headache and improvement with bed rest, hydration, and symptomatic treatment. Although there is no consensus view on either the cause or management of IIH, it is possible to reverse the visual impairment with timely medical intervention as in the reported cases.

Conclusions

We present the first case series of 3 patients who were diagnosed with postoperative IIH at a high-volume pediatric practice of spine deformity correction surgery. The cause of this extremely rare postoperative condition could be related to the structural venous outflow changes related to surgery and/or due to the hyperfibrinogenemia resulting from EACA for perioperative blood conservation. While this condition is a very uncommon occurrence after spinal surgery, we believe that if it is recognized early enough, it can be effectively treated with medication such that a long-term visual field loss can be prevented.

Disclosure

Dr. Thompson is a co-editor of the Journal of Pediatric Orthopedics. 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 to the study and manuscript preparation include the following. Conception and design: Cohen, Kunes, Thompson, Poe-Kochert. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: Cohen, Thompson, Manjila. Reviewed submitted version of manuscript: Cohen, Thompson, Manjila. Approved the final version of the manuscript on behalf of all authors: Cohen. Study supervision: Cohen, Thompson.

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