LEARNING OBJECTIVES

1. The attendee will be able to discuss the evidence for venous sinus stenosis in patients with idiopathic intracranial hypertension (IIH) and the theoretical rationale for evaluating venous stenting as a potential therapy.

2. The attendee will be able to list the available retrospective and anecdotal evidence so far in support or against the use of venous stenting for patients with IIH.

3. The attendee will be able to list the possible complications and their frequency in patients who undergo venous stenting for IIH.

CME QUESTIONS

1. Current models of cerebrospinal fluid (CSF) absorption at the arachnoid granulations show a relationship with all of the following except:
   a. Blood pressure
   b. CSF pressure
   c. Superior sagittal sinus pressure
   d. Resistance of CSF outflow across the arachnoid villi

2. Which of the following statements is true?
   a. Intracranial pressure has decreased in some patients following venous sinus stenting.
   b. Venous sinus stenosis has improved in some patients following CSF diversion procedures.
   c. Both A and B
   d. Neither A or B

3. Observed complications of venous sinus stenting include all of the following except:
   a. Reversible hearing loss
   b. Meningitis
   c. Stent thrombosis
   d. Subdural hemorrhage
   e. Anaphylaxis

KEYWORDS

1. Idiopathic Intracranial Hypertension
2. Venous Sinus Stenosis
3. Venous Stenting
4. Venous Sinus Hypertension
5. Pseudotumor Cerebri

INTRODUCTION

Venous sinus stenosis has been observed in patients with idiopathic intracranial hypertension (IIH) over the last two decades. Uncertainty remains as to whether this stenosis is the result or cause of intracranial hypertension in certain patients with the disease or whether it may be both. The association of venous sinus stenosis with IIH has led to multiple case reports and retrospective studies detailing the outcomes of patients following venous sinus stenting. The rate of serious irreversible complications appears to be relatively small, but more studies with long-term follow up are needed to fully evaluate its safety. Rates of post-procedure improvement in symptoms, papilledema and visual field defects are promising, but a controlled, prospective trial is needed to properly evaluate its efficacy in stabilizing or reversing symptoms and visual loss in patients with IIH.

1. INTRODUCTION

Idiopathic intracranial hypertension (IIH) is a disease of elevated intracranial pressure in the absence of a structural lesion, venous sinus thrombosis or meningitic process that occurs primarily in obese woman of childbearing age. Recognition of an association of IIH with transverse sinus stenosis has led to the theory that this stenosis contributes to intracranial hypertension or might even be the primary cause, but a causative relationship remains controversial. Stenting of the transverse sinus has emerged as a potential therapy for IIH, based on theoretical evidence and an accumulation of retrospective, uncontrolled data over the last decade. However, prospective, controlled studies are needed to truly understand the safety and efficacy of this procedure in stabilizing or even reversing visual loss.
2. CASE PRESENTATION

A 25 year old woman with a history of obesity and nephrotic syndrome with end stage renal disease on hemodialysis presented with several weeks of transient visual obscurations, intermittent headaches in the setting of a 20 pound weight gain.

Automated Permetry using Humphrey Visual field analyzer showed significant enlargement of the blind spot in both eyes and mild nasal and inferior depressions in the left eye. There was Frisén grade IV papilledema on funduscropy. She was admitted to the hospital where MRI was normal but MRV showed focal bilateral narrowing at the transverse sinus/sigmoid sinus junction. Lumbar puncture showed normal contents but opening pressure was >55 cm of water.

Acetazolamide was started, but was kept at a low dose of 250 mg a day at the request of nephrology. There was an improvement in the frequency of visual obscurations but they worsened again at three weeks in the setting of non-compliance with the medication. Visual fields demonstrated new inferonasal defects in both eyes and papilledema had progressed in severity. Acetazolamide was restarted but repeat lumbar puncture several days later still demonstrated opening pressure of 45 cm of water.

The procedure was complicated by a retroperitoneal hemorrhage that resolved without any permanent effects.

The indications in this case included progression of field defects and papilledema despite treatment with the maximal medication dose deemed safe by nephrology. While alternative medications could have been attempted, the patient had demonstrated poor compliance with acetazolamide, and there was concern that vision would deteriorate further during a medication trial that she might not comply with. The patient was a candidate for stenting as angiogram confirmed the transverse-sigmoid junction venous stenosis seen on MRV and demonstrated a cross-sinus pressure gradient.

The outcome of the case demonstrated resolution of symptoms within a few days, but papilledema took months to improve. Visual field defects also took more than a month to improve and never resolved completely. While these results suggest a positive effect of venous stenting, it is important to note that some, if not all of this improvement may have occurred anyway with time.

3. THEORETICAL RATIONALE FOR STENTING

The theoretical underpinnings of venous sinus stenosis as a contributor to high intracranial pressure in IIH begin with the long-held knowledge that venous sinus thrombosis or compressive occlusions are well-known causes of increased intracranial pressure. This resulted in the addition of venography in the diagnosis of IIH to rule out thrombosis. Although the Dandy criteria for IIH require a “normal” MRI, in fact it has been recognized for years that venous sinus stenosis is common patients with IIH, specifically along the transverse sinuses.

In 1995, King et al demonstrated venous hypertension in the superior sagittal sinus and proximal transverse sinuses of 7 patients with IIH, with a drop in the lateral third of the sinus. Interestingly, they reported that this was not the case in 2 patients with minocycline-induced IIH. In 1996, Karahalios found dural sinus outflow obstruction in only 5/10 patients with IIH but 8/8 patients who underwent manometry demonstrated elevated venous sinus pressures, suggesting that venous hypertension is common in IIH, although whether it was cause or effect was not elucidated.

The absorption of cerebrospinal fluid (CSF) at the arachnoid granulations has been modelled by the equation: CSF absorption = (P_{CSF} - P_{SSS}) / R_{out}, where P_{CSF} is the CSF pressure, P_{SSS} is the SSS pressure, and R_{out} is the resistance of CSF outflow across the arachnoid villi. Thus, CSF absorption is dependent on the venous pressure in SSS. According to this model, relieving a venous sinus obstruction responsible for venous hypertension in the SSS will therefore promote CSF absorption and eventually reduce CSF pressure. In 2007 however, Rohr et al demonstrated reversibility of sinus stenosis in patients after CSF-diversion procedures, arguing that in these patients the stenosis is secondary to the elevated ICP, and cautioning that venous sinus stenting should not be performed in such patients.
stenting have countered that sinus stenosis may be both secondary to elevated ICP and a contributor to elevated ICP, thus participating in a vicious cycle. Venous stenting as a means to breaking that cycle may still be efficacious even in patients where the stenosis would be reversible with lowering of the ICP by shunting, they argue. Furthermore, venous stenosis may recur in some patients who experienced resolution with a drop in ICP.

Patients with IIH who are refractory to medical management may undergo optic nerve sheath fenestration or ventricular or lumbar-shunt placement, but these procedures are not without risk of complication or failure. Based on the early findings of manometry and in the context of the limitations of alternative surgical therapies, some groups have set out to examine the safety and utility of cerebral venous sinus stenting for IIH.

Data from uncontrolled retrospective studies of venous stenting will be presented below. At this time however, venous stenting for IIH remains an experimental procedure, without controlled, retrospective data proving its safety and efficacy. At this time, there are no randomized controlled trials and all data is anecdotal. The studies that have been performed, for the most part, do not address long term efficacy: the longest follow up is 136 months but the mean clinical follow up time was just under a year at 11.9 months.

4. PROCEDURE
It is important that practitioners understand what is involved in the procedure of venous stenting (video). Since there is a risk of peri and post-procedural stent thrombosis, an anti-thrombotic regimen is generally prescribed prior to and after the procedure. In our institution, patients receive daily aspirin 81mg and clopidogrel 75mg for 5 days prior to the intervention. The procedure may be divided into 5 steps:

1) Direct Retrograde Cerebral Venography (DRCV): Vascular access is obtained from the femoral vein with placement of a 6 French sheath. Systemic heparin is administered and a catheter is inserted through the iliac vein and brought to the right or left (depending on the location of the stenosis on the MRV or CTV) internal jugular vein and cerebral venous sinuses under fluoroscopic guidance.

2) Manometry: A smaller catheter is further advanced to the area of stenosis and pressures are measured before and after the stenosis.

3) Angioplasty: This procedure, along with stenting, may immediately follow the DRCV or can be done on separate day. Subjects will be placed under general anesthesia to prevent peri-operative movement. A catheter is again brought to the point of stenosis and a balloon is advanced through the catheter and positioned across the stenosis. The balloon is carefully inflated for a few seconds to partially re-open the stenosis, making room for the stent. The balloon is removed.

4) Stenting. The stent will be advanced through the catheter in neck across the stenosis and carefully deployed.

5) Repeat Manometry. After stent placement, the pressure gradient across the stenosis is measured again.

Anesthesia: Direct Retrograde Cerebral Venography and manometry are performed with local anesthetic and moderate sedation because general anesthesia may cause artificially elevated venous sinus pressure, confounding the results. If angioplasty and stenting are indicated, we convert to general anesthesia (GA) before proceeding, as these procedures are painful. If necessary, patients may return the next day for angioplasty and stenting under GA, but the former protocol is preferable as it requires only one venipuncture.

Post-procedure care: After the procedure the subject will stay in the intensive care unit for 24 hours for observation. Clopidogrel 75mg is continued for 1 month and ASA 81mg for a total of 6 months. We ask patients to avoid contact sports for the period in which they are on both anti-platelet medications. We also ask female patients to avoid becoming pregnant during the month in which they are taking both medications. Other than emergency surgeries or procedures, we ask patients not to schedule any elective surgeries for the first month because they are at high risk for in-stent thrombosis if either the clopidogrel or ASA is stopped. We also ask that elective procedures requiring ASA cessation be avoided in the first 6 months, since stopping the ASA would confer a mild risk of thrombosis, especially in the first few months.

5. FOLLOW-UP
Follow-up goals are to ensure stent patency and efficacy in lowering ICP and to monitor for long-term complications. The follow-up in our study includes:

a. Neurological and ophthalmological evaluation including perimetry will be performed at 1, 3, 6, 12, 18, and 24 months after treatment, or more frequently if indicated.

b. Non-invasive imaging studies: Computed tomography venogram (CTV) will be performed at 3, 12 and 24-months after treatment. If there is clinical concern about stent patency, an expedited or intermediate CTV will be performed.

c. Invasive Procedures: Follow-up DRCV will be performed if there is clinical or imaging (CTV) concern for restenosis or decreased stent patency.

d. A lumbar puncture will be repeated between 2–3 months and at or around 24 months after treatment to measure the intracranial pressure.

6. RISKS / SAFETY DATA
Venous stenting is not without risk. Based on a literature review inclusive to July, 2012, there were 17 reported complications among 151 patients. They included:

a. Stent thrombosis: 2 (1.26%)—treated with thrombolitics and were asymptomatic.

b. Subdural hematoma: 3 (1.9%) One was associated with an AVM.
c. Transient contrast extravasation: 1 (0.63%)\(^{13}\)

d. Transient headache: 1 (0.63%)\(^{13}\)

e. Allergic reaction: 2 (1.26%)\(^{14}\)

f. Anaphylaxis to general anesthesia: 1 (0.63%)

g. Transient hearing loss: 2 (1.26%)\(^{14}\)

h. Anaphylaxis to GA: 1 (0.63%)\(^{14}\)

i. Thrombosis R TS: 1 (0.63%)\(^{10}\)

j. UTI: 1 (0.63%)\(^{10}\)

k. Syncope next day: 1 (0.63%)

l. Retroperitoneal hemorrhage: 2 (including 1 of our patients, unpublished) (1.3%)\(^{15}\)

m. Femoral artery Pseudoaneurysm: 1 (0.63%)

7. EFFICACY DATA

After-stent results are reported, based on a literature review inclusive to July, 2012. There were a total of 158 cases identified, 55 of which were from the US. (35%)

a. Headache: 142 with headache pre-stent are described in the literature. Among them, 117 (82%) resolved or improved.

b. Objective visual defects: 66 with visual field defects pre-stent are described

  - Resolved/improved: 45/66 (68%)
  - Unchanged: 7/66 (11%)
  - Worsened: 1/66 (2%)
  - No data: 13/66 (19%)

c. Elevated CSF pressure: 109 with elevated ICP pre-stent are described

  - Resolved/improved: 26/109 (24%), 26/27 checked (96%)
  - Unchanged: 1/109 (0.9%)
  - No data: 81/109 (74.3%)

d. Papilledema: 128 with papilledema pre-stent are described

  - Resolved/improved: 118/128 (92%)
  - Unchanged: 4/128 (3.1%)
  - No data: 6/128 (4.6%)

Please reference table #1 on page 358 for a review of the safety and efficacy of venous sinus stenting in the literature.

8. BEST INDICATIONS

As venous sinus stenting has not been proven to be an long-term effective therapy for IIH, and the long term risks have not been clearly established, there is no clear indication as of yet. As such, it is reasonable to conclude that at present it is best reserved for patients with IIH who have shown a decline in reliable perimetry (in the setting of persistent or worsening papilledema) either despite maximal medical therapy, or who are unable to tolerate or are non-compliant with best medical therapy. Patients with IIH who present with severe visual loss initially and are deemed to require urgent and persistent lowering of intracranial pressure may theoretically benefit from the procedure, although the latency between reduction in stenosis and any effect on intracranial pressure is as of yet unclear.

9. WEILL CORNELL VENOUS STENTING TRIAL

Along with co-investigator Athos Patsalides, MD, we have set out evaluate the safety and efficacy of venous stenting for patients with IIH in our institution.\(^{17}\) Our primary objectives include evaluating the safety of sinus venous sinus stenting in patients with refractory IIH and evaluating the efficacy of venous stenting in improving visual function in patients with refractory IIH. (Refractory IIH is defined as absence of stabilization or improvement in visual function after one month of best medical treatment or intolerance to the medical regimen) In this study, which is the first FDA-approved trial in US, we aim to quantify change in mean deviation after stenting and quantify changes in papilledema on clinical examination and using optical coherence tomography (OCT).

10. FUTURE DIRECTIONS

While the available retrospective and anecdotal data on venous stenting suggests that it may be an effective alternative therapy for IIH, a prospective, randomized head to head trial of venous stenting vs. ventriculoperitoneal shunting vs. optic nerve sheath fenestration is ultimately needed to truly assess its value in the therapeutic options for this disease. While the interventional radiologist and surgeons will know the treatment used, evaluating neuro-ophthalmologists should be blinded as they asses visual function and improvement in papilledema.

Audience Response Question: After this talk, would you consider sending a patient with IIH refractory to acetazolamide with a worsening visual field for treatment with venous stenting at an institution with several years of experience with the procedure?

a. Yes

b. No

CME ANSWERS

1. A. Blood pressure is not directly related to csf absorption at the arachnoid granulations

2. C. Venous stenting has been followed by a decrease in intracranial pressure in some patients and csf shunting has been followed by an improvement in venous sinus stenosis in others.

3. B. Meningitis has not been reported as a complication of venous sinus stenting as of August, 2012.

REFERENCES


<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Age (yr)</th>
<th>HA</th>
<th>PE</th>
<th>VD</th>
<th>RH</th>
<th>O</th>
<th>Procedure</th>
<th>PUI</th>
<th>Follow (months)</th>
<th>Efficacy on HA</th>
<th>Effect on Vision</th>
<th>Efficacy on Visual Field</th>
<th>Effect on CSF Pressure</th>
<th>Long-term Complications</th>
<th>General Efficacy Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higgins 2002</td>
<td>1</td>
<td>30</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>Improved. 1</td>
<td>Remaining. 1</td>
<td>Improved. 1</td>
<td>Remaining. 1</td>
<td>Remaining. 1</td>
<td>Patient. 1</td>
<td></td>
</tr>
<tr>
<td>Higgins 2003</td>
<td>12</td>
<td>19-52</td>
<td>12</td>
<td>6</td>
<td>0</td>
<td>11</td>
<td>11</td>
<td>0</td>
<td>240 (14)</td>
<td>Remaining. 2</td>
<td>Improved. 2</td>
<td>Remaining. 4</td>
<td>Improved. 2</td>
<td>Remaining. 1</td>
<td>Not stated. 10</td>
<td></td>
</tr>
<tr>
<td>Cowan 2001</td>
<td>4</td>
<td>17-55</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>5-12 (8)</td>
<td>Remaining. 2</td>
<td>Improved. 2</td>
<td>Not improved. 2</td>
<td>Unchanged. 2</td>
<td>Unchanged. 5</td>
<td>Not stated. 1</td>
<td></td>
</tr>
<tr>
<td>Cynober 2002</td>
<td>1</td>
<td>27</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>Improved. 1</td>
<td>Improved. 1</td>
<td>Not improved. 1</td>
<td>Remaining. 1</td>
<td>Not stated. 1</td>
<td>Patient. 1</td>
<td></td>
</tr>
<tr>
<td>Kapil 2003</td>
<td>1</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>Improved. 1</td>
<td>Remaining. 1</td>
<td>Not improved. 1</td>
<td>Remaining. 1</td>
<td>Not stated. 1</td>
<td>Patient. 1</td>
<td></td>
</tr>
<tr>
<td>Meissner 2005</td>
<td>1</td>
<td>31</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>Improved. 1</td>
<td>Remaining. 1</td>
<td>Not improved. 1</td>
<td>Remaining. 1</td>
<td>Not stated. 1</td>
<td>Patient. 1</td>
<td></td>
</tr>
<tr>
<td>Ribeiro 2007</td>
<td>1</td>
<td>21</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Improved. 1</td>
<td>Remaining. 1</td>
<td>Not improved. 1</td>
<td>Remaining. 1</td>
<td>Not stated. 1</td>
<td>Patient. 1</td>
<td></td>
</tr>
<tr>
<td>Casas 2007</td>
<td>1</td>
<td>30</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Improved. 1</td>
<td>Remaining. 1</td>
<td>Not improved. 1</td>
<td>Remaining. 1</td>
<td>Not stated. 1</td>
<td>Patient. 1</td>
<td></td>
</tr>
<tr>
<td>Bota 2008</td>
<td>1</td>
<td>50</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>Improved. 1</td>
<td>Remaining. 1</td>
<td>Not improved. 1</td>
<td>Remaining. 1</td>
<td>Not stated. 1</td>
<td>Patient. 1</td>
<td></td>
</tr>
<tr>
<td>Lomel 2003</td>
<td>10</td>
<td>25-50</td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5-35 (17)</td>
<td>Remaining. 2</td>
<td>Improved. 2</td>
<td>Remaining. 6</td>
<td>Improved. 2</td>
<td>Remaining. 1</td>
<td>Patient. 10</td>
<td></td>
</tr>
<tr>
<td>Srinivas 2004</td>
<td>9</td>
<td>37-55</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>Not stated. 1</td>
<td>Not stated. 1</td>
<td>Not stated. 1</td>
<td>Not stated. 1</td>
<td>Not stated. 1</td>
<td>Patient. 10</td>
<td></td>
</tr>
<tr>
<td>Buitr 2013</td>
<td>10</td>
<td>15-55</td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4-60 (17)</td>
<td>Remaining. 8</td>
<td>Improved. 2</td>
<td>Remaining. 6</td>
<td>Improved. 2</td>
<td>Remaining. 10</td>
<td>Not stated. 10</td>
<td></td>
</tr>
<tr>
<td>Zhang 2010</td>
<td>1</td>
<td>34</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>Not improved. 1</td>
<td>Remaining. 1</td>
<td>Not improved. 1</td>
<td>Remaining. 1</td>
<td>Not stated. 1</td>
<td>Patient. 10</td>
<td></td>
</tr>
<tr>
<td>Kakoulakis 2010</td>
<td>16</td>
<td>12-51</td>
<td>16</td>
<td>MA</td>
<td>MA</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>2-40 (20)</td>
<td>Remaining. 2</td>
<td>Improved. 10</td>
<td>Not stated. 1</td>
<td>Remaining. 3</td>
<td>Unchanged. 1</td>
<td>Not stated. 1</td>
<td></td>
</tr>
<tr>
<td>Ariza 2011</td>
<td>28</td>
<td>30-54</td>
<td>28</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3-50 (24)</td>
<td>Remaining. 16</td>
<td>Improved. 16</td>
<td>Remaining. 3</td>
<td>Improved. 3</td>
<td>Remaining. 2</td>
<td>Not stated. 1</td>
<td></td>
</tr>
<tr>
<td>Freitas 2011</td>
<td>15</td>
<td>20-60</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>1-24 (1)</td>
<td>Remaining. 3</td>
<td>Improved. 3</td>
<td>Unchanged. 3</td>
<td>Unchanged. 3</td>
<td>Unchanged. 3</td>
<td>Not stated. 1</td>
<td></td>
</tr>
<tr>
<td>Paesky 2011</td>
<td>2</td>
<td>NR</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>Not improved. 2</td>
<td>Remaining. 1</td>
<td>Not improved. 1</td>
<td>Remaining. 1</td>
<td>Not stated. 1</td>
<td>Patient. 2</td>
<td></td>
</tr>
<tr>
<td>Ranje 2012</td>
<td>14</td>
<td>30-52</td>
<td>14</td>
<td>4</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>11-130 (45-7)</td>
<td>Remaining. 16</td>
<td>Improved. 16</td>
<td>Not improved. 1</td>
<td>Remaining. 16</td>
<td>Remaining. 16</td>
<td>Not stated. 1</td>
<td></td>
</tr>
</tbody>
</table>