Learning Objectives:
By the end of the presentation, the participant should have become familiar with the anatomy, etiology, and clinical spectrum of spontaneous CSF leaks/intracranial hypotension, the diagnostic tests, and various imaging abnormalities of the disorder, as well as treatment modalities, outcome, and complications.

CME Questions:
1. In spontaneous intracranial hypotension CSF opening pressure may be:
   a. Below 60 mm H2O or even immeasurable
   b. Low normal
   c. Normal
   d. All of the above

2. In spontaneous intracranial hypotension:
   a. Headache is the most common clinical manifestation
   b. The headache always has orthostatic features
   c. Patients may display a variety of different manifestations, but headache is always present
   d. Decreased CSF absorptions or increased CSF absorptions are the two common causes of spontaneous intracranial hypotension

Key Words: Magnetic resonance imaging, spontaneous intracranial hypotension, cerebrospinal fluid, hypovolemia

MR imaging has revolutionized identification of patients with spontaneous intracranial hypotension (SIH) and CSF leaks and has increased our understanding of CSF volume depletion. A far broader clinical and imaging spectrum of the disorder is now recognized.

CSF Dynamics: A Few Points Pertinent to this Discussion

CSF FORMATION: Choroid plexus forms most of the CSF. It has structural and functional similarities to the distal and collecting tubules of the kidneys. It maintains the compositional stability of the CSF. A minor portion of CSF is secreted by brain capillaries into the neurophil and enters the ventricular system through the ependyma.

CSF VOLUME: For many years, based on old and autopsy data, the CSF volume was estimated to be about 150 mL. Recent MRI volumetric studies show significant variations in CSF volume:
   A) The volume of cranial CSF has been calculated to be 157 +1- 59 mL (for both sexes and for all ages from 24 to 80 years). This figure is larger for men and is smaller for women. Not surprisingly, it is much smaller for younger individuals than the older persons who have larger ventricles and more generous subarachnoid spaces and cisterns.
   B) The volume of spinal CSF from T11-12 interspace to the sacral dural terminus has been calculated to be 49.9 +1- 12.1 mL. This can range from 28 to 81.1 mL. The volume is significantly less for the obese than non-obese persons.

RATE OF CSF FORMATION: In adults, this is about 0.35 mL per minute or about 500 mL per day. The CSF is absorbed via the arachnoid villi into the cerebral venous sinuses and veins, mostly through a valve-like direct flow -“bulk flow”. A minor portion of CSF is absorbed into the cerebral vessels by simple diffusion. In general, the rate of CSF formation in humans is maintained relatively constant. Choroid plexus papilloma perhaps is the only condition that can cause increased CSF formation sufficient enough to lead to intracranial hypertension. A reduction in the rate of CSF formation likely is noted only when intraventricular pressure is sufficiently elevated for a sufficient period of time.

EFFECT OF POSTURE ON CSF PRESSURE: In horizontal position, lumbar and cisternal, and presumably the intracranial or vertex CSF pressures are equal (approximately 60 to 180 mm of water). In an erect posture, these pressures diverge, and vertex CSF pressure becomes negative. The relationship between CSF pressure and volume is exponential. Withdrawal of approximately 10 percent of the estimated CSF volume can induce headaches in upright posture. This 10% CSF volume loss leads to approximately 40 percent decrease in the already negative vertex CSF pressure.
Historical Background

Some Historical Landmarks of CSF Hypotension and CSF Hypovolemia
1891: Quincke introduced lumbar puncture.
1898: Bier suffered post-LP headaches and was the first to report them.
1938: Schaltenbrand emphasized the term "Aliquorrhea" with clinical descriptions that we now recognize as the clinical picture of intracranial hypotension. Patients had very low, unobtainable, or even negative opening CSF pressures. This had been described earlier in French literature under the term "hypotension of spinal fluid" or "ventricular collapse". Schaltenbrand tended to think that decreased CSF production was the cause. Of course, technology of the time would not have allowed him to study the patients properly for CSF leak. Schaltenbrand should be credited for drawing attention to spontaneous occurrence of this entity.

1950s to 1990s: The details of the clinical manifestations of intracranial hypotension and CSF leak were described in several publications. Introduction of radioisotope cisternography provided more information on CSF dynamics and its leak. Myelography-CT myelography using water-soluble contrast emerged as a useful and reliable diagnostic test to demonstrate CSF leaks.

Early 1990s: MR imaging features of intracranial hypotension/CSF leaks were recognized. Detection of more cases and broadening of the clinical and imaging spectrum of the disease has followed and is continuing. It is now recognized that the majority if not all cases of spontaneous intracranial hypotension result from spontaneous CSF leaks.

Etiology

The overwhelming majority of spontaneous CSF leaks occur at the level of the spine, particularly the thoracic spine. Spontaneous leaks at the level of the skull base (i.e. cribriform plate) occur, but only rarely. CSF leak leads to CSF volume depletion (CSF hypovolemia), which is also the pathogenetic core in over-draining CSF shunts and post-surgical CSF leaks. Reduced total body water (true hypovolemic state) also should be expected to cause reduced CSF volume (Table 1).

Table 1. Etiology of CSF volume loss

I. True hypovolemic state (reduced total body water)
II. CSF shunt overdrainage
III. CSF leaks
A. Traumatic
   1. After definite trauma
   2. After spinal tap or epidural injections
   3. After spinal or cranial surgical procedures
B. Spontaneous (SIH)
   1. Unknown cause (often)
   2. Weakness of the dural sac
      a. Meningeal diverticula
      b. Abnormalities of connective tissue matrix
   3. Dural tear from spondylosis or disk herniation
   4. Trivial trauma

When the etiology is discussed, it is the spontaneous group that presents the real challenge. The exact cause of a spontaneous CSF leak often remains unclear. Two factors should be considered: trivial trauma and weakness of the dural sac. Dural sac abnormalities, meningeal diverticula, and CSF leaks are noted in Marfan syndrome and stigmata of connective tissue disorder, are observed in a notable minority of the patients who have spontaneous CSF leaks.

Clinical Manifestations

The most common clinical manifestation is orthostatic headache - a headache in upright position relieved by recumbency. This may or may not be throbbing, is often but not always bilateral, and can be frontal, fronto-occipital, holocephalic, or occipital. Two important points ought to be emphasized: a) not all patients with orthostatic headaches have CSF leaks b) not all headaches that result from CSF leaks are orthostatic. These headaches may have a variety of different features (Table 2). Other clinical manifestations of SIH/CSF hypovolemia are listed in Table 3.

Table 2. Headaches in Intracranial Hypotension/CSF Hypovolemia
1. Orthostatic headaches (present when upright, relieved by recumbency)
2. Cervical or interscapular pain preceding orthostatic headache by days or weeks
3. Vague or steady non-orthostatic headaches preceding orthostatic headaches by days, weeks, or months
4. Orthostatic headaches evolving into chronic linger-
ing headaches, after months
5. Non-orthostatic chronic daily headache
6. Exertional headaches without any orthostatic features
7. Acute thunder clap-like onset of orthostatic headaches
8. Second half of the day headaches (often with some orthostatic features)
9. Paradoxic orthostatic headaches (present in recumbency, relieved when upright)
10. Intermittent headaches of intermittent leaks
11. No headaches (acephalgic form)

Table 3. Clinical Features of SIH/CSF Leaks/CSF Hypovolemia Other than Headaches
1. Pain or stiff feeling of neck -sometimes orthostatic
2. Nausea, sometimes emesis -often orthostatic
3. Horizontal diplopia (unilateral or bilateral sixth cranial nerve palsy)
4. Third and fourth cranial nerve palsies (much less common than sixth cranial nerve palsy) or any combination of palsies of cranial nerves 3rd, 4th, 6th
5. Visual blurring
6. Photophobia
7. Visual field cut (superior binasal)
8. Dizziness
9. Change in hearing (muffled, distant, distorted, echoed)
10. Interscapular pain
11. Low back pain
12. Facial numbness or weakness
13. Galactorrhea
14. Labyrinthine hydrops
15. Radicular upper limb symptoms
16. Stupor, diencephalic compression
17. Coma
18. Parkinsonism, ataxia, bulbar weakness
19. Frontotemporal dementia
20. Encephalopathy
21. Trouble with control of bowel or bladder
22. Gait disorder
23. Subdural hematomas that may or may not be symptomatic

Subdural hematomas that may be symptomatic may complicate SIH. The location of cervical, thoracic, or lumbar pain in SIH should not necessarily be expected to correspond to the site of the leak (often it does not).

Mechanisms of clinical manifestations

One consequence of CSF volume depletion is descent of the brain that leads to traction on anchoring pain-sensitive structures of the brain and therefore leading to the headaches that have orthostatic features.
Dilatation of intracranial venous structures also plays a likely role in causing headaches.
Similarly, traction, distortion, or compression of some of the cranial nerves, the brain or brainstem, and diencephalic structures may be responsible for the various cranial nerve palsies, the CNS manifestations (Table 4).
Diagnostic Studies

A. CSF EXAMINATION

a. Opening pressure: Very low (sometimes atmospheric and unmeasureable, very occasionally even negative), low normal, normal
b. Analysis:
   Color: clear (often) or xanthochromic (occasionally)
   Protein: Normal or high (protein concentrations of up to 100 mg/dL are not uncommon and higher concentrations are not rare).
   Glucose: Never low
   RBC: Normal or elevated
   WBC: Normal or elevated (a primarily lymphocytic pleocytosis of up to 50 cells/mm³ is not uncommon and higher counts are not rare)
   Cytology and microbiology: Always negative

B. HEAD CT

Negative, typically
Subdural fluid collections and/or increased tentorial enhancement seen only occasionally
Overall, head CT is often normal and of very limited value in diagnosis of CSF leaks

C. RADIOISOTOPE CISTERNOGRAPHY

Indium-111 is the radioisotope of choice
Radioactivity does reach convexities at 24 or even 48 hours May show level of the leak
Early appearance of activity in the kidneys and the bladder «4 hours vs. 6-24 hours)
If desired, enables measurement of CSF opening pressure at the time of IT injection of radioisotope.

D. MRI

1. Head MRI
   a. Meningeal enhancement
      Limited to pachymeninges
      No evidence of leptomeningeal enhancement - Enhancement is: Both supra- and infratentorial, linear and uninterrupted, and non-nodular.
   b. Subdural Collections
      Usually, but not always, bilateral
      Thin (2-7 mm maximum thickness)
      No compression or effacement of underlying sulci
      Variable signal intensity depending on fluid composition (protein concentration, blood)
   c. Descent of brain (sagging)
      Descent of cerebellar tonsils (may mimic Type T Chiari) - Decrease in size of pre-pontine cistern - Inferior displacement of optic chiasm - Effacement of perichiasmatic cisterns
      Sometimes relatively large subdural hematomas may form and cause pressure effect and shift of the mid-line structures.
   d. Enlargement of pituitary
e. Engorgement of cerebral venous sinuses
f. Decrease in size of the ventricles ("ventricular collapse")
   2. Spine MRI
      Extra-arachnoid fluid - fairly common
      Extra-dural fluid extending to paraspinal soft tissues - rather uncommonly
      Diverticulae
      Level of the leak (i.e. cervical, thoracic, lumbar) - fairly commonly
      Actual site of the leak - very uncommonly
      Dural enhancement
      Engorgement of epidural venous plexus

Table 4. Proposed Mechanisms of Clinical Manifestations of Cerebrospinal Fluid Volume Depletion

<table>
<thead>
<tr>
<th>CLINICAL MANIFESTATION</th>
<th>PROPOSED MECHANISMS</th>
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<tbody>
<tr>
<td>Headache</td>
<td>Sinking of the brain, stretch and distortion of pain-sensitive suspending structures, congestion of cerebral venous sinuses and large veins</td>
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<tr>
<td>Cranial nerve palsies (3rd, 4th, 5th, 6th, 7th, chorda tympani)</td>
<td>Stretching and distortion of these nerves</td>
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<tr>
<td>Blurred vision, visual field defect</td>
<td>Compression or vascular congestion of intracranial portions of optic nerves</td>
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<tr>
<td>Cochleovestibular manifestations: change in hearing (muffled, distant, distorted, echoed), tinnitus, dizziness/vertigo</td>
<td>Stretching of 8th cranial nerve or pressure changes in perilymphatic fluid of the inner ear</td>
</tr>
<tr>
<td>Galactorrhea and increased prolactin</td>
<td>Distortion of pituitary stalk</td>
</tr>
<tr>
<td>Radicular upper limb symptoms</td>
<td>Stretching of cervical nerve roots or structural</td>
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Mechanisms of MRI abnormalities:
Loss of CSF volume leads to (1) ventricular collapse and decrease in size of the ventricles and (2) sinking of the brain with descent of the cerebellar tonsils, decrease in the size of basal subarachnoid cisterns (i.e. pre-pontine or peri-chiasmatic cisterns), flattening of the optic chiasm, and crowding of the posterior fossa. Furthermore, according to the Monro-Kellie doctrine the loss of CSF volume has to be compensated. This is accomplished by increase in intracranial venous hypervolemia leading to (1) diffuse pachymeningeal gadolinium enhancement (a consequence of meningeal venous hyperemia), (2) engorgement of cerebral venous sinuses, and (3) pituitary hyperemia and thus pituitary enlargement. Subdural fluid collections and engorgement of epidural venous plexus also are volume compensatory phenomena in reaction to loss of CSF volume.

E. MYELOGRAPHY/CT -MYELOGRAPHY
(water-soluble contrast)
Extra-arachnoid/Extradural egress of contrast f-Diverticula
Level of the leak (i.e. cervical, thoracic, lumbar).
Acutal site of the leak (so far CT -myelography is the most reliable test for this purpose).
Also enables measurement of opening pressure Slow-flow and fast-flow CSF leaks: These create diagnostic challenges during CT -myelography.
In slow flow leaks, when CT is carried out, not enough of CSF/contrast has leaked to allow detection by CT.
There are a couple of potential options:
   a) Obtaining another CT in 3-4 hours may sometimes allow detection of the site of the leak.
   b) Spine MRI after intrathecal injection of gadolinium (MR myelography) may prove to be also a valuable tool in this regard.
In fast flow leaks, by the time the CT scanning is carried out, large amount of CSF/contrast has egressed and has extended across several spinal segments, making detection of the actual site of the leak virtually impossible. One method to deal with this challenge would be to skip the initial myelographic phase of the study and right after the IT injection of contrast proceed with CT scanning. Use of high-speed spiral CT is especially desirable in these situations to help enable detection of the site(s) of the leak. This technique has been described as "Dynamic CT myelography".

Pathologic findings
Gross: normal pachy- and lepto-meninges
Micro: dura: normal
"Subdural" area (deep levels of dura): variable thin zone of fibroblasts, small thin-walled vessels in amorphous matrix, histologic appearance resembles an organizing subdural hygroma, occasional secondary subdural hematomas may form.

Treatment
Several treatment modalities have been implemented in patients with SIH /CSF leaks (Table 5).

Table 5. Treatment modalities in CSF leaks
Bed rest
Hydration/over-hydration
Caffeine
Theophylline
Steroids
Abdominal binder
Epidural blood patch (EBP)
Continuous epidural saline infusion
Epidural infusion of Dextran
Epidural injection of fibrin glue
CSF shunting
Intrathecal fluid infusion
Surgical repair of the leak

Fortunately, many patients improve spontaneously. Bedrest has traditionally been advocated. However, as the majority of patients have significant orthostatic symptoms, they tend to stay recumbent anyway. The effectiveness of hydration or over-hydration, yet another traditionally advocated measure, has not been definitively established. Caffeine and theophylline have been demonstrated to be effective in some studies, but the effect is often unimpressive and of doubtful durability. The efficacy of steroids is unproved and mostly anecdotal. Some patients may report a partial improvement with steroids, but a substantial and lasting effect would be exceptional. Intrathecal fluid infusions or epidural infusions of crystalloids such as saline or colloids such as Dextran have produced variable results, but can be tried with limited expectations in patients who have failed repeated EBP, and when surgery is not an option.
One would be concerned about the introduction of infection in prolonged infusions, especially when the results are not durable.

EBP has emerged as the treatment of choice in patients who have failed an initial trail of conservative management. Its effect is twofold: (1) an immediate effect related simply to volume replacement by compressing the dura; and (2) a subsequent latent effect related to sealing of the leak. In SIH the success with each EBP is approximately 30%. Many patients require more than one blood patch. Sometimes as many as four or six blood patches have been given before achieving a lasting relief. This rate of success is significantly less impressive than in post-lumbar puncture headaches.

Surgery in well-selected cases is effective and is typically considered for those patients who fail the conservative and less invasive approaches such as EBP. The surgery is not always entirely straightforward. Sometimes the surgeon may encounter the extravasated CSF, but may not be able to locate the site of the leak and may therefore have to proceed with packing the area with blood-soaked Gelfoam, muscle, fibrin glue, etc., and hope for the best. Sometimes a dural defect may be noted with borders so markedly attenuated that they may not yield to stunting. It is essential to try to locate the site of the CSF egress before surgery. With careful case selection, successful results are often achieved. Recent reports suggest the utility of epidural patching with fibrin glue. This awaits further experience but the preliminary reports are encouraging.

**Prognosis**

Most patients make complete recovery either spontaneously, with conservative management, or with more invasive therapeutic approaches such as epidural blood patch, epidural injection of fibrin glue, or even surgery. In a small minority all attempts to stop the leak may fail. Recurrences may occur only in a minority and within variable intervals, sometimes after several years. The exact rate of recurrence is not known. Overall, patients with underlying disorders of connective tissue matrix and multiple meningeal diverticula may be more prone to recurrences or to have leakage from more than one site and from more than one level.

**Complications**

The major complication of spontaneous CSF leak is the development of symptomatic unilateral or bilateral subdural hematomas which may create significant therapeutic challenges. Cerebral venous sinus thrombosis an uncommon complication of spontaneous CSF leak has been occasionally reported. Following treatment of spontaneous CSF leaks, whether by EBP or surgery, sometimes a symptomatic syndrome of intracranial hypertension may develop. This is typically self-limiting. Treatment with Acetazolamide has shown encouraging results.

**Conclusion**

SIH almost entirely results from spontaneous CSF leaks. The previous theories of increased CSF absorption or decreased CSF production have fallen out of favor. Loss of CSF volume is the core pathogenetic factor as the independent variable whereas CSF pressure, MRI findings, and the clinical manifestations are variables dependent on the loss of CSF volume. The overwhelming majority of these leaks take place at the level of the spine, particularly the thoracic spine.

Considerable variability exists in clinical manifestations and CSF findings in spontaneous CSF leaks. Cases of unusual presentations have been reported and undoubtedly more will be reported in the future. Overall, however, the spontaneous CSF leaks often present as one of the following four types: 1) the classic form: headaches (typically orthostatic), low CSF pressure, and pachymeningeal enhancement are all present; 2) normal pressure form: despite typical clinical and imaging findings, CSF opening pressure are consistently within normal limits; 3) normal meninges: despite typical clinical manifestations and low CSF pressure, no meningeal abnormality is seen on the MRI; 4) acephalgic form: despite low CSF pressures and typical MRI abnormalities, headaches is absent.

The anatomy of these leaks can be complex. One should not expect a simple hole or rent or equate the spontaneous CSF leaks with post-lumbar puncture headaches despite their frequent similarities. Some of the patients with spontaneous CSF leaks may reveal clinical stigmata of heritable connective tissue disorder. This may be responsible for weakness of the
References


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Answers to CME Questions
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2. a