Cerebrospinal Fluid Leaks of the Skull Base

Physiology and Pathophysiology

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KEYWORDS

• Cerebrospinal fluid • Cerebrospinal fluid rhinorrhea • CSF physiology
• Anterior skull base surgery • Lateral skull base surgery • Neurotology • Rhinology
• Neurosurgery

KEY POINTS

- Cerebrospinal fluid (CSF) and its circulation are critical for proper nervous system function.
- Modern experimental methods challenge the classic hypothesis of CSF production and absorption. CSF may be produced and absorbed through the entirety of the neuroaxis, not exclusively in discrete locations.
- Cephaloceles can lead to CSF leaks, which disrupt flow and can introduce pathogenic bacteria to the central nervous system.
- Traumatic CSF leaks are common, but an increasing number of spontaneous leaks are being identified in certain populations.

INTRODUCTION

Cerebrospinal fluid (CSF) is a colorless body fluid present within the central nervous system that is generated through the ultrafiltration of plasma. It has essential functions in carrying vitamins and nutrients, providing buoyancy and shock absorption, and removing waste products. Leaks of CSF from the anterior and lateral skull base are commonly encountered in otolaryngology and neurosurgery practice, which can occur spontaneously, be associated with skull base tumors, or be the result of injury. Unaddressed, CSF leaks may lead to potentially devastating complications. Knowledge of the anatomy and physiology of CSF production is essential for the optimal management of these challenging clinical scenarios by otolaryngologists and neurosurgeons.

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Abbreviations	
AQP4	aquaporin-4
CSF	cerebrospinal fluid
GLP1R	glucagon-like peptide-1 receptor
OSA	obstructive sleep apnea

Discussion

Function and physiology of cerebrospinal fluid

CSF envelopes the brain, reducing the operational weight of the brain from approximately 1200 g to 45 g by the Archimedes principle.[1] The neutral buoyancy of the brain protects it from sudden impacts and changes in velocity. CSF contains numerous micro- and macronutrients and proteins essential for neurodevelopment and brain health, including vitamin C, folate, immunoglobulins, amino acids, and hormones.[1] CSF also functions as a "waste sink," removing toxic wastes and metabolites from the central nervous system, which is discussed further below.

Despite making up approximately 1.9% of total body weight, the brain receives up to 20% of total cardiac output.[2] Due to the brain being surrounded by the inflexible calvarium, blood flow must be tightly regulated to prevent intracranial hypotension or hypertension and to maintain the flow of nutrients to the highly metabolically active brain tissue. Cerebral blood flow is modulated by processes within and outside of the central nervous system.[3] Partial pressure of arterial carbon dioxide, mean arterial pressure, and the sympathetic and parasympathetic nervous systems are the primary contributors to cerebral blood flow. Intracranial pressures are maintained between a physiologic pressure of 5 to 15 mm Hg. Computational analysis of whole body magnetic resonance imaging indicates total CSF volume of 326 mL, distributed across the ventricles, cortical subarachnoid space, and spinal subarachnoid space (**Table 1**).[4]

CSF is an ultrafiltrate of plasma. As reviewed by Hladky and Barrand,[5] adult CSF has a greater than 100 times lower concentration of protein and cholesterol than plasma, as well as reduced content of glucose and amino acids. The composition of CSF is very similar to the interstitial fluid that surrounds the brain parenchyma in the extracellular space between neural and glial cells. These fluids are constantly exchanged through perivascular spaces (the "Virchow-Robin spaces"). The interstitial fluid comprises 15% to 20% of the brain volume.[6] CSF has a sodium concentration that is similar to, but generally lower than plasma. Chloride and magnesium concentrations are higher compared to plasma, while potassium is lower.[1,7]

In an age-dependent fashion, CSF is a promoter of stem cell differentiation and growth. In animal models, embryonic CSF is notable for having a higher protein concentration than adult CSF.[8] Proteomic analysis has revealed the presence of dozens of

Table 1
Computed distributions of cerebrospinal fluid volume by compartment

Compartment	CSF Volume in mL, ± Standard Deviation (% of Total)
Ventricles	28 mL ± 10 mL (8.5%)
Cortical subarachnoid space	222 mL ± 84 mL (68.1%)
Spinal subarachnoid space	76 mL ± 23 mL (23.3%)
Total	326 mL ± 88 mL (100.0%)

Data adapted from Lebret A, Hodel J, Rahmouni A, et al. Cerebrospinal fluid volume analysis for hydrocephalus diagnosis and clinical research. *Comput Med Imaging Graph*. 2013;37(3):224–233.[4]

proteins in embryonic CSF responsible for regulating the proliferation, survival, and differentiation or neural progenitors.[9] The osmotic properties of embryonic CSF also result in a controlled expansion of the neuroepithelial cavity.[10] Too much or too little expansion results in severe developmental anomalies of the central nervous system. In adult CSF, the secretome contains growth factors, which affect stem cell dynamics and neurogenesis.[11] Some growth factors have been shown to decline with age,[12,13] which may explain the reduced ability of neurogenesis to occur with aging.[14]

Production of cerebrospinal fluid and role of the choroid plexus

The hourly rate of CSF production rapidly rises during the first year of life**.** Experimental studies conducted by Rubin and colleagues[15] as well as Cutler and colleagues[16] in the 1960s demonstrated the mean rate of CSF production is approximately 0.3 to 0.4 mL/min in adults and children of at least 5 years of age (ie, 432–576 mL/d). These methods eliminated the effect of reabsorption from their calculations by measuring the fractional dilution of CSF in an artificial perfusate rather than simply measuring output from lumbar drainage. Their data showed that CSF pressure has no apparent effect on the rate of production–one subject had persistently elevated outflow pressures that exceeded 300 mm of water, yet their CSF production remained from 0.27 to 0.34 mL/min. The absorption rate, however, is linearly related to intraventricular pressure.

Modern studies involving MRI with flow quantification have demonstrated that while children younger than 2 years of age have a comparable rate of CSF production compared with adults (0.4 mL/min), there is a significant difference in the flow of CSF from the aqueduct to ventricle in children younger than 2 years of age compared with those older than 2 years of age.[17] These findings suggest there is an infantile pattern of CSF absorption across the deep capillary bed and no absorption across the arachnoid granulations. The rate of CSF turnover decreases with age, from approximately 4.5 turnovers per day in young adults to 3 turnovers per day in the elderly.[18] There is also an increase in protein concentrations within the CSF in the elderly compared with young adults.

Based on classic experiments by Dandy[19] and others in the early 20th century, CSF was thought to be primarily generated by the choroid plexus, a specialized epithelial sheet present in the 4 ventricles of the brain. The modern Bulat-Klarica-Orešković hypothesis of CSF hydrodynamics[20,21] postulates that rather than the choroid plexus being the sole producer of CSF, it is instead generated (and absorbed) along the entire craniospinal axis. Water exchange is driven by hydrostatic and osmotic gradients across pericapillary spaces. The pia does not contain tight intercellular junctions, which allows for rapid distribution of large molecules between the subarachnoid space and the parenchyma of the brain.[22] Furthermore, rather than a linear flow of CSF from its production site (the choroid plexus) to its absorption site (the arachnoid granulations), CSF is carried in a bidirectional, to-and-fro motion as a result of the cardiac cycle. This hypothesis is supported by several key pieces of experimental evidence.

- CSF pressure gradients change with body position. The highest CSF pressure in an upright position occurs in the lumbar spine and the lowest is in the lateral ventricle, which would make unidirectional flow from the spine to the cranium impossible.[23]
- Complete blockage of the Sylvian aqueduct in an animal model results in no change in CSF pressures measured in the ventricles and the cisterna magna, and there was no development of hydrocephalus.[24]
- Mice deficient in aquaporin-1, an integral membrane protein unique to the choroid plexus, demonstrated no significant reduction in water influx. Mice deficient in aquaporin-4, which is expressed throughout the central nervous system, have significant reductions in water influx[25]

- Ablation or removal of the choroid plexus does not result in alterations of CSF production or intracranial pressures, which has been demonstrated in animal models as well as in humans.[26]

To elucidate the cellular landscape and ventricle and age-dependent functions of the choroid plexus, Dani and colleagues recently performed a large-scale analysis of single-cell RNA sequencing from developing and adult choroid plexus cells.[27] The cell types within the choroid plexus include epithelial, mesenchymal, endothelial, immunologic, neuronal, and glial cells. Their study revealed that each of these cell types secretes proteins into the CSF that regulate growth, such as insulin-like growth factor 2. Gene expression across the cells varied both by stage of central nervous system development and by ventricle. Previous research has demonstrated that the choroid plexus generates multiple other types of neuropeptides, growth factors, and cytokines.[28] The choroid plexus epithelium also expressed many receptors for growth factors and hormones. This allows for a response to a variety of physiologic conditions, including regulation of fat balance,[29] participating in immunosurveillance,[30] and regulation of the circadian rhythm.[31] Glucagon-like peptide-1 receptor (GLP1R) agonists such as semaglutide and exenatide have experienced a rapid growth in popularity due to their effects of potent appetite suppression and body weight reduction. GLP1R has also been found to be expressed in human choroid plexus samples, and administration of a GLP1R agonist in a rat model demonstrated a reduction of intracranial pressure to approximately 50% of baseline shortly after receiving the medication.[32] This is theorized to be a result of the effect of GLP1R on reducing activity of the Na+-K+-ATPase localized on the apical surface of the choroid plexus, although this was based on experiments with cultured monolayers of choroid plexus. A randomized clinical trial demonstrated a less pronounced reduction in intracranial pressure within 2.5 hours of administration of a GLP1R agonist.[33]

Additional studies have further examined the relationship of the choroid plexus with immune response. In a mouse model of meningitis, Xu and colleagues[34] found direct evidence of a coordinated response that inflammation within the central nervous system is centered at the choroid plexus, suggesting that the choroid plexus is an immune organ of the brain. The choroid plexus is the primary site where leukocytes infiltrate the ventricles and CSF. Macrophages within the CSF migrate toward the epithelial sheet of the choroid plexus. The permeability of tight junctions between the choroid plexus epithelial cells is modified during the immune response.

Absorption of cerebrospinal fluid

Classic theory indicates that arachnoid granulations primarily absorb CSF within the dura.[35] This became increasingly disputed over time after it was discovered that arachnoid granulations do not develop until the postnatal period,[36] despite the fact that the choroid plexus develops early in gestation.[37] The lack of hydrocephalus in utero, as well as studies that have found absorption directly from the CSF into lymphatics surrounding the skull, suggests that there are alternative methods of absorption.[38]

The study by Iliff and colleagues in 2012[22] utilized 2 photon laser scanning microscopy to visualize the movement of CSF into the interstitial space of the brain parenchyma, which is followed by perivenous clearance across the water channel aquaporin-4 (AQP4). Mice with deletions of *Aqp4,* the gene which encodes AQP4, had a significant reduction in clearance rates of radiolabeled mannitol, dextran-10, and amyloid β. This interstitial and perivascular drainage pathway was termed the glymphatic system (glial-lymphatic). Subsequent research has identified the glymphatic system as an essential method of eliminating tau and other waste products from the central nervous system, resulting in increasing scientific interest in the mechanistic details of

this system.[39] As elevated levels of tau have been associated with neurodegenerative diseases such as Alzheimer's disease, the most common cause of dementia,[40] the role of impairment of adequate CSF flow and dysregulated glymphatic function is being investigated in neurodegenerative diseases. The glymphatic system is likely to be most active during sleep and anesthesia compared with wakefulness in murine models,[41] during which time there is an increased clearance rate of β-amyloid. Slowing of the glymphatic system may impair the clearance of neuropeptides associated with migraine and post-traumatic headache, including calcitonin gene-related peptide and pituitary adenylate cyclase-activating polypeptide.[42]

Ependymal cells, which line the ventricles of the brain and the central canal of the spinal cord, contain motile cilia on their surface. Loss-of-function/knockout experiments in genes responsible for cilia development demonstrate impaired CSF absorption with resultant hydrocephalus and developmental anomalies.[43]

Role of the cribriform plate in drainage of cerebrospinal fluid

The cribriform plate has been suggested as an additional route for solutes from the CNS to enter the cervical lymphatic system. Kida, Pantazis, and Weller's article from 1993[44] investigated the clearance of India ink injected into the cisterna magna of rats and found that the nasal route was the only direct connection between the CSF and the lymphatic system. In a sheep model, Mollanji and colleagues in a 2002 paper[45] performed external ethmoidectomy with removal of soft tissue (including the olfactory nerves) on the cribriform plate, followed by application of tissue sealant. This led to a significant rise in intracranial pressure compared with the sham surgery group. Despite the importance of CSF efflux into the sinonasal lymphatics in murine and sheep models, in vivo assessments in humans have been less conclusive,[46,47] suggesting variation in trans-cribriform drainage rates across species. Independent of any means for recirculation through the cervical lymphatics, these pathways distinctly exclude frank egress of CSF into the aerated spaces of the lateral or anterior skull base, which we define as CSF leaks.

Etiology and pathophysiology of lateral skull base cerebrospinal fluid leaks

CSF leaks of the lateral skull base result from osteodural defects in the temporal bone at the middle and posterior cranial fossae, creating a communication between the subarachnoid space and pneumatized petrous apex, middle ear, and/or mastoid air cells. Although congenital causes (such as inner ear malformations) can cause CSF leaks, acquired forms of CSF leak are far more common. Acquired forms include spontaneous leaks from increased intracranial pressure, blunt and penetrating injuries causing fractures of the temporal bone (particularly otic-violating fractures), neoplasms, infections, and as iatrogenic or postoperative complications.[48–50] Less commonly, a defect in the petrous portion of the temporal bone causes CSF leak. Other routes of lateral skull base CSF fistulae include translabyrinthine (via the internal auditory canal, into the inner ear, and subsequently through the oval window), a patent tympanomeningeal fissure, a widened fallopian canal, or through the petromastoid canal.[51] The exact incidence of lateral skull base CSF leaks is difficult to ascertain due to the heterogeneous etiology of the condition.

Tegmen defects and middle cranial fossa cephaloceles are common[52] occurring in approximately 20% to 30% of the population.[53,54] The term "cephalocele" includes any protrusion of intracranial contents through the skull. An encephalocele (interchangeable with "meningoencephalocele") contains neural tissue (most commonly the brain parenchyma), meninges, and CSF, whereas a meningocele (also referred to as "pits") only contains meninges and CSF.[55] These differences are represented

in Fig. 1. In a study of 203 patients who received high-resolution (≤0.5 mm section thickness) axial T2-weighted MRI using the internal auditory canal protocol, 22.2% of patients had incidental middle cranial fossa pits and 5% had incidental encephaloceles.[52] Fig. 2A–C demonstrates a coronal computed tomography and T2-weighted MRI of the left temporal bone, demonstrating temporal lobe encephalocele with CSF leak. Chronic inflammation, previous surgery of the lateral skull base, trauma, neoplasms, obesity, and idiopathic intracranial hypertension are risk factors for the development of these findings.[56,57]

Etiology and pathophysiology of anterior skull base cerebrospinal fluid leaks

Acquired CSF leaks from the anterior skull base (ie, resulting from noncongenital causes) are most frequently post-traumatic or spontaneous. Patients with spontaneous leaks have significantly thinner bone of the skull base in the region of the ethmoid roof, lateral lamella, and anterior face of the sella compared with controls.[58] Whether this is a causative factor of the leak or a consequence of predisposing factors (idiopathic intracranial hypertension and obesity) is unknown. Spontaneous anterior skull base CSF leaks most commonly involve the posterior cribriform plate, fovea ethmoidalis, and sphenoid sinus, as seen in Fig. 3.[59] For leaks involving the sphenoid sinus, the majority of patients have pneumatization of the lateral recess of the sphenoid sinus, which is the most common site of CSF leak within the sphenoid sinus.[60] The development of spontaneous leaks is likely to result from a combination of anatomic and physiologic factors.

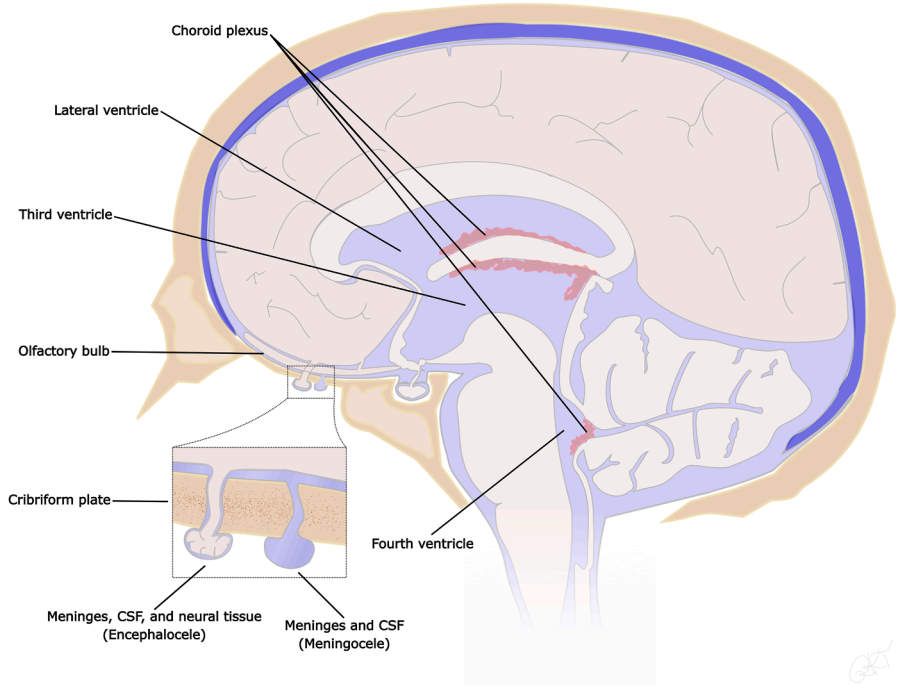

Fig. 1. Cranial central nervous system with osteodural defects. Encephaloceles contain meninges (eg, dura), CSF, and neural tissue, whereas menigoceles contain only meninges and CSF. In this cartoon, the osteodural defects are present in the anterior skull base at the posterior cribriform plate.

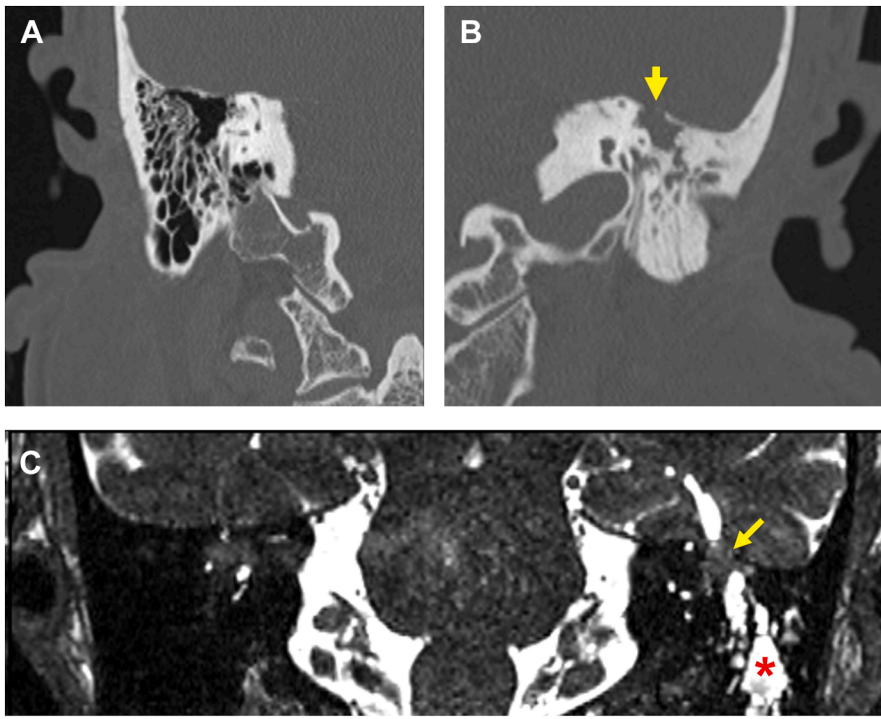

Fig. 2. Tegmen dehiscence and temporal lobe encephalocele. (*A*) Normal high-resolution computed tomography (CT) of right temporal bone (coronal view). (*B*) Dehiscence of tegmen tympanicum (*yellow arrow*) on coronal CT of left temporal bone. (*C*) Coronal T2-weighted constructive interference in steady state (CISS) sequence on magnetic resonance imaging showing isointense brain herniation (or encephalocele) into temporal bone (*yellow arrow*) and associated hyperintense CSF in mastoid air cells (*).

The most likely cause of anterior skull base leak varies based on studies, with spontaneous causes being the most common in some cohorts and iatrogenic causes being the most common in other studies.[61,62] This may be a result of geographic differences, which may be influenced by factors such as prevalence of idiopathic intracranial hypertension. The incidence of spontaneous CSF leaks has increased over recent decades. A study of national trends demonstrated 2 fold increase in number of spontaneous CSF leak repairs between 2002 and 2012, whereas the rate of nonspontaneous CSF leak repairs remained the same.[63] On a population-wide scale, the rate of spontaneous CSF leak repair is correlated to prevalence of obesity in the population. Obstructive sleep apnea (OSA) has been identified as an independent risk factor for the development of CSF leaks, likely due to thinning of the skull base resulting from transient increases of intracranial pressure during sleep.[64] Although confounded by the heterogenous and retrospective nature of the included publications, a meta-analysis from 2015 found patients with spontaneous CSF leak were 4.73 times more likely to have OSA than those in a control cohort.

Infectious causes of anterior skull base CSF leaks are rare, but can occur in the context of aggressive or chronic infections. While intracranial involvement by invasive fungal sinusitis can occur, CSF leaks are rarely associated with these infections, only

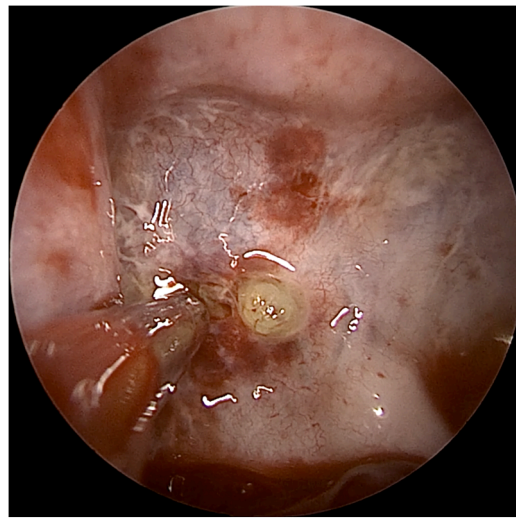

Fig. 3. Typical appearance of spontaneous encephalocele related to chronic intracranial hypertension. This encephalocele is located within the sphenoid sinus in the clival recess in a patient with cerebrospinal fluid rhinorrhea. The sella is visible superiorly. The encephalocele is stained yellow due to the preoperative injection of fluorescein dye.

being described in occasional case reports.[65] CSF leaks due to neoplastic invasion of the skull base are equally rare, but should be considered when evaluating the presence of a spontaneous CSF leak.

SUMMARY

CSF is critical to the routine function of the central nervous system, and disruption of the production, absorption, or flow of CSF has been associated with severe neurologic pathology. Modern studies have radically changed our understanding of the production and absorption dynamics of CSF and the newly identified glymphatic system further informs the nuanced nature of fluid flow in and around the central nervous system. Further, with its novel role in the removal of nervous system metabolic byproducts and waste, the glymphatic system and its function are increasingly studied with implications in neurodegenerative diseases. Disruption of the meningeal barrier via trauma, iatrogenic injury, or due to other intracranial processes has profound implications, both disrupting normal fluid cycling as well as introducing potential pathogens. Both the lateral and anterior skull bases are susceptible to defects, with spontaneous leaks representing a growing number of cases. A growing body of knowledge implicates the rise in obesity and obstructive sleep apnea in the increase in the rate of spontaneous CSF leaks.

CLINICS CARE POINTS

- CSF is a critical component of the central nervous system, with a primary function of mechanical protection of the brain and spinal cord, regulation of intracranial pressure, delivery of nutrients, removal of metabolic waste, and maintenance of central nervous system development and homeostasis.

- Modern research studies favor a model of CSF production and absorption throughout the entire craniospinal axis rather than a linear route of production from the choroid plexus toward absorption in the arachnoid granulations.
- Emerging research implicates the glial lymphatic (or "glymphatic") system and the nasal mucosa around the cribriform plate as additional sites of CSF absorption.
- Slowing of CSF absorption occurs with age, resulting in a higher CSF protein concentration in the elderly.
- Elevated levels of tau and β-amyloid in the CSF are associated with neurodegenerative disease
- Cephaloceles can be divided into meningoceles, which only contain meninges and CSF, and encephaloceles, which contain neural tissue, meninges, and CSF.
- CSF leaks from lateral or anterior skull base are most frequently spontaneous or traumatic, and incidence of spontaneous leaks has been increasing due to factors including obesity and obstructive sleep apnea.

DISCLOSURES

The authors have no financial disclosures or conflicts of interest relevant to the presented information.

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