Cerebrospinal Fluid in Critical Illness

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ABSTRACT

Objective: *To detail the physiology, pathophysiology and recent advances in diagnostic analysis of cerebrospinal fluid (CSF) in critical illness, and briefly review the pharmacokinetics and pharmaco-dynamics of drugs in the CSF when administered by the intravenous and intrathecal route.*

Data Sources: *A review of articles published in peer reviewed journals from 1966 to 1999 and identified through a MEDLINE search on the cerebrospinal fluid.*

Summary of review: *The examination of the CSF has become an integral part of the assessment of the critically ill neurological or neurosurgical patient. Its greatest value lies in the evaluation of meningitis. Recent publications describe the availability of new laboratory tests on the CSF in addition to the conventional cell count, protein sugar and microbiology studies. Whilst these additional tests have improved our understanding of the pathophysiology of the critically ill neurological/neurosurgical patient, they have a limited role in providing diagnostic or prognostic information. The literature pertaining to the use of these tests is reviewed together with a description of the alterations in CSF in critical illness. The pharmacokinetics and pharmacodynamics of drugs in the CSF, when administered by the intravenous and the intrathecal route, are also reviewed.*

Conclusions: *The diagnostic utility of CSF investigation in critical illness is currently limited to the diagnosis of an infectious process. Studies that have demonstrated some usefulness of CSF analysis in predicting outcome in critical illness have not been able to show their superiority to conventional clinical examination. With further advances in our understanding of neurological function and refinement in biochemical analysis there remains the possibility of useful cerebrospinal fluid diagnostic and prognostic markers in the future.* (**Critical Care and Resuscitation 2000; 2: 42-54**)

Key words: Cerebrospinal fluid, physiology, critical illness, intrathecal, intraventricular monitoring

Hippocrates is credited with the first description of the structure of the ventricular system and the meninges in approximately 400BC, but it was in the second century that Claudius Galen described in his animal studies, the clear fluid residue within the ventricles. The next historical reference to CSF comes from Antonio Valsalva, who in 1672 drained clear fluid from the lumbar sac of a dog and likened it to synovial fluid. The real barrier to CSF analysis was its accessibility, and formal examination of CSF started with the develop-ment and perfection of the technique of lumbar puncture in 1891 by Heinrich Quincke.[1] The important historical landmarks in the development of knowledge of CSF physiology and pathophysiology are outlined in Table 1.[2]

CSF physiology

Cerebrospinal fluid fills the ventricles, the aqueduct of Sylvius, the central canal inside the spinal cord and the subarachnoid space of the brain and spinal cord. The ventricular anatomy is comprised of two lateral ventricles (in the cerebral hemispheres), the third ventricle (in the midbrain) and the fourth ventricle (in the lower half of the brain stem). The lateral ventricles communicate with the third ventricle via the foramina of Munro, the third ventricle with the fourth via the aqueduct of Sylvius and the fourth ventricle with the subarachnoid space via a median foramen of Magendie and 2 lateral foramina of Luschka. The subarachnoid space lies between the connective tissue layers of the pia mater and the arachnoid surrounding the brain and the

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spinal cord, extending down to the level of the second sacral vertebra (Figure 1).

Table 1: Historical landmarks in the development of knowledge of the CSF

BC

400   Anatomy of ventricular system and meninges described by Hippocrates

AD

200   Galen described clear fluid residue in the ventricles

1764 Cotugno provides the first clear description of CSF

1854 Faivre recognised the choroid plexus as the producer of CSF

1891 Lumbar puncture described by Quincke. He is also credited with the development of CSF cell count analysis and identification of bacteria in pathological states

1893 Lichteim reported the diagnostic value of CSF glucose in bacterial and tuberculous meningitis

1912 CSF proteins measured using the colloidal gold test

1959 Frick described oligoclonal banding of CSF IgG in patients with multiple sclerosis

CSF is secreted mainly by the choroid plexuses of the lateral, IIIrd and IVth ventricles with a small additional contribution from the cerebral subarachnoid space and the ependymal lining of the ventricles. The choroid plexuses are outpouchings of blood vessels that are covered by an epithelium and float in the CSF. The choroidal epithelial cells are joined together on the CSF side by tight junctions. This constitutes the site of the blood-CSF barrier in the choroid plexus. Unlike the majority of the cerebral vasculature, the choroidal capillaries are fenestrated and freely permeable to small molecules. The epithelial cells of the choroid plexus feature many mitochondria within the cytoplasm, microvilli and cilia on the CSF side, and complex intracellular clefts on the vascular side of the cell, suggesting this epithelium is involved extensively in active transport.

CSF is distinct from extracellular fluid that constitutes the extracellular milieu of neurones. Estimates vary as to the exact proportions but approximately 70% of CSF is produced by the choroid plexuses through a process of ultrafiltration and active transport. In man the total volume of CSF (determined from autopsy studies) is about 140 mL and is secreted at a rate of approximately 0.35mL/min. The turnover rate of this fluid is 3-4 times per day. A single lumbar puncture performed on a patient will therefore only reflect the composition at that particular time. The formation of CSF by the choroidal epithelium is an active process involving Na^+/K^+ ATPase mediated transport of Na^+ ions from the cell into the CSF, accompanied by facilitated transport of HCO_3^-, Cl^- and water. Although CSF synthesis can be reduced with the use of ouabain, frusemide and acetazolamide, these drugs are of limited clinical value in the management of hydrocephalus.[3,4]
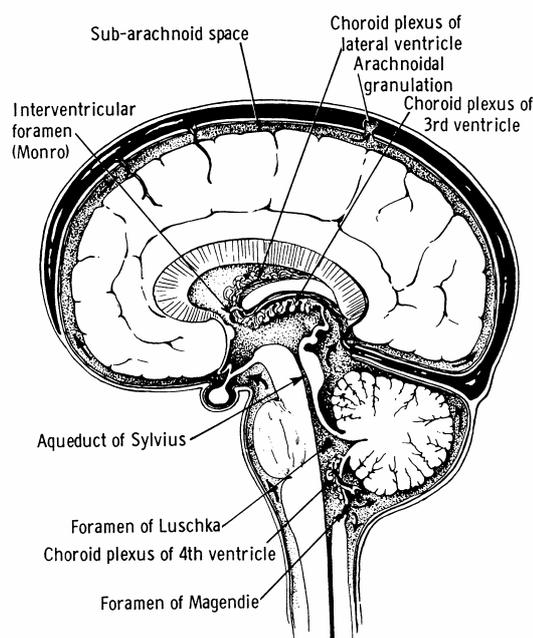
Figure 1. The cerebrospinal fluid circulation (Modified from Gardner E. Fundamentals of neurology, WB Saunders, Philadelphia 1963)

CSF circulates from the lateral ventricles into the third and the fourth ventricle. From the fourth ventricle, the fluid flows into the basal cisterns and subarachnoid space of the spinal cord. In the subarachnoid space, the flow is predominantly cephalad over the convexities toward the cerebral sinuses, where it is passively absorbed by the arachnoid granulations (Figure 1).[2] The arachnoid granulations are outpouches of arachnoid membrane into the dural sinus and have a valvular function. Some are also found in spinal nerve roots.

The normal CSF pressure varies between 5 - 18 cm H_2O.[5] When CSF pressure is greater than venous pressure, fluid drains from the CSF into the blood. If the pressure is greater in the veins, the arachnoid villi collapse and no flow occurs.[4] The mechanism of transfer of CSF across the granulations is controversial but may involve transcellular vacuoles. The absorption rate increases linearly with CSF pressure. At a CSF pressure of 11 cmH_2O, the formation and absorption rates are

equal.[2] A significant fraction of CSF drains via the spinal nerve roots into the local lymphatic networks. Anatomical studies in animals suggest some CSF may also drain via lymph vessels along routes adjacent to cranial nerves, particularly the olfactory tract, and thence to the deep cervical lymph nodes. However, in humans, the olfactory system is less well developed and thus likely to be a less important route of drainage for CSF.[6,7]

The functions of the CSF include, provision of buoyant physical support to the brain (e.g. the effective brain weight is reduced from 1500g to as little as 50g), maintenance of constant intracranial pressure, defense against bacterial invasion,[8] intracerebral transport of biomolecules, and a drainage pathway for waste products, electrolytes and excess neurotransmitters (i.e. the 'sink action' of CSF).[9]

Two barriers exist between the blood and brain which limit the diffusion of electrolytes and other substances from blood into the CSF or brain extracellular fluid and also isolate the CNS from systemic immune responses. The *blood-CSF barrier* is formed by tight junctions between cells of the epithelial lining of the choroid plexus and by tight junctions between cells of the arachnoid membrane.[10] The *blood brain barrier* (BBB) is formed by tight junctions between endothelial cells of capillaries of the central nervous system (CNS). These capillaries are surrounded by astrocytic foot processes, which regulate and maintain the endothelium.[11] The endothelial tight junctions are more permeable at the dorsal root ganglia than in the rest of the CNS vasculature.[10]

CSF has an electrolyte composition similar to plasma, the main difference being the former has a lower K^+, lower pH and a higher Cl^- concentration. The protein concentration of the CSF is about 250 mg/L. Antibodies and complement are normally absent in the CSF.[12] Proteins found in CSF in substantial quantities either cross the blood brain barrier by facilitated diffusion using specific transporters or are produced within the CNS. However, all serum proteins are found in the CSF in at least trace quantities due to simple diffusion, despite the tight junction barriers. Protein concentrations are higher in lumbar CSF than cisternal CSF due the greater permeability of the barrier at the lumbar level. The composition of the normal adult CSF (relevant to diagnostic analysis[13]) is shown in Table 2.

The physiological variations in CSF composition are listed in Table 3.

Analysis of CSF in critical illness

A common reason for sampling CSF in critical illness is to diagnose an intracranial infection. Other reasons include diagnosis of Guillain-Barré syndrome,

to reduce intracranial pressure, and sampling of CSF from an indwelling intraventricular drain for infection surveillance. The advent of CT scanning has diminished the role of CSF analysis for the diagnosis of subarachnoid haemorrhage (SAH).

CSF is most commonly obtained by means of a lumbar puncture. Some of the commonly reported complications post lumbar puncture include,
- post puncture headache (12% - 39%)[14]
- traumatic tap (15% - 20%)[15]

Table 2. Normal adult CSF composition

	Normal values	Comment
Total WBC	0-5 cells/mm^3	Differential mainly lymphocytes and monocytes
Glucose	500 - 800 mg/L (2.8-4.5mmol/L)	CSF equilibrates with glucose with a lag time of 2-4 hours
CSF: blood glucose ratio	0.6	Ratio only valid for blood sugars under 3000 mg/L (16 - 17 mmol/L) as CSF glucose transport kinetics become saturated. Glucose entry to the CSF is insulin independent
Protein	170 - 550 mg/L	There are 4 marker proteins in the CSF corresponding to the local cell type: Neurons - enolase, astrocytes - glial fibrillary acidic protein, oligodendrocytes - myelin basic protein, microglia - ferritin

Table 3: Physiological variations in CSF composition

Differences between spinal and cisternal CSF
1. Higher protein concentration in spinal fluid
2. Lower glucose concentration in spinal fluid

Age related variations in CSF
1. CSF volume is about 30-60ml in the neonate
2. The normal cell count in term newborn can be up to 30 cells/mm^3 (60% polymorphs, 40% monocytes)[88]
3. Higher CSF: blood glucose ratio in new born of 0.8[89, 90]
4. Higher protein concentration in the newborn up to 1700 mg/L[88]
5. (3 & 4 reflect immaturity and greater permeability of the blood brain barrier in the new born)

The rarer complications include,

- brain herniation: This is a potential complication seen with conditions associated with raised intracranial pressure due to a space-occupying lesion. The removal of CSF results in a transient lowering of lumbar CSF pressure, which can

predispose to tonsillar herniation. Herniation normally occurs a few hours after the procedure due to ongoing CSF leak through the arachnoid. The risk of brain herniation following lumbar puncture in the setting of viral or bacterial meningitis is small. The common clinical conditions which predispose to herniation include brain abscess, subdural empyema, intracerebral bleed and in conditions associated with gross cerebral oedema such as herpes simplex encephalitis,

- cortical blindness and cervical spinal cord infarction due to compression of posterior cerebral arteries against the tentorium cerebelli (due to downward displacement of the brain) and compression of the anterior spinal artery by the herniating cerebellar tonsils resulting in occipital lobe and spinal cord infarction, respectively,
- infection of the subarachnoid space, and
- spinal haematoma with cord compression. This complication is more likely to be found when a lumbar puncture is performed on a patient who is coagulopathic or thrombocytopenic.

A traumatic spinal tap frequently obscures laboratory analysis, particularly when a lumbar puncture is performed for the diagnosis of subarachnoid haemorrhage. The features of a traumatic tap include, CSF which becomes less bloody in successive collection bottles and absence of xanthochromia (see later). The presence of blood in the CSF also alters the cell count and protein levels, making the diagnosis of an infection more difficult. Under these circumstances, the ratio of white blood cell (WBC) count to red blood cell (RBC) count in the CSF is compared with that of blood. If the ratios are similar, CSF pleocytosis is presumed to be absent.[16,17] Whilst mathematical formulae have been proposed to calculate the expected number of WBC in the CSF, most clinicians assume a peripheral blood WBC: RBC ratio of 1: 500 - 1: 700. If the CSF WBC count is greater than predicted by the ratio, this indicates the presence of CSF pleocytosis. Similarly, protein concentrations are elevated in the presence of blood in the CSF. For every 1000 RBC, the protein concentration is increased by 10 mg/L.[18]

The CSF is analysed by: a) inspection of the gross appearance, b) total and differential white cell count, c) CSF glucose and protein concentrations, d) Gram stain, bacterial cultures, and e) special tests.

Gross appearance of CSF
The CSF in health is colourless and clear. Under pathological conditions, the CSF may become turbid or discoloured or both.

Turbidity

This may be caused by,
- elevated numbers of RBC or WBC in the CSF. Counts of >200 WBC per mm^3 or > 400 RBC per mm^3 cause turbidity.[18]
- high bacterial or fungal count in the CSF even in the absence of a raised cell count.
- epidural fat aspirated at the time of the lumbar puncture.[19]

Xanthochromia

A yellowish discolouration of the CSF supernatant due to bilirubin is termed xanthochromia, which can be measured by spectrophotometry.[20] The causes of xanthochromia include,

- blood in the subarachnoid space. Two to four hours after haemorrhage, RBC lyse and release oxyhaemoglobin, which after 12 hours is metabolised to bilirubin. This persists for 15 -35 days after a subarachnoid bleed. Because it takes from 2 -4 hours for RBC lysis, bilirubin will not be present in the CSF supernatant of a traumatic tap.
- methaemoglobin in the CSF.
- high protein content in the CSF (> 1500 mg/L) due to protein bound bilirubin.
- systemic hyperbilirubinaemia (> 100 μmol/L).

CSF pleocytosis
CSF pleocytosis refers to an increase in the CSF WBC count. The causes are listed in Table 4. Of these, the most common aetiologies are meningitic and encephalitic processes. While a WBC count of >500/mm^3 with a preponderance of neutrophils is characteristic of a bacterial meningitis, and a WBC count of >100/mm^3 with a preponderance of monocytes is characteristic of a viral meningitis a considerable pattern overlap is often found. There are also reports of normal CSF cell counts in otherwise well patients with bacterial meningitis.[21-27] This may be found when there is peripheral leucopenia or if the lumbar puncture is performed early in the illness. As significant neutrophil lysis occurs in the CSF within 1-2 hours of collection, delay in analysis may also lead to an artificially low CSF cell count.[28] Little published data exist on the rapidity of onset of CSF pleocytosis following the development of meningitis but one published case study has reported the development of pleocytosis in as little as 30 minutes after the onset of meningitis.[29]

Alterations in CSF glucose

CSF glucose levels less than 450 mg/L or a CSF:blood glucose ratio of < 0.6 constitute hypoglycorrhachia. Conditions that cause hypoglycorrhachia, and the underlying mechanisms responsible for the altered glucose levels, are listed in Table 5. As equilibration between CSF and blood glucose takes 2-4 hours, the timing of the blood sample is important. Owing to a lag in glucose transport into the CSF in hyperglycaemic states, the normal ratio in diabetics is 0.4 and values < 0.3 are considered to be abnormal.[30]

Table 4. Causes of CSF pleocytosis in critical illness

Predominantly neutrophilic	*Predominantly lymphocytic*
Infectious	*Infectious*
Bacterial meningitis	Meningitis (tuberculous,
Early phases of meningitis	fungal, viral)
(viral, tuberculous, fungal)	Partially treated bacterial
	meningitis
	Encephalitides
Non infectious	*Non infectious*
Subarachnoid haemorrhage	Guillain-Barré syndrome
Intrathecal drugs	CNS vasculitis
Haemorrhagic cerebral infarction	

Table 5. Causes of reduced CSF glucose

Meningitis (bacterial, fungal, tuberculous)
 - alterations in glucose transport from blood to CSF
 - metabolic consumption by leukocytes and bacteria
Subarachnoid haemorrhage
 - metabolic consumption by RBC
Meningeal infiltration by neoplasms
 - metabolic consumption by tumour cells
Systemic hypoglycaemia
 - absolute decrease in the CSF glucose concentration

CSF glucose levels are used to distinguish bacterial meningitis (where it is usually decreased) from aseptic meningitis (where the glucose levels are usually unaltered). Using a CSF:blood glucose ratio of < 0.4, the sensitivity and specificity for distinguishing between the two are reported to be 80% and 98% respectively.[31] As CSF glucose levels return to normal within 36-48 hours of commencing effective therapy, serial CSF glucose measurements have been proposed to monitor the efficacy of treatment.[32]

Alterations in CSF protein

An increase in the CSF protein concentration may be found in a variety of conditions in the intensive care unit (Table 6). Elevations are due to increased permeability of the blood brain barrier, release of proteins by cells within the CNS, or CSF hyper-cellularity. CSF protein concentrations are usually higher in bacterial meningitis compared with aseptic meningitis. At a 'cut off' value of 1000 mg/L, the sensitivity and specificity for distinguishing bacterial from aseptic meningitis are 82% and 98%, respectively.

Table 6. Alterations in CSF protein concentration in critical illness

Increased CSF protein	Normal CSF protein	Decreased CSF protein
Infective	Critical illness polyneuropathy[78]	Chronic CSF leakage
Meningitis - bacterial, viral,[91] fungal,[92] tuberculous[93]	Septic encephalopathy[95]	
Cerebrovascular disease[94]	Systemic inflammatory response syndrome	
Subarachnoid/intracerebral haemorrhage		
Cerebral thrombosis		
Demyelinating processes		
Guillain Barré syndrome[78]		
Status epilepticus		

Gram stain

The Gram stain is of paramount importance when identifying the pathogen in bacterial meningitis. The diagnostic accuracy of the Gram stain is directly proportional to the number of organisms present,[33] with false negative results seen in cases with less than 1000 organisms/mL of CSF or in partially treated meningitis.[34] False positive results are uncommon and result from poor sampling or processing technique, or bacterial contamination of the reagents. The Gram stain diagnostic yield with Gram positive bacterial meningitis is higher than with Gram negative meningitis.

CSF microbial antigen testing

Quantification of microbial antigen may be useful, when there is a strong clinical and CSF picture suggestive of meningitis, but the Gram stain and cultures are negative or when there is a suspicion of viral meningitis. Counter immuno-electrophoresis and latex agglutination tests have been replaced by the more sensitive ELISA test for the detection of microbial antigens.[35,36] There are also data to suggest that bacterial antigen quantitation might be a valuable prognostic factor correlating with the clinical course and the outcome of meningitis. Higher antigen loads have been correlated with increased length of stay and a greater likelihood of developing subdural effusions.[37,38] The antigen specific studies on CSF currently available are

listed in Table 7. CSF antigen testing is of limited use in nosocomially acquired meningitis.[39]

Table 7. Microbial antigen studies on the CSF

Bacteria	Viruses	Others
S. pneumoniae	Measles	Malaria
N. meningitidis	HSV I & II	Toxoplasmosis
H. influenzae	Rubella	Aspergillus
M. tuberculosis	Mumps	Cryptococcus

Polymerase chain reaction (PCR)

The PCR test has recently become available for the diagnosis of tuberculous meningitis and herpes simplex encephalitis. The test identifies a specific gene sequence in the microbial DNA. While high success rates have been reported for the diagnosis of HSV infection,[40] the sensitivity and specificity for the diagnosis of tuberculous meningitis has been reported to vary from 65% to 90%.[41] As mycobacterial DNA has been detected in the CSF a month after initiation of therapy, the test allows the confirmation of diagnosis in those patients in whom empiric therapy has been commenced.

Special tests

Lactate

The usefulness of measuring CSF lactate levels has undergone detailed investigation. CSF concentrations are largely independent of serum lactate as lactate is ionized at normal pH values and its transfer across the BBB is limited in the ionized form. Brain glycolysis is the principal source of CSF lactate, although elevation in CSF lactate is a non specific finding and occurs in a number of diseases such as meningitis,[42,43] hypoxic cerebral injury,[44] subarachnoid haemorrhage,[45,46] and head injury.[47,48]

Higher CSF lactate levels are found in bacterial meningitis compared with aseptic meningitis and CSF levels of > 4.2 mmol/L have been reported to be useful in distinguishing bacterial and viral meningitis.[42] However, as CSF lactate remains elevated for a prolonged period despite successful treatment, it is not a useful marker of response to therapy. As D-Lactate is a product of bacterial metabolism only, CSF levels of this metabolite have been used as a marker of bacterial meningitis with a 92% sensitivity and 99% specificity.[49]

An increase in CSF lactate in patients with head injury has been correlated with surges in intracranial pressure and portends a poor neurological outcome.[48] The increase in lactate is thought to result from brain glycolysis, catecholamine surge associated with head injury, altered permeability of the blood brain barrier, subarachnoid haemorrhage and neuronal mitochondrial dysfunction.[50]

Lactate dehydrogenase (LDH)

In health, the CSF concentrations of LDH are approximately 10% of the normal serum levels and is a nonspecific marker of CNS cell injury. Viral meningitis is usually associated with normal or mildly elevated LDH levels, while bacterial meningitis is usually associated with significantly higher levels. LD isoenzymes carry greater specificity.[51] The additional value of this test over protein/glucose estimation is unclear.

Creatine kinase (CK)

As the brain is rich in CK, increased CSF CK levels have been reported in a variety of CNS disorders including SAH,[52] cerebral infarction,[53] head trauma,[54,55] hydrocephalus and tumours. CK-BB is the predominant isoenzyme (90%) found in the brain. CK-mt (mitochondrial) makes up the remaining 10% of the total. CK-MM and CK-MB fractions are not normally present. The presence of CK-MM in the CSF implies blood contamination. CK-BB increases in the CSF 6 hours after a hypoxic or an anoxic insult and gives an estimate of overall brain damage and prognosis for patients suffering global ischaemia or anoxia.[56-58] CK-BB levels less than 5 U/L are associated with mild or no neurological damage, 5 - 20 U/L moderate damage and levels between 21 - 50 U/L are associated with prolonged coma and levels above 50 U/L are usually associated with death.

β-2 transferrin

Transferrin is an iron binding glycoprotein synthesised primarily in the liver. In the CSF, two isoforms are found, β-1transferrin (same as serum) and β-2 transferrin. The latter is absent in the serum and is formed in the CSF from its beta-1 analogue by the action of neuraminidase. It is specific for CSF and its presence has been used as a diagnostic test to detect CSF leakage.[59]

CSF gas tensions and pH

CSF PCO_2 and PO_2 have been used to investigate the normal dynamics of acid-base changes in arterial blood and CSF during hyperventilation and apnoea.[60] CSF oxygen tension has been used as a prognostic index in patients with ruptured berry aneurysms.[61] Statistically significant differences in CSF and blood gas tensions have been reported between survivors and non survivors following hypoxic brain injury after cardiac arrest.[62]

While significant CSF gas tensions measurement inaccuracies exist with the measurement in blood gas analysers,[63] continuous measurement of CSF gas tensions using a tissue gas sensor have been shown to trend cerebral perfusion.[64] (Figure 2)

CSF cytokines

Increases in CSF IL-1, IL-6 and TNF have been reported in CNS infections,[65] trauma and injury.[66,67] While there are published data showing that bacterial meningitis is associated with higher concentrations of cytokines in the CSF compared with viral meningitis, and that higher peak values correlate with a poor outcome,[68,69] it is important to note that the concentrations of these inflammatory markers depend on the host's ability to mount an adequate immune response. Therefore, the timing of sample acquisition and the selection of the patient will influence the sensitivity of these assays.

Alterations in the CSF in critical illness

#### Infections of the central nervous system

The CSF changes in the various meningitis types are described in detail in Table 8. Although investigators have attempted to differentiate between bacterial and viral meningitis in culture negative meningitis, based on the extent of alterations in CSF cell count, glucose, proteins, lactate, LDH and cytokine levels, the limited sensitivity and specificity of these measurements preclude a confident distinction.

Head injury

Although there are no typical features of CSF in neurotrauma, the CSF protein level may be elevated due to disruption of the blood brain barrier and may also be blood stained. CSF levels of nitrite and nitrate have been shown to be correlated with the severity of brain injury and higher levels are associated with increased mortality.[70]

Table 8. Characteristic CSF findings in major CNS infections

Disease	Cell count	Protein	Sugar	Microbiology stain	Comments
Bacterial meningitis	Increased, predominantly polymorphs	Elevated, 1000 - 5000 mg/L	Reduced, CSF/Plasma ratio < 0.4 CSF glucose normal in about 9% of cases	High yield on Gram stain	14% of patients have predominant lymphocytosis. Lymphocytosis also common in Listeria meningitis and in neonatal gram negative meningits.
Partially treated bacterial menin-gitis[96-98]	Predominantly lymphocytic pleocytosis	Elevated	Reduced to normal	Reduced yield on Gram stain by 20%	Immunological studies for bacterial antigens may be useful
Tuberculous meningitis[36,41,93,99]	Predominantly lymphocytic pleocytosis. Minimal cellular response with coexisting AIDS	Elevated in 75% of patients, usually 1000 -5000 mg/L. Higher levels in severe cases.	Reduced. In about 17% of cases, levels are normal.	Ziehl-Niellsen stain positive in about 10-12%	Culture takes 6 - 8 weeks and the yield is about 50 -75%. ELISA tests for antigen. CSF adenosine deaminase levels used as marker (increased in the acute phase and reduction with treatment). PCR may be useful
Viral meningitis/ Meningoenceph-alitis[40,100]	Predominantly lymphocytic pleocytosis, although PMN frequently present in the first 24 - 36 hr	Elevated, usually 500-1000mg/L	Usually normal, although reductions in CSF glucose have been reported.	Nil	Haemorrhagic CSF in HSV encephalitis Predominantly PMN pleocytosis in Coxsackie virus CNS infections PCR may be useful CSF/serum serology
Fungal meningitis[101]	Predominantly lymphocytic pleocytosis	Elevated	Reduced	India ink studies positive in 50% of cryptococcus meningitis	Cryptococcal antigen Coccidioides antibodies in CSF positive in 95% of cases of meningitis

CSF PCO$_2$ and PO$_2$ changes in brain death
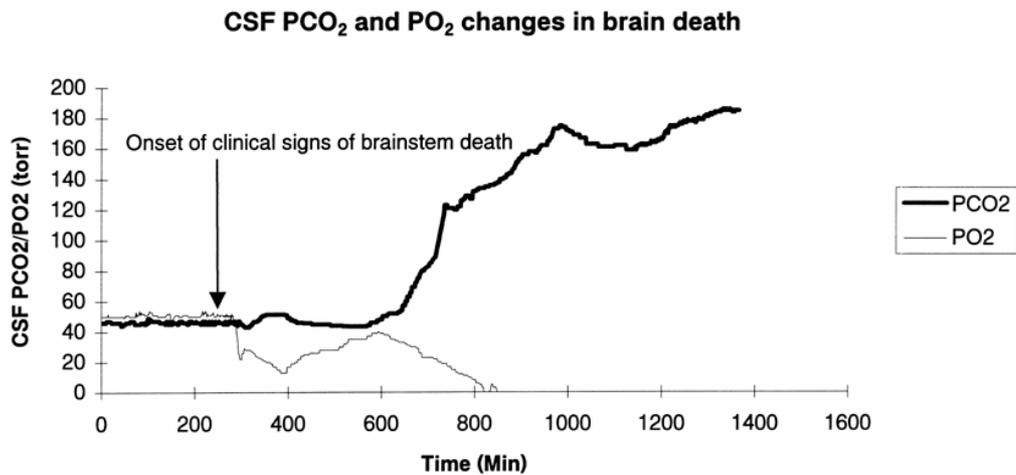
Figure 2. Continuous measurement of CSF PO2 and PCO2 during the onset of brain death (Reproduced with permission from Venkatesh et al. Intens Care Med 1999;29:599-605)

Recently, CSF quinolinic acid, a macrophage derived metabolite of the tryptophan - kynurenine pathway and an activator of the NMDA receptor, has been identified as a marker of neurological damage. Increased CSF levels of quinolinic acid have been shown to be associated with increased mortality.[71] CSF lactate levels may also be elevated and may be a marker of poor neurological outcome.[48] Elevations in CSF CK, LDH and neuron specific enolase (NSE) are non-specific findings.

CSF changes in the presence of an external ventricular drain (EVD), ventriculo-peritoneal shunt and after neurosurgery

The development of fever in a patient with an indwelling ventricular drain or a shunt raises the question of ventriculitis. The common infecting organisms are Staphylococcus epidermidis, Staphylococcus aureus, Gram negative organisms and propionibacterium.[72] The infection rates of indwelling ventricular catheters vary from 0.8 to 6% and increase after the EVD has been in place for more than 3 days. The difficulty in diagnosing an infection in the presence of an EVD lies in the fact that the mere placement of an EVD evokes an inflammatory response due to tissue trauma, focal haemorrhage, foreign body reaction and hypersensitivity to the silicone rubber, all of which may contribute to CSF pleocytosis or a raised protein level. Elevated eosinophil counts in the CSF may suggest hypersensitivity to the silicone. While there are no clear points of distinction in the CSF picture between inflammation and infection, the presence of clinical symptoms and signs would point to an infectious aetiology.

A similar CSF picture has been described in patients undergoing posterior fossa intradural surgery. In the immediate postoperative period, patients develop neck stiffness, CSF pleocytosis and an increase in CSF protein. This constellation of clinical and laboratory features has been termed the 'posterior fossa syndrome'.[73] The differentiation between a bacterial meningitis and the posterior fossa syndrome is difficult and neither the clinical signs nor alterations in CSF cell count, protein and sugar concentrations have been shown to be helpful in the diagnosis.[74]

Subarachnoid haemorrhage

There are no characteristic patterns of CSF abnormalities in SAH. It results in a blood stained CSF with xanthochromia, elevated RBC count, an appropriate RBC to WBC ratio, elevation of protein (10 mg/L for every 1000 RBC in the CSF) and a low glucose (due to consumption by the RBC). In suspected SAH with a negative CT scan and an equivocal CSF study, the presence of methaemoglobin and ferritin in the CSF are reported to be sensitive indicators of mild SAH.[75] Similar changes in the CSF have been reported in the CSF in the presence of a haemorrhagic cerebral infarction.

Guillain Barré syndrome (GBS) and critical illness polyneuropathy

CSF analysis in GBS may reveal a pleocytosis with lymphocytes and monocytes in a small proportion of patients, especially later in the disease. The pathognomonic CSF finding in GBS is an increase in CSF protein of greater than 400 mg/L within a week of the onset of symptoms (in > 80% of patients).

The protein levels begin to rise in the first week and usually reach a peak by the third or the fourth week.[76] As the elevated CSF protein may persist for months, serial CSF protein measurements are not a useful indicator for disease resolution. While the classic picture in GBS is an albumino-cytologic dissociation (i.e. raised CSF protein with a normal cell count), the cell count in the CSF may be increased in about 20% of patients.[76] Elevations in CSF NSE have been reported in GBS and are associated with a longer recovery period.[77]

Critical illness polyneuropathy is also characterised by a similar CSF picture to that of GBS except that protein levels were much higher in GBS (1009 $\pm$ 790 mg/L) compared with 450 $\pm$ 340 mg/L in critical illness polyneuropathy.[78]

Hypoxic brain injury

CSF levels of lactate, LDH and CK-BB following hypoxic injury to the CNS have been examined as indicators of clinical outcome. Elevated levels of these markers 72 hours after insult were correlated with poor neurological recovery in both adult and paediatric patients.[44] NSE is also reported to be a marker of brain damage and in one study of survivors of out of hospital cardiac arrest, CSF NSE levels correlated with neurological outcome better than CSF CK levels.[79] Whilst the performance of these assays are relatively straightforward, these markers do not distinguish between reversible and irreversible tissue damage and there is little published data demonstrating the superiority of CSF biochemical markers compared with Glasgow Coma Score as prognostic indicators in hypoxic encephalopathy.

Brain death

The CSF concentrations of neuron specific enolase have been used by certain investigators as markers of hypoxic brain injury[62] and extreme elevations of serum NSE have been noted in brain death.[80]

Status epilepticus

The CSF is frequently acellular and the protein concentration may be elevated as a marker of increased permeability of the blood brain barrier in status epilepticus.[81] CSF- NSE levels have been reported be marker of brain damage and increased levels correlate with a poor outcome in patients with status epilepticus.[81] Elevated levels of NSE have also been proposed as a marker to differentiate organic from psychogenic epilepsy.[82]

CSF leak

Traditionally, the detection of glucose in the clear fluid draining from the nose, ear or the orbit was considered diagnostic of a CSF leak. This test has a number of false positives and has now been replaced by the β-2 transferrin assay (previously known as the tau protein) which is highly specific for CSF.[59]

Metabolic encephalopathies

Glutamine is a product of CNS ammonia metabolism and increased levels of CSF glutamine concentrations have been reported in patients with hepatic encephalopathy and in Reye's syndrome.[83,84] A correlation has been demonstrated between the grade of encephalopathy and the absolute CSF glutamine concentration. Elevated levels of CSF glutamine have also been reported in septic encephalopathy, although its clinical significance remains unclear. Altered phenylalanine metabolism and an increase in aromatic amino acids in the CSF have been reported in both hepatic and septic encephalopathy and are thought to be important in the pathogenesis of these syndromes.

Antibiotic pharmacokinetics in the CSF following systemic administration

As the major determinant of CSF penetration of an antibiotic is its lipophilicity, quinolones and rifampicin (being lipophilic) diffuse rapidly into the CSF in health and in disease.[12] Hydrophilic antibiotics (e.g. beta lactams and vancomycin) enter CSF less readily during health, although in meningitis, owing to an increase in BBB permeability, adequate bactericidal concentrations of these drugs are achieved. Steroids have been shown to decrease the permeability of the BBB resulting in reduced penetration of hydrophilic agents.[85,86]

The half-lives of most hydrophilic antibiotics in the CSF are longer than in serum, whilst the half-lives of the lipophilic agents are similar to their serum values. Antibiotics are not metabolised in the CSF and therefore the antibiotic CSF half-lives are determined by their diffusion into and reabsorption from the CSF.

Intrathecal administration of drugs in critical illness

The passage of drugs across the blood brain barrier is determined by their lipid solubility and molecular size. Lipid soluble drugs cross readily whereas water soluble drugs do not. To achieve adequate concentrations at targeted biophases within the CNS, water soluble drugs may be injected intrathecally in critically ill patients. The most common indication is treatment of shunt infection and ventriculitis where intraventricular injection of antibiotics are used. Other indications include gram negative and fungal meningitis. However, little information exists on the pharmacokinetics of intrathecal antibiotics.

Table 9. Commonly administered drugs by the intrathecal or intraventricular route

Drug	Clinical indication	Dosage	Comments
Vancomycin[102,103]	Shunt infections with coagulase negative Staph epidermidis and Propionibacterium	8 - 10 mg/day	No significant side effects reported
Gentamicin[104,105]	Gram negative meningitis	2 - 4 mg/day	Reports of neurotoxicity attributed mainly to the preservative
Amphotericin B[106]	Fungal meningitis	0.25 – 0.5 mg/day	Reports of neurotoxicity
Opioids[87]	Post – op analgesia	Variable depending on the opioid used	Respiratory depression
Baclofen[107]	Relief of spasms in tetanus	0.5 mg/day (initially as a bolus followed by an infusion)	Sedation, hypotonia, bradycardia, respiratory depression
Thrombolytics[108]	Intraventricular haemorrhage	Depends on the thrombolytic used.	Still an emerging therapy. Potential risk of worsening of haemorrhage.

It is important to note that the circulation of CSF is unidirectional (i.e. from the ventricle to the subarachnoid space and into the systemic circulation), therefore intrathecal injection of drugs via the spinal route may not achieve adequate concentrations in the ventricular CSF. Other drugs administered into the subarachnoid space in intensive care are opioids for pain relief, and baclofen for tetanus. Table 9 lists the drugs and their dosages when administered intrathecally or by the intraventricular route. Perioperatively, local anaesthetics and opiates may be administered at the spinal level to achieve surgical anaesthesia or subsequent analgesia.[87] However, side effects of respiratory depression, nausea and vomiting, pruritus and urinary retention may still occur.

Conclusions

Despite a wealth of information on the alteration in composition of the CSF in various disease processes, the diagnostic utility of CSF investigation in critical illness is limited largely to the diagnosis of an infectious process. Many CSF analytes, whilst highly sensitive, are non-specific and the impact of alterations in blood brain barrier in critical illness on the composition of CSF needs further investigation. The few studies which have demonstrated the usefulness of CSF analysis in predicting outcome in critical illness have not been able to show its superiority to conventional clinical examination. In this context, the timing of CSF sampling in relation to clinical picture and alterations in BBB function assumes importance. With further advances in our understanding of neurological function and refinement in biochemical analysis, our quest for surrogate markers which provide useful information in critical neurological illness may prove fruitful in the future.

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