

## When Ventricular Cerebrospinal Fluid Assessment Misleads: Basal Meningitis and the Importance of Lumbar Puncture Sampling

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The diagnosis of central nervous system (CNS) infection relies upon analysis of cerebrospinal fluid (CSF). We present 4 cases of CNS infections associated with basal meningitis and hydrocephalus with normal ventricular CSF but grossly abnormal lumbar CSF. We discuss CSF ventricular–lumbar composition gradients and putative pathophysiological mechanisms and highlight clinical clues for clinicians.

**Keywords.** cerebrospinal fluid; cryptococcal meningitis; lumbar puncture; meningitis; tuberculous meningitis.

Analysis of cerebrospinal fluid (CSF) is a fundamental component in diagnosing central nervous system (CNS) infection. The most common methods of sampling CSF are via lumbar puncture (LP) and the sampling of ventricular CSF via insertion of an external ventricular drain (EVD) or a CSF shunt into the lateral ventricle [1–3]. In 1937, Merritt and Freemont-Smith first described the patterns of biochemical and cytological change in CNS infection. Among their seminal findings, they observed differences in composition between ventricular and lumbar CSF [1–3].

We present 4 cases of CNS infections with discrepant ventricular and lumbar CSF parameters. Published reports of such CSF discrepancies are limited [2, 4–10]. Our case series includes 2 cases of cryptococcal meningitis, for which discrepant CSF has not been previously reported.

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### CASE 1—CRYPTOCOCCAL MENINGITIS

A 43-year-old Vietnamese male, immunosuppressed secondary to a liver transplantation 6 years prior, presented with 12 weeks of increasing confusion, ataxia, and blurred vision. The patient was involved in a motor vehicle accident and underwent a trauma series computed tomography (CT) scan of the brain, which revealed communicating hydrocephalus, prompting the insertion of an external ventricular drain (EVD). The ventricular CSF sample taken at the time of EVD insertion was biochemically normal with normal cell counts (Table 1). The patient's confusion and ataxia improved with insertion of the EVD. Magnetic resonance imaging (MRI) of the brain revealed a basal meningitis and communicating hydrocephalus. On day 8 of admission, an LP was performed for further diagnostic evaluation. The lumbar CSF demonstrated low glucose, high protein, lymphocytic pleocytosis (Table 1), and a positive cryptococcal antigen. The patient was commenced on therapy for cryptococcal meningitis, and a ventriculo-peritoneal (VP) shunt was inserted for management of intracranial pressure and refractory hydrocephalus. The patient made a complete recovery.

### CASE 2—CRYPTOCOCCAL MENINGITIS

A 40-year-old male with a history of quiescent pulmonary sarcoidosis never requiring immunosuppression presented with subacute onset of headache, vomiting, and confusion. CT of the brain demonstrated obstructive hydrocephalus, and an EVD was inserted. Ventricular CSF was biochemically normal, with normal cell counts and a negative cryptococcal antigen (Table 1). A MRI demonstrated basal meningitis and obstruction of CSF flow at the fourth ventricle due to narrowing and obstruction at the foraminae of Magendie and Luschka. A lumbar CSF obtained 4 days later demonstrated low glucose, high protein, and lymphocytic pleocytosis (Table 1). The lumbar CSF tested positive for cryptococcal antigen, and *Cryptococcus neoformans* was subsequently isolated. The patient commenced therapy for cryptococcal meningitis, did not need long-term CSF shunting, and made a complete recovery.

### CASE 3—TUBERCULOUS MENINGITIS

A previously well 57-year-old female from Timor Leste presented with 2 weeks of fever, thoracic back pain, ataxia, and an acute decline in consciousness on the day of presentation. A CT of the brain and thoracic spine demonstrated hydrocephalus and bony destruction of the T7/8 vertebrae. An EVD was inserted, and ventricular CSF biochemistry and cell counts were normal (Table 1). MRI of the brain demonstrated nodular basal

**Table 1. Cerebrospinal Fluid Biochemical, Cytological, and Microbiological Results**

		Ventricular CSF	Lumbar CSF
Case 1 CM	Glucose (2.2–3.9 mmol/L)	5.1	1.1
	Protein (<0.45 g/L)	0.08	11.78
	WCC, cells ×10 <sup>6</sup> /L	0	86
	Lymphocytes, cells ×10 <sup>6</sup> /L	0	74
	Polymorphs, cells ×10 <sup>6</sup> /L	0	12
	Erythrocytes, cells ×10 <sup>6</sup> /L	132	132
	Microbiological testing	CrAg NP, CSF culture negative	CrAg positive, CSF culture negative
Case 2 CM	Glucose (2.2–3.9 mmol/L)	3.3	1.0
	Protein (<0.45 g/L)	0.27	1.03
	WCC, cells ×10 <sup>6</sup> /L	1	242
	Lymphocytes, cells ×10 <sup>6</sup> /L	0	205
	Polymorphs, cells ×10 <sup>6</sup> /L	1	37
	Erythrocytes, cells ×10 <sup>6</sup> /L	85	65
	Microbiological testing	CrAg negative, no prozone effect detected, CSF culture negative	CrAg-positive CSF culture: <i>Cryptococcus neoformans</i>
Case 3 TBM	Glucose (2.2–3.9 mmol/L)	4.4	1.7
	Protein (<0.45 g/L)	0.27	4.26
	WCC, cells ×10 <sup>6</sup> /L	4	540
	Lymphocytes, cells ×10 <sup>6</sup> /L	4	508
	Polymorphs, cells ×10 <sup>6</sup> /L	0	32
	Erythrocytes, cells ×10 <sup>6</sup> /L	2100	8
	Microbiological testing	TB PCR-positive CSF culture: <i>Mycobacterium tuberculosis</i>	TB PCR-negative CSF, AFB c culture negative
Case 4 NCC	Glucose (2.2–3.9 mmol/L)	4.2	1.1
	Protein (<0.45 g/L)	0.30	1.01
	WCC, cells ×10 <sup>6</sup> /L	6	196
	Lymphocytes, cells ×10 <sup>6</sup> /L	4	190
	Polymorphs, cells ×10 <sup>6</sup> /L	2	6
	Erythrocytes, cells ×10 <sup>6</sup> /L	760	380
	Microbiological testing	Cysticercosis serology positive	Cysticercosis serology positive

Abbreviations: CM, cryptococcal meningitis; CrAg, cryptococcal antigen; CSF, cerebrospinal fluid; NCC, neurocysticercosis; NP, not performed; PCR, polymerase chain reaction; TB, *Mycobacterium tuberculosis*; TBM, tuberculous meningitis; WCC, white cell count.

meningitis. Lumbar CSF obtained on day 4 demonstrated low glucose, high protein, and lymphocytic pleocytosis (Table 1). The ventricular CSF tested positive for *Mycobacterium tuberculosis* with polymerase chain reaction (PCR), and multiple ventricular CSF specimens were culture positive for *M. tuberculosis*. Despite the significant biochemical and cytological abnormalities, the lumbar CSF was *M. tuberculosis* PCR negative and culture negative after 8 weeks. The patient was initiated on TB therapy and corticosteroids but developed refractory hydrocephalus and extensive brain stem infarction. Medical care was withdrawn, and the patient died on day 38 of admission.

#### CASE 4—NEUROCYSTICERCOSIS

A previously well 66-year-old Laotian male presented with 2 years of progressive headache, gait disturbance, and eventual urinary incontinence. Noncontrast CT of the brain demonstrated hydrocephalus without focal abnormality. An LP demonstrated low glucose, high protein, and a lymphocytic pleocytosis (Table 1). MRI demonstrated basal meningitis, with numerous subarachnoid cystic structures throughout

the prepontine basal cisterns and the lumbar cisterns, with no intraparenchymal lesions. Cysticercosis serology on CSF and serum was strongly positive, and a diagnosis of racemose neurocysticercosis was made. The patient was transferred to our hospital for neurosurgical management. A VP shunt was inserted for obstructive hydrocephalus. Ventricular CSF results at the time of insertion demonstrated normal biochemistry, with CSF cell counts within the upper limits of normal after adjusting for an elevated CSF erythrocyte count (Table 1). Cysticercosis serology on the ventricular CSF was also positive. The patient received a prolonged course of combination antiparasitic therapy and tapering steroids and was symptomatically well at last follow-up 15 months after diagnosis.

#### DISCUSSION

These 4 cases highlight the phenomenon of discordant CSF parameters from different CSF compartments. Remarkably, the ventricular CSF results fell within normal limits, highlighting the potential for diagnostic error and delay.

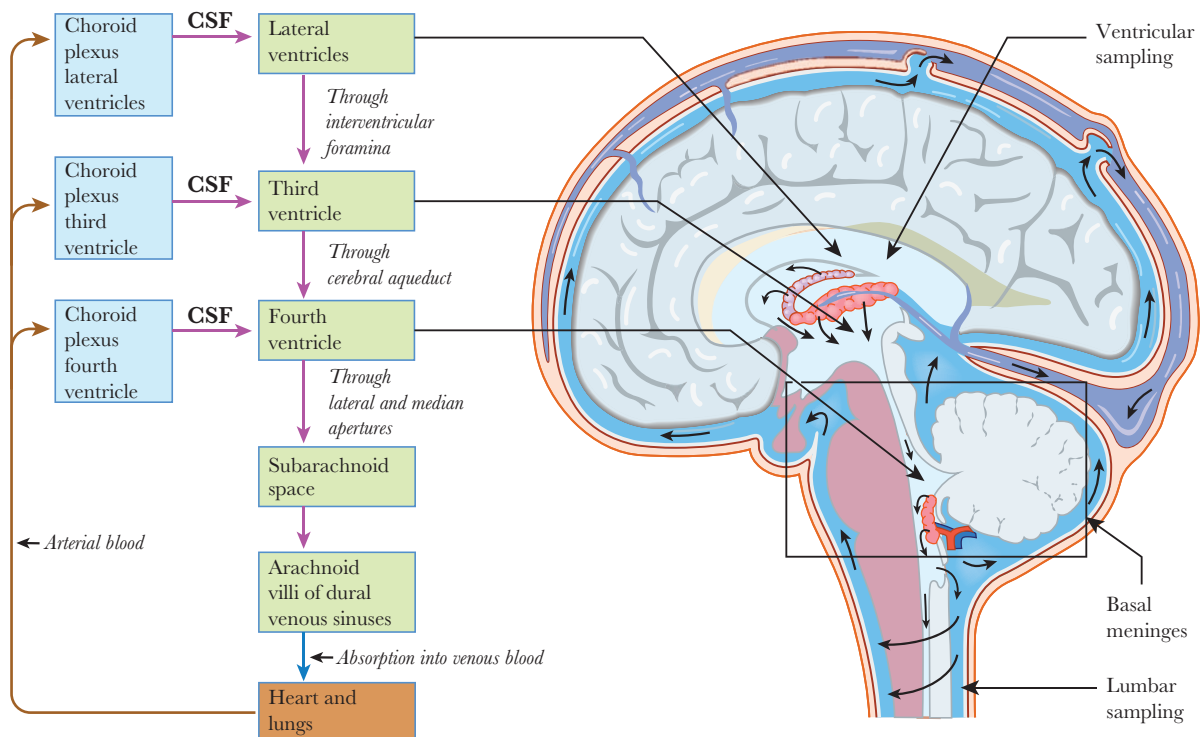
**Table 2. Table Comparing Differences Between Ventricular CSF and Lumbar CSF in States of Health and Disease**

Parameter	Ventricular CSF	Lumbar CSF	Normal Physiology	Changes in Pathology
Protein	Lower	Higher	Protein is progressively added through normal CSF circulation. 80% is derived from serum. Normal ventricular:lumbar ratio of 0.25:0.60 in health.	Increased ventricular–lumbar gradient in most disease processes; the magnitude of difference varies.
Glucose	Similar	Similar	Similar concentrations in healthy individuals. Strong correlation to serum levels of glucose.	Ventricular glucose significantly higher than lumbar glucose in most CNS infections. Multifactorial mechanisms and varies in disease states. Proposed mechanisms include increased microbial consumption, increased brain metabolic activity, consumption by WBC or malignant cells, and impaired function of the BBB & choroidal plexus.
WBCs	Lower	Higher	WBC gradient exists in health based on limited data. Mechanisms not clear.	Increased gradient in most disease processes, but degree depends on cause and location of abnormality in the CNS. Reversal of gradient can occur with predominant ventricular pathology.
Lactate	Similar	Similar	A mild cranio-caudal gradient exists, but much more uniform distribution through all compartments. Produced within the CSF and generally independent of serum levels.	Elevated levels from CNS anaerobic glycolysis due to any condition that results in cerebral hypoperfusion, or produced by increased concentration of WBCs. Retains more uniform distribution even in states of disease.

Abbreviations: BBB, blood brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; WBC, white blood cell.

Table 2 summarizes the normal biochemical and cytological gradients that are thought to exist in the CSF and general changes in pathological states. The majority of CSF is formed by the choroid plexus within the cerebral ventricles. CSF flows through the

interventricular foramina into the subarachnoid space, with the majority of CSF flowing over the cerebral hemispheres to be re-absorbed into the sagittal venous sinus (Figure 1). Only a small proportion of CSF circulates down into the lumbar cistern.



**Figure 1.** CSF is produced in the choroid plexus of the lateral, third, and fourth ventricles. The CSF flows unidirectionally from the lateral ventricle to the third ventricle, to the fourth ventricle, and then to the subarachnoid space in the region of the basal meninges. Ventricular sampling of the CSF is from the lateral ventricles, and lumbar sampling is from the lumbar cisterns in communication with the subarachnoid space. Only a minority of CSF flows into the lumbar cisterns, with the rest reabsorbed by the arachnoid villi of the dural venous sinuses. Abbreviation: CSF, cerebrospinal fluid.

The magnitude of differences between ventricular and lumbar CSF can vary, especially in pathological states [1–4]. Even in advanced CNS infection, the ventricular CSF can be biochemically normal with normal cell counts, while being grossly abnormal in the lumbar compartment [1, 2, 4–12]. This phenomenon is most strikingly demonstrated in patients who have developed hydrocephalus, which is the usual indication for ventricular drain insertion [4–7, 11, 12]. An underappreciation of these nuances is an important source of diagnostic error, which can lead to delay in or misdiagnosis of life-threatening CNS infection [4–7].

Three of the 4 cases were associated with a degree of mechanical obstruction to flow as a contributing factor to the development of hydrocephalus. None of these cases involved cases of iatrogenic meningitis (following CSF drainage), which is the main patient population in which ventricular and lumbar CSF comparisons have been performed [2, 4, 12]. Our cases had minimal ventriculitis, with predominantly basal meningitis. Case 4 with neurocysticercosis had subarachnoid cysts located around the basal meninges, with minimal intraventricular and no intraparenchymal cysts.

All etiological diagnoses in our case series are classical causes of basal meningitis. The basal meninges are notable for their intimate location within the median and lateral apertures, through which CSF exits the fourth ventricle, and for a predisposition to complications of hydrocephalus. Basal meningitis syndromes, such as tuberculous meningitis, cryptococcal meningitis, and neurocysticercosis, are shown here to be potentially associated with discrepant ventricular and lumbar CSF, especially when there is associated hydrocephalus.

Microbiological testing can also be discordant between ventricular and lumbar CSF. Case 2 demonstrated a negative cryptococcal antigen on ventricular CSF compared with lumbar CSF in the context of ventricular obstruction. In Case 3, interestingly, the ventricular CSF was TB PCR positive and repeatedly culture positive despite normal biochemistry and cell counts, whereas the lumbar CSF was TB PCR negative and culture negative but had abnormal biochemistry and cell counts. The total volume of lumbar CSF tested was 4 mL for Case 3, and may have reduced the diagnostic yield. Studies in extensive subarachnoid neurocysticercosis highlight similar problems of compartmentalization affecting testing [7, 8].

Case 1 highlights that mechanical obstruction to CSF flow is not always present. Even in nonobstructive hydrocephalus, discordance in CSF results can still exist. It is likely that 3 main factors contribute to the large CSF concentration gradients in basal meningitis syndromes. First, the normal direction of CSF flow, where sampling “downstream” of intense basal inflammation results in more significant abnormalities compared with the CSF “upstream” in the ventricles. Second, the pathophysiological addition or subtraction of solute (as described in Table 2) closely relates to sampling downstream to the direction of the flow. Third is gravity, where solutes collect in higher concentrations in dependent areas of CSF such as the lumbar cistern. Similarly, although antigens and nucleic acid products may be soluble within CSF, the direction of CSF flow may create a

“concentration gradient” with resultant differential yield on diagnostic assays depending on location of sampling.

## CONCLUSIONS

We describe 4 instructive cases of CSF discordance between ventricular and lumbar CSF parameters in patients presenting with hydrocephalus associated with basal meningitis syndromes. A normal ventricular CSF does not rule out a CNS infection. In addition to clinical and radiological clues, host factors such as country of origin and immunocompromised states should heighten awareness of basal meningitis. In patients with hydrocephalus, where there is diagnostic uncertainty or clinical suspicion of basal meningitis syndromes, an LP should be performed. Our experience highlights to clinicians an important source of potential diagnostic error in this patient group.

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