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Review Article

Cerebrospinal fluid (CSF) analysis and role in clinical neurology

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ABSTRACT

Cerebrospinal fluid (CSF) is a clear fluid coursing in the intracranial and spinal compartments. By estimating the levels of various CSF components utilizing relevant techniques, diagnosis, severity and prognostication of neurological conditions like infections, subarachnoid hemorrhage, demyelinating conditions, tumor like conditions, etc. can be done.
Cerebrospinal fluid (CSF) provides an extremely valuable matrix for biomarker research for several purposes such as diagnosis, prognosis monitoring and identification of prominent leads in pathways of neurological disease.

1. Introduction

Cerebrospinal fluid an ultra filtrate of plasma is secreted by the choroid plexus inside the brain ventricles. It is a dynamic fluid with various active metabolites which circulates in the subarachnoid space of the brain and spinal cord. The principle capacity of the CSF is to reduce buoyancy of the brain, to maintain supplies of nutrients and helps in clearing of amino acids, neurotransmitters and metabolic byproducts.

Lumbar puncture is frequently performed because cerebrospinal fluid (CSF) is a significant demonstrative window to the central nervous system (CNS). Appropriately interpreted tests can make cerebrospinal fluid (CSF) a critical tool in the diagnosis and differentiation of a variety of diseases. Proper evaluation of CSF depends on knowing which tests to order, normal ranges for the patient's age, and the test's limitations. Protein level, opening pressure, and CSF-to-serum glucose ratio vary with age.

CSF analysis normally comprise of opening pressure measurement, biochemical analysis, cytology, biomarkers assay, and microbiological evaluation.[1] In some clinical conditions, lumbar puncture and drainage of can be a therapeutic measure also.[2]

Table 1: The normal composition and pressure (lumbar) of CSF consists

Parameters	Normal range
Color	Clear
Specific gravity /ph	1.006-1.007 /7.4
Opening pressure	50-200mmh_2o
RBC count	Nil
WBC count	0-5 (up to 30 neonates)
Cell differential	Predominantly lymphocytes
CSF protein	15-40 mg/dl
CSF glucose	50-80mg/dl (two thirds of blood glucose)
Microbiological examination	No microorganism

1.1. Sample collection

Lumbar puncture is performed either in lateral or sitting posture. Generally, under sterile precautions, 22–24 G

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spinal needle is inserted after identifying the lumbar L2–3 or L3–4 space and local infiltration. When the spinal subarachnoid space is distinguished utilizing loss of opposition, controlled expulsion of stylet is done to forestall inordinate seepage of CSF.[3]

It is imperative to time the lumbar puncture (LP) to get maximum diagnostic and indicative yield. The Common indications of doing a lumbar puncture are enumerated in Table 2.

Table 2: Indications of a lumbar puncture

Diagnostic
CNS infections
Autoimmune CNS diseases like Guilliain Barrie syndrome
CNS vasculitis
CT negative subarachnoid hemorrhage
Malignant cells in metastasis
For injection of dye like fluorescein to identify site of CSF leaks
Therapeutic
Benign intracranial hypertension
Acute communicating hydrocephalus
Cryptococcal meningitis in HIV infections
For CSF leaks

In the cases with patient's having coagulopathy or on anticoagulants/antiplatelet drugs, LP should be conducted in accordance with the duration of medication activity and rules laid by American Society of Regional Anesthesia-ASRA can be followed.[4]

In patients with seizures suspected to be due to certain metabolic illness, a fasting LP is taken for CSF analysis. In patients whose sensorium is obstructed, a CT scan of brain must be done to rule of signs of raised ICP or mass lesions due to risk of brain herniation due to LP.

Table 3 lists the various contraindications to a lumbar puncture.

Table 3: Contraindications for LP

Relative contraindications
Platelet count of less than 20000–40000/cu mm
Thienopyridines therapy
Absolute contraindications
Non-communicating obstructive hydrocephalus
Uncorrected bleeding diathesis
Anticoagulant therapy (timing of LP depends on the stopping of anticoagulant drug)
Platelet count less than 20000/ cu mm
Spinal canal stenosis or spinal cord compression above level of puncture
Local skin infections

2. Interpretation of CSF Findings and Associated Conditions

2.1. Opening pressure

To quantify CSF opening pressure, the patient must be in the lateral decubitus position with the legs and neck in a neutral position. Normal opening pressure ranges from 10 to 100 mm H_20 in young children, 60 to 200 mm H20 after eight years of age, and up to 250 mm H_20 in obese patients.

Intracranial hypotension is characterized as an opening pressure of less than 60 mm H_20. This finding is rare but observed in patients with a history of trauma causing a CSF leak, or whenever the patient has had a previous lumbar puncture.

The diagnostic of intracranial hypertension occurs when opening pressures are above 250 mm H_20. Increased intracranial pressure occurs in various pathologic conditions i.e. meningitis, intracranial bleeding and tumors.CSF should be removed gradually in such cases and tight monitoring of the opening pressure should be maintained.[5]

2.2. Supernatant color

Normal CSF is crystal clear. Notwithstanding, as not many as 200 white blood cells (WBCs) per mm^3 or 400 red blood cells (RBCs) per mm3 will cause CSF to appear turbid. Xanthochromia is a yellow, orange, or pink discoloration of the CSF, frequently brought about by the lysis of RBCs resulting in hemoglobin breakdown to oxyhemoglobin, methemoglobin, and bilirubin. Discoloration begins after RBCs have been in spinal fluid for about two hours, and remains for two to four weeks.[6]

Xanthochromia is present in more than 90 percent of patients within 12 hours of subarachnoid hemorrhage onset.[7]Table 4 lists various causes of an abnormal colour of supernatant.

Table 4: CSF supernatant colors associated with various conditions

Color of CSF supernatant	Conditions or causes
Yellow	Blood breakdown products Hyperbilirubinemia CSF protein ≥150 mg per dL (1.5 g /l) >100,000 red blood cells per mm3
Orange	Blood breakdown products High carotenoid ingestion
Pink	Blood breakdown products
Green	Hyperbilirubinemia Purulent CSF
Brown	Meningeal melanomatosis

2.3. Cell count

Normal CSF may contain up to 5 WBCs per mm^3 in adults and 20 WBCs per mm3 in newborns.[8] Eighty-seven percent

of patients with bacterial meningitis will have a WBC count higher than 1,000 per mm, 3 while 99 percent will have more than 100 per mm3 . Having less than 100 WBCs per mm3 is more common in patients with viral meningitis.[8]

Elevated WBC counts also may occur after a seizure[9] in intracerebral hemorrhage, with malignancy, and in a variety of inflammatory conditions.

A traumatic tap occurs in approximately 20 percent of lumbar punctures. Fundamental practice is to quantify cell counts which are included in three sequential containers of CSF. If the number of RBCs is relatively constant, then it is assumed that the blood is caused by an intracranial hemorrhage. A falling count is credited to a traumatic tap. The three-tube technique, however, is not always reliable[10] Xanthochromia is a more reliable predictor of hemorrhage. If a traumatic tap occurs within 12 hours of a suspected subarachnoid hemorrhage, it is reasonable to repeat the lumbar puncture one interspace up to try and attempt clear CSF.[11]

2.4. Cell differential count

In a normal adult CSF, the differential leucocyte count is approximately 70 percent lymphocytes, 30 percent monocytes with an occasional eosinophil or polymorphonucleocyte (PMN).[7] In the CSF of a neonate few PMNs can be observed.[8] In early acute stages of tubercular, viral and fungal infections of the CNS there is a predominance of PMNs and in due course of time lymphocytosis gets established.

2.5. Microscopic examination

Gram stain is positive in 60 to 80 percent of untreated cases of bacterial meningitis and in 40 to 60 percent of partially treated cases. The sensitivity according to the causative organism ranges from 90 percent in pneumococcal or staphylococcal meningitis to less than 50 percent in Listeria meningitis. Presence of yeast like budding cells, round cells with a halo around and hyphae are characteristically observed in Candidal, cryptococcal and mould fungal meningitis respectively.

ZN staining reveals the presence of acid fast bacilli in case of tubercular meningitis. Sensitivity can be increased if 4 smears are done.[12] Sensitivity also can be increased by examining the CSF sediment.[13] Cryptococcus is better identified up to 50 percent by India ink preparation whereas Wright or Giemsa stain is used for Toxoplasmosis.

2.6. CSF protein

In CSF, protein concentration is normally less since serum proteins cannot cross the Blood brain barrier owing to their large size. Albumin is the most prevalent form of protein present in the CSF. Rise of protein concentration in CSF indicate two broad phenomenons - there is increased rate of protein synthesis due to inflammatory or cancerous cells and the passage of high molecular weight proteins increases to the BBB because of its elevated permeability.

Presence of mild CSF protein concentration is observed in viral meningitis neuro syphilis, brain tumors, multiple sclerosis, cerebral thrombosis, and subcellular hematoma. Modulate or pronounced CSF protein concentration is raised in acute bacterial meningitis, tuberculosis meningitis, Guillain- barre syndrome, cerebral hemorrhage, spinal cord tumor and radiation myelopathy.

Low CSF protein levels indicate a chronic CSF leak, repeated & recent lumbar tap, acute water intoxication or may be normal if age <2 years, untreated hyperthyroidism & certain forms of leukemia.[14]

2.7. CSF glucose

Also known as glycorhachia is used to determine the concentration of glucose in CSF. Normal range is in indicated between 45-80 mg/dl. Low glucose level ie. Hypo glycorhachia is observed in CNS infection, inflammatory pathogenesis, hypoglycemia, metastatic carcinoma, chemical & bacterial meningitis, bacterial TB, sarcoidosis & subarachnoid hemorrhage.[15]

High glucose levels generally reflect hyperglycemia & is indicative of 2/3 rds of serum glucose. Disease association with increase CSF glucose levels is not observed.

2.8. Intrathecal immunoglobulin

Presence of intrathecal oligoclonal Ig in CSF is diagnostically significant especially in patients of multiple sclerosis. Both qualitative & quantitative estimation proves useful in patient diagnosis along with the Isoelectric focusing (IEF) technique. Various patterns present indicate the possibility of CNS disorders i.e. multiple sclerosis, SLE, GBS, myeloma and other neurological pathogens.[16]

2.9. Culture

Cultures done on 5 percent sheep blood agar, chocolate agar and MacConkey agar, incubated in carbon dioxide rich environment remain the gold standards for diagnosing bacterial meningitis.[17] First vial of collected CSF is used for culture. Antibiotics, delay in transport and processing uncentrifuged CSF are the factors which reducing culture sensitivity, hence should be avoided.

Enterovirus, the leading cause of viral meningitis, can be recovered in 40 to 80 percent of cases. Culture for herpes simplex virus is 80 to 90 percent sensitive but can take five to seven days to become positive.[18]

Culture is less sensitive for Mycobacterium tuberculosis but yield is increased when multiple large volume samples of CSF is used. CSF culture is the gold standard for confirming the diagnosis of bacterial meningitis.

Table 5: List of common CSF findings in various types of meningitis

Test	Bacterial	Viral	Fungal	Tubercular
Opening pressure	**Elevated**	**Usually normal**	**Variable**	**Variable**
White blood cell count	>1000mm3	<100mm3	Variable	Variable
Cell differential	Predominance of PMNS	Predominance of lymphocytes	Predominance of lymphocytes	Predominance of lymphocytes
Protein	Mild to marked elevated	Normal to elevated	Elevated	Elevated
CSF -serum glucose ratio	Normal to marked decrease	Usually normal	Low	Low

3. Approach to CSF Analysis in Acute Neurological Conditions

3.1. CSF in subarachnoid hemorrhage (SAH)

SAH is an acute neurological pathology referring to the bleeding within subarachnoid spaces. A traumatic head injury, berry aneurysm, arteriovenous malformations, bleeding disorders, excessive use of blood thinners, cocaine abuse, sickle cell anemia, pituitary apoplexy are common causes of SAH. A plain CT or CT angiogram shows the blood in CSF. CSF analysis plays a vital role in determination of SAH by gross examination, RBC count, Bilirubin, oxyhemoglobin and ferritin level measurements by spectrophotometry and CSF cytology.[19]

RBC lysis release oxyhemoglobin which is converted to bilirubin by enzyme heme oxidase. This conversion takes place by 9-10 hours. Presence of xanthochromia i.e. A brown-yellow color present following the degradation of hemoglobin indicates a previous hemorrhage. A raised RBC count (>1000 cells/cu mm) or presence of xanthochromia are considered as valuable evidence of SAH.[20]

3.2. CSF in meningitis

An early CSF examination in patients with CNS disorders will elucidate presence of meningitis. CSF analysis based measurement of pressure, Cytology, biochemistry analytes i.e. CSF – Glucose & protein and culture aids in diagnosis of meningitis produced by bacterial, fungal and mycobacterial pathogens. Cytological studies include pleocytosis and gross examination. CSF – Culture analysis by gram stain latex agglutination or Rapid diagnostic tests (especially meningococcal meningitis) are routinely done.

The presence of elevated CSF lactate and Procalcitonin are observed in bacterial ventriculitis and meningitis. Nucleic acid amplification tests i.e. PCR has ability to diagnose the infective pathogen in a short turnaround time. The presence of β- D- glucan and galactomannan in CSF usually indicates the presence of fungal ventriculitis and meningitis. CSF analysis gives valuable information regarding the diagnosis, progression or relapse of the disease as well as effect of treatment.[21] (Table 5).

CSF analysis in acute demyelinating/ autoimmune diseases.

In acute demyelinating disease, there is impairment of nerve conduction signals, which further leads to malfunction in sensation, movement & other cognitive functions. The disease spectrum includes both myelinoclastic and leukodystropic demyelination disorders. In multiple sclerosis there is pleocytosis during CSF examination. CSF concentrations for Immunoglobulins and albumin can be a useful indicator for study pattern of pathogenesis & relapse of multiple sclerosis. CSF restricted oligoclonal IgG bands are seen. In neuromyelitis optica (NMO) neutrophils, eosinophils, activated lymphocytes and plasma cells are observed in CSF analysis with high CSF protein levels.[22]

In acute disseminated encephalomyelitis (ADEM) where children are commonly infected, CSF analysis reveals a mild pleocytosis and increased CSF protein concentration.[23]

3.3. Brain and spinal cord neoplasms

CNS neoplasms are usually differentiated on the basis of type of cells involved in tumorogenesis or categorized by the area of brain where they originated from. Gliomas, astrocytomas, brain stem gliomas, ependymomas, oligo dendroglioma, meningiomas, craniopharyngioma, medulloblastomas are major forms of brain & spinal area tumors.[26]

A thorough neurological examination, CT scan, MRI, myelogram, PET scan and a spinal tap are various diagnostic modalities present to diagnose the neoplasms.

The tumor derived DNA is proposed to be found in CSF. Wang et al in 2015 concluded that DNA from tumor, WBC's and CSF can be utilized to defect somatic mutations and can be proved useful as a biomarker to monitor tumor invasion & progression.[27]

3.4. CSF analysis in spinal cord diseases

3.4.1. CSF analysis in spinal cord diseases

Guillain Barre Syndrome is a potentially life threatening acute onset disorder with polyneuropathy where CSF examination plays a vital role. It shows in increased

Table 6: CSF changes in acute demyelinating/inflammatory disease [24,25]

Condition	CSF findings
Transverse myelitis	Signs of inflammation (pleocytosis, elevated protein concentration, oligoclonal bands, or elevated IgG index)
	Elevated CSF IL-6
	PCR negative of infections.
	CSF sugar, pressure usually normal.
Multiple sclerosis (different types)	Pleocytosis (5–50 cells / cu mm; lymphocytes)
	Elevated protein
	OCB may be present. (highly diagnostic)
	Ig G index (increase CSF IgG compared to serum IgG levels)
Neuromyelitis optica	Nonspecific Pleocytosis (5–50 cells/ cu mm; lymphocytes)
	Elevated protein
	OCB may be present. (most cases)
	Normal glucose levels
Guillain Barrie syndrome	Normal CSF cell count.
	Elevated CSF protein levels Cyto-albuminergic disassociation

pretein levels with normal cell count which is often termed as "cytoalbuminologic dissociation". CSF/serum albumin quotient (Q_{alb}) should also be analyzed [28]

Neurofilament light protein levels predict long term progress and clinical outcomes for neurophysiological recovery of the patient. [29]

3.4.2. CSF in amyotrophic lateral sclerosis (ALS)

ALS is a highly progressive non curable neurodegenerative disease. The CSF analysis for various biomarkers i.e. chitotriosidase-1 (CHIT-1), monocyte chemoattractant protein (MCP-1), chitnase-3 like protein 1 (YKL-40) can be proved useful for patient stratification and monitor the therapy response. [30]

3.4.3. Spinal cord ependymoma

In spinal cord ependymoma with micropapillary morphology or anaplastic features the CSF analysis could be done to monitor the stage prognosis &appropriate treatment. CSF positive specimens showed hypercellularity with aggregates of the epitheloid cells. [31]

4. CSF Analysis in Inborn Errors of Metabolism

CSF analysis plays a significant role in the diagnosis of the inherited neurotransmitter disorders with biochemical analysis of CSF for routine biochemistry, amino acids, neurotransmitters and pteridines. For various disorders i.e. Lactic acidoses, Non-ketotic hyperglycemia, and serine deficiency disorders, GABA metabolism disorders, dopamine, serotonin and catecholamine disorders and pteridine disorders, Succinic semialdehyde dehydrogenase deficiency, Inborn errors of monoamines targeted CSF analysis is observed on LC-MS/MS analysis platform. [32]

5. New Biomarkers in CSF Analysis

Spinal cord injury can cause elevation of various biomarkers. These include micro-RNA (mRNA), neuron specific enolase (NSE), neurofilaments (NF), glial fibrillary proteins, Interlukein (IL6) and cleaved Tau protein. Analysis of various biomarkers in the CSF in patients who have sustained injury to spinal cord can help in assessing the severity of injury as well as in further prognosis. [33]

Cerebrospinal fluid (CSF) biomarkers based on the core pathological proteins associated with Alzheimer's disease (AD), i.e., amyloid-β (Aβ) and tau protein, are widely regarded as useful diagnostic biomarkers. [34] New biomarkers i.e. Chromogranin-A, contactin-2, myelin basic protein, neurofascin, Neurofilament light, Progranulin, Osteopontin have been identified as promising markers for early diagnosis of Alzheimer's disease. Mass spectrometry (MS) based CSF evaluation has taken a central & pivotal role to analyze and quantify proteins.

Glial fibrillary acidic protein (GFAP) increases in CSF & serum of patience with alzheimers disease and it's directly proportional to the deterioration of the cognitive function.

6. Conclusion

CSF analysis is a major diagnostic & prognostic tool in disorders related to central nervous system. Significant investigations on CSF include protein & glucose level, CSF cytology, gross examination & culture analysis. Inflammatory biomarkers and CSF cytochemical analysis aid in early diagnosis of bacterial meningitis. PCR and latex agglutination can be added as modalities in effective and rapid diagnosis of CNS disorders. More recently to assess the neurological complications in COVID-19 patients, CSF RT-PCR and CSF IgM testing can be highly useful.

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8. Conflict of Interest

The authors declare that there is no conflict of interest.

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