Cerebrospinal Fluid Analysis in Infectious Disease

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Abstract

Cerebrospinal fluid (CSF) study gives important clues to quick diagnosis and prompt management of neurologic disease, which is often life-threatening and disabling in young children. Following is a compilation of commonly done tests on CSF in pediatric infections or infection mimics.

Keywords: Analysis, Cerebrospinal fluid, Infectious disease.

Pediatric Infectious Disease (2022): 10.5005/jp-journals-10081-1346

Introduction

Cerebrospinal fluid (CSF) study gives important clues to quick diagnosis and prompt management of neurologic disease which is often life-threatening and disabling in young children. Following is a compilation of commonly done tests on CSF in pediatric infections or infection mimics.

Visual Inspection

Normal CSF is clear and colorless. Turbid CSF indicates the presence of >200 white blood cells (WBCs)/mm^3. Grossly bloody CSF indicates >6000 red blood cells (RBCs)/mm^3. Xanthochromia is yellow or pink-colored CSF. It is detected visually by comparing CSF color to that of water in white light. It indicates hyperbilirubinemia (>10–15 mg/dL as in a neonate) or high CSF protein values (>150 mg/dL). It may also indicate traumatic tap or subarachnoid hemorrhage when clinical correlation exists.

Cytology

Cerebrospinal fluid must be examined immediately in the counting chamber after lumbar puncture. A delay of >60 minutes can give a falsely low cell count as the WBCs adhere to tubes/settle. After centrifugation, a stained smear of the sediment is used for differential counting. CSF is normally acellular. In newborns, up to 15 WBCs/mm^3 and in infants <3 months up to 9 WBCs/mm^3 are taken as normal. In children, ≥3 months of age, up to 6 WBCs/mm^3 can be normally present in the CSF.

In a traumatic tap, the number of RBCs and WBCs increases dramatically. No method is accurate to predict the exact CSF-WBC count in such cases. A good rule of thumb is to subtract one WBC for every 1000 RBC.[1]

Almost all cells are always lymphocytes. A total of 95% of the children older than 3 months have no polymorphonuclear cells in the CSF and, the presence of even one such cell is abnormal. Any febrile, symptomatic child with even one polymorphonuclear cell in CSF requires close observation and treatment till diagnosis is confirmed.[2]

CSF eosinophilia may be seen in infections with parasites, fungi, mycobacterium tuberculosis, mycoplasma, and rickettsia. In suspected malignancy, 10–15 mL of CSF should be sent for examination for abnormal cells.

CSF Protein Levels

Normal CSF protein levels are between 23 and 38 mg/dL. Levels rise (>40 mg/dL) in CNS infections. In term neonates, the median CSF protein levels are higher (66 mg/dL in a large study). Cut-off levels for meningitis are 100 mg/dL in term and 125–150 mg/dL in preterm neonates. Protein levels may also rise in traumatic tap (1 mg/dL of protein elevation per 1000 RBCs/mm^3) and subarachnoid bleed. In CSF obstruction, as in subarachnoid block extremely high levels in the range of 3–6 gm/dL may be found. Albuminocytologic dissociation is characteristic of Guillain-Barré syndrome, in which, after the first week of illness, up to two-thirds of patients have CSF protein elevation (>40 mg/dL) with normal cell count (<5 cells/mm^3).

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How to cite this article: Gupta T. Cerebrospinal Fluid Analysis in Infectious Disease. Pediatr Inf Dis 2022;4(2):76–77.

Source of support: Nil

Conflict of interest: None

CSF Sugar Levels

The normal CSF to blood glucose ratio for all practical purposes is 0.66 or 66%. Although it has been reported to range from 0.5–0.8 and shows variations due to age or timing of food intake.[3] It is mandatory to test blood sugar at the time of doing lumbar punctures for correct interpretation of CSF glucose values. It is important to consider the range of CSF to blood glucose ratios to interpret CSF glucose levels in a hyper or hypoglycemic child who may have CNS symptoms with or without CNS infection.

CSF glucose values <18 mg/dL strongly predict bacterial meningitis. Levels are also low in fungal, mycobacterial, and mycoplasmal CNS infections. Most viral infections have normal values. Noninfectious conditions with low CSF glucose are CNS lymphoma, leukemia, and large subarachnoid hemorrhage.

CSF Smear

Gram stain of the smear can give quick clues about the causative organism. The possibility of detecting bacteria increases with the bacterial load. Smear positivity is 97% with >100,000 CFU/mL, while it is only 25% if the bacterial load is <1000 CFU/mL. The yield is lower if the child has received prior antibiotic treatment. Acid-fast stain is used in suspected cases of tubercular meningitis.

CSF Rapid Antigen Detection

Latex agglutination kits are available for common pathogens like *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, *E. coli*, etc. It is important to remember that a negative test does not rule out infection from that pathogen and that false positive, though uncommon may occur. It may be useful in traumatic lumbar punctures or when a patient has received prior antibiotics.

CSF Culture

Cerebrospinal fluid should always be cultured even when it is clear on visual inspection or acellular on cell count. In early disease, culture may come positive in the absence of pleocytosis. It should be transported at room temperature and must be plated at the laboratory within 1 hour of collection for optimum yield.

Culture yield decreases with prior oral or intravenous antibiotic treatment; hence it is prudent to expedite lumbar puncture as soon as the diagnosis of CNS infection is suspected. Sterilization of CSF can occur within 1–4 hours of receiving intravenous antibiotics.[4]

Data from various surveillance studies on pyogenic meningitis in children in India has revealed *S. pneumoniae* as the most isolated organism in culture.[5]

Molecular Diagnosis

Molecular tests or nucleic acid amplification tests (NAT) detect DNA or RNA specific to the microorganism causing infection. These tests have higher sensitivity and specificity in CSF than in other body fluids, as most CNS infections are monomicrobial (except brain abscess). Also, CSF does not contain heme which is an inhibitor of amplification methods like polymerase chain reaction (PCR). The limitations are that drug susceptibility cannot be determined.

A total of two types of tests are available, targeted and multiplex PCR.

Targeted

These are more sensitive than conventional cultures and may also detect uncultivable or dead organisms. At present standalone PCR test for HSV one and two is available.

Multiplex or CSF Panel-based Tests

These combine multiple NATs into one test so that many organisms can be tested together. The available test in India is the film array CSF meningitis/encephalitis panel which tests for 13 organisms, that, six bacteria, six viruses, and one fungus. It is FDA approved, and a meta-analysis of eight studies revealed a pooled sensitivity of 90% and specificity of 97%.[6] However, false positives and false negatives may occur, and results must be interpreted in the background of clinical presentation and other CSF findings.

Causes of false positive:

- Amplification of a contaminant organism
- Amplification of a latent organism
- Amplification of an organism that is not causative but present in cells that crossed the blood-brain barrier
- Poor specificity of the assay probe.

Causes of false negative:

- Inadequate sample (low nucleic acid concentration)
- Inhibitors of amplification (hemorrhagic tap)
- Low clinical sensitivity (prolonged treatment or low CSF organism load as per disease pathophysiology)
- Low laboratory sensitivity (nucleic acid concentration is below the limit of detection of the assay).

CSF Oligoclonal Bands

These are limited classes of antibodies found as a discrete band on an agarose gel. They are characteristic of multiple sclerosis in young adults and are also found in neuropathies and viral syndromes.

CSF NMDA Receptor Antibodies

Cerebrospinal fluid levels of IgG antibody to a subunit of NMDA receptor is highly sensitive and specific for autoimmune encephalitis, an infection mimic in children. These antibodies are always present at the time of presentation and titer correlates with disease severity.

Summary of Characteristic CSF Findings in Disease States

Acute Bacterial Meningitis

The usual cell count is >1000 cells/mm^3 with polymorphonuclear predominance. The range may be several hundred to >60,000 cells. In early meningitis or meningococcal disease, the cell count may be <100 cells/mm^3. Protein levels are usually 100–500 occasionally >1000 mg/dL. Sugar levels are <40 in more than half cases.

Aseptic or Viral Meningitis

The usual cell count is 5–100 cells/mm^3 with mononuclear predominance. The number may go up to 1000 cells/mm^3. In early disease, there may be polymorphonuclear predominance. The protein levels are usually <150 mg/dL; however the range of CSF protein values is 100–500 mg/dL. CSF glucose levels are usually normal or slightly reduced. Low levels are found in meningoencephalitis due to herpes simplex, herpes zoster, mumps, and enterovirus.

Tubercular Meningitis

The usual cell count is 25–100 cells/mm^3, rarely >500. Lymphocytic predominance is found except in early stages when it may be polymorphonuclear. CSF protein levels are between 100 and 200 mg/dL but may be higher if there is a CSF block. In 75% cases, the CSF glucose is <50 mg/dL.

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