جامعة الملك سعود
King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Biochemistry437

Cerebrospinal Fluid

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

Neuropsychiatry block

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Objectives:

- To define CSF and its functions, formation and circulation
- To discuss the CSF sampling procedure (Lumbar puncture) and its indications and contraindications
- To describe the physical and biochemical laboratory investigations of CSF and the electrophoretic pattern of CSF proteins
- To study the composition of normal CSF and discuss the abnormal findings in pathological conditions
- To define otorrhea and rhinorrhea

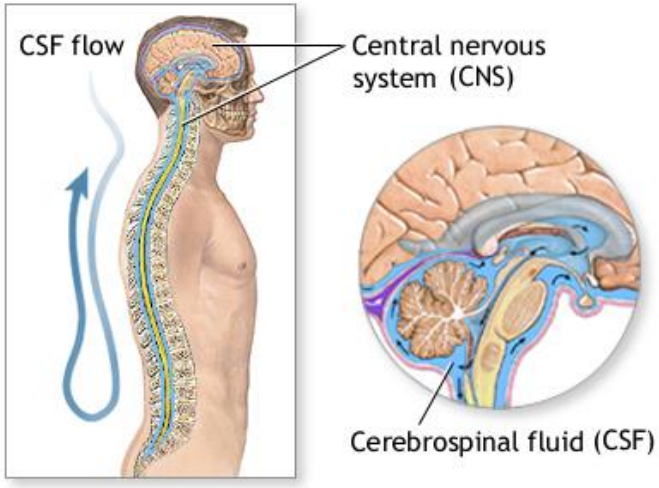
CSF Definition & Function

CSF definition:

The liquid surrounding the brain and spinal cord
It flows in subarachnoid area (the space between the arachnoid & pia mater)

Main Functions:

- Physical support & protection
- Provides a controlled chemical environment → nutrient supply & waste removal
- Waste is removed through CSF which gets absorbed across the arachnoid villi into the venous circulation

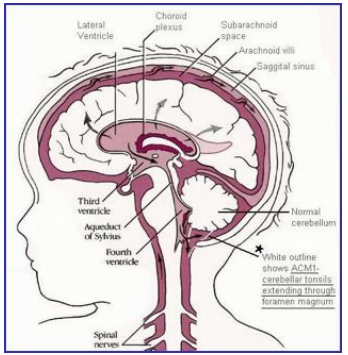


CSF Formation & Circulation

CSF is formed at the choroid plexuses & by the cells lining the ventricles.

Normal blood brain barrier is important for the normal chemistry results of CSF.

Mechanism of formation	**Selective ultrafiltration of plasma**	**Active secretion by epithelial membranes**
	Ultrafiltration through BBB	Synthesized locally by CNS
Mechanism of excretion (absorption)	**Excretion volume = Production volume → Constant CSF volume**	**Absorption occurs at the arachnoid villi protruding through the dura to the venous sinuses of the brain →bloodstream**



Rate of formation:

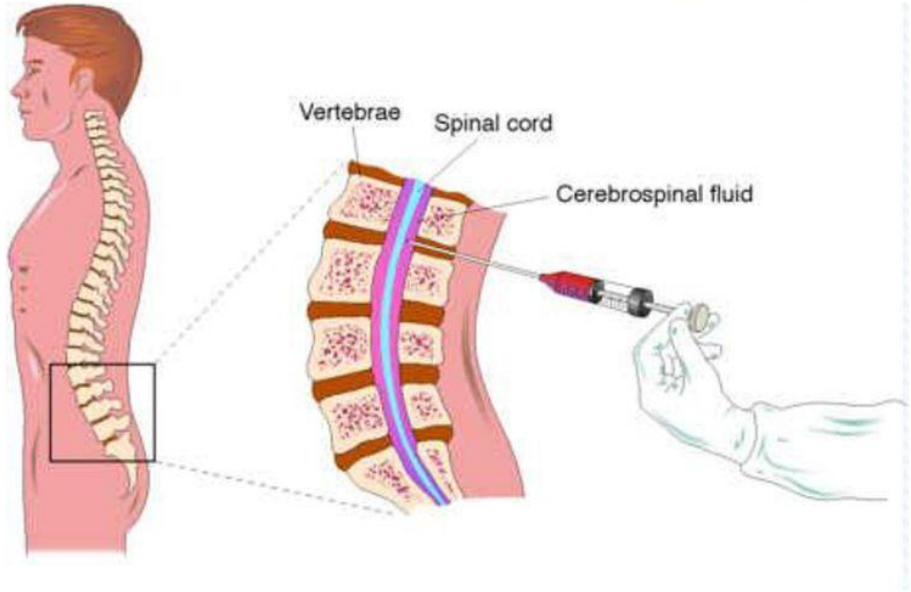
500ml/day

CSF Specimen Collection

- Obtained by Lumbar puncture (At the interspace L3-L4, or lower)
- Using aseptic technique, to prevent the patient from getting meningitis.
- CSF is separated into 2 aliquots (2 small tubes):
  - For chemistry & serology
  - For microbiology
- Immediate analysis
- It's a **precious*** sample: Preserve any remaining sample

*Precious because it's difficult and dangerous to get, it needs skills.
Because of that they keep it for 6 months in a special freezer in case they need it for other tests, unlike blood samples which are thrown every week.

Method of CSF Sampling



Traumatic tap (damage to blood vessel during specimen collection)
→ blood in CSF

Traumatic tap happens usually when the person doing the collection is not so experienced.
It is iatrogenic, the blood in the sample isn't really present in the CSF, but is in the sample because of damaging the blood vessels during collection (contaminated sample).

Important!

Blood & Hemoglobin Pigments in CSF

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Traumatic tap

- Bright red color
- RBCS in decreasing number as the fluid is sampled
- Not a haemorrhage , rupture of a blood vessel during specimen collection → blood in the CSF (contimainted CSF)
- CSF sample in the beginning RBCs are found (red) as a result of rupturing the blood vessel, then as the needle gets deeper it's not found (white)

Subarachnoid hemorrhage (SAH)

- **Xanthochromia** (hemoglobin breakdown pigments) = RBCs lysis & metabolism previously occurred (at least 2 hr earlier)
- Real haemorrhage due to trauma or any other causes
- Blood in the CSF , rupture of RBCs (like a bruise) [heme degrades-biliverdin (green)-bilirubin(yellow)]

When would Xanthochromia indicate hemorrhage?

If you exclude:

- Prior traumatic tap
- Hyperbilirubinemia (bilirubin > 20 mg/dL) لو كان اقل من 20 نقدر نقول انه xenthochromia

Contraindications for Performing Lumbar Puncture

- Bleeding diathesis (bleeding tendency ; hemophilia, Thalassemia)
- Increased intracranial pressure (high volume of CSF — sudden collapsed due to the sudden decrease in the pressure)
- Infection at site of needle insertion

Indications for Laboratory Investigation of CSF

- CNS infection
- Demyelinating diseases (multiple sclerosis, meningitis)
- CNS Malignancy
- Hemorrhage In CNS

Examination of CSF

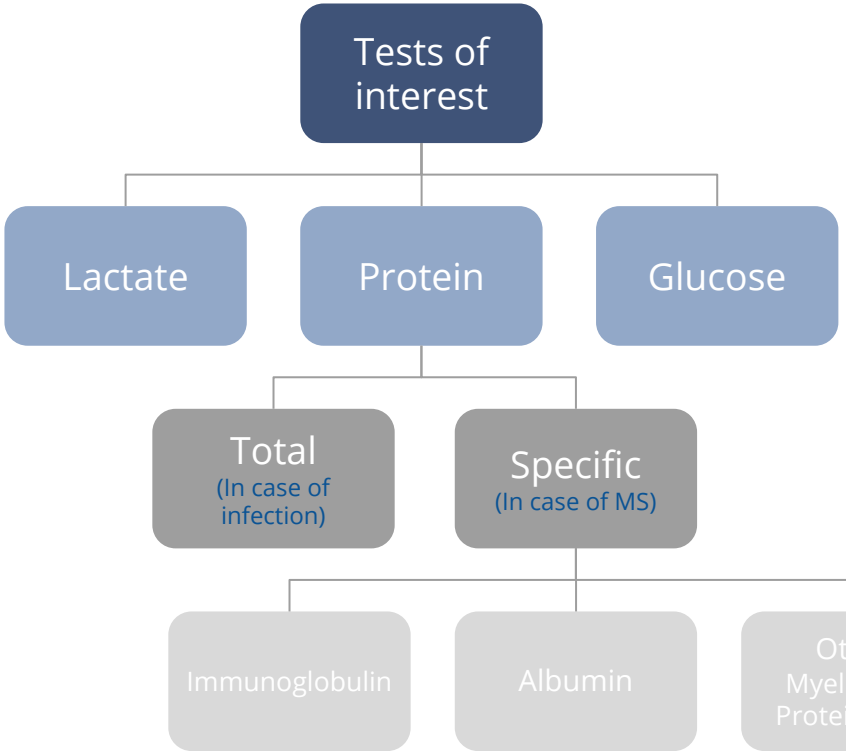
1- Physical examination

- **Normal CSF is:**
  - Colorless
  - Clear
    (if you put a paper behind it you can read it, if it's turbid it means there are microorganisms or leukocytes)
  - Free of clot
  - Free of blood
  - No smell

- **If CSF is cloudy (turbid) → perform microscopic examination:**
  - Is usually due to leucocytes
  - May be due to micro-organisms

Examination of CSF

2- Biochemical analysis of CSF



Glucose and protein are the most reliable diagnostically & accessible analytically

Don't memorize numbers, the only thing you need to know it that CSF [glucose] is ~ 2/3 that of plasma

Glucose in CSF

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- Glc enters CSF via **facilitative transporter (GLUT)**[1]
- CSF [glucose] is ~ **2/3** that of plasma "50 - 80 mg/dl"
  E.g. 100 in blood, 66 in CSF
- A plasma sample must be obtained ~ 2-4 hr before CSF sample[2]
  - In hypoglycemia: [CSF glucose] may be very low
  - In hyperglycemia: [CSF glucose] is raised
- Measure CSF [Glucose]:
  - Immediately
  - or preserve the specimen with an antiglycolytic e.g. fluoride ion[3]

1: Facilitated diffusion from high concentration to low concentration and does not consume energy that's why you should know that the CSF glucose is less than that in the blood.

2: We should take both blood sample and CSF we start by taking blood sample 2-4 h before CSF, why?
To compare the plasma glucose with CSF glucose level eg. plasma glu If the patient has hyperglycemia is 140 mg/dl and the CSF is 120 mg/dl you will think that he has high glucose in the CSF and that's not real because the plasma glu is already high.

3: When we measure the glucose in the stored sample the glucose will start to degrade so it won't reflect really what is my current glucose, that's why we keep the sample in tube containing fluoride which inhibits one of the enzymes in the glycolysis to stop the glycolysis and have the real glucose level.

Abnormal CSF [Glucose]

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↑ CSF [glucose]

- Not clinically informative
- Provides only confirmation of hyperglycemia

Not clinically important for diagnosis of meningitis.
we won't go on dangerous procedure just to confirm the patient is having a diabetes

↓ CSF [glucose](Hypoglycorrhachia)

1. **Disorder in carrier-mediated transport e.g.** TB meningitis, sarcoidosis

Can affect the glucose transport thus will not allow the glucose to move into the CSF

2. **Active metabolism of glucose by cells or organisms e.g.** acute purulent, amebic, & fungal meningitis

Because they need energy so they take it from the glucose in the CSF

3. **Increased metabolism by the CNS e.g.** by CNS neoplasm

Tumor =>increase number of cells => need more energy for metabolism => decrease glu

↔ CSF [glucose]

- In viral meningitis CSF [glucose] is usually normal

Usually in viral infection you will see everything is normal

You don't have to know the numbers

Protein in CSF

- Proteins, mostly albumin are found in the CSF (0.15-0.45 g/L)

  Why mostly albumin ? The formation of CSF is by ultrafiltration since the albumin is very small it can cross the BBB

- **Source of CSF proteins**:

80% from **plasma by ultrafiltration**
Mainly Albumin

20% from **intrathecal synthesis**
Mainly **Immunoglobuline** it is Local synthesis it does not come from the blood or liver

Abnormal CSF [Total Proteins]

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↑ CSF [total protein]

- Must be compared to the serum [protein]
- Useful **nonspecific** indicator of pathological states:
  - Lysis of contaminant blood (traumatic tap) Sometimes it will be high in the CSF because of the traumatic tap so we have to exclude it
  - ↑ **Permeability of the epithelial membrane due to**:
    - Bacterial or fungal infection There will be destruction of BBB which will allow the entering of albumin mostly
    - Cerebral hemorrhage Due to RBCs lysis
  - ↑ **Production by CNS tissue eg. in**:
    - Multiple sclerosis (MS) Most common
    - Subacute Sclerosing Panencephalitis (SSPE)
  - **Obstruction e.g. in:**
    - Tumors
    - Abscess

CSF Albumin

Albumin is produced solely in the liver

Its presence in CSF must occur through BBB

CSF Immunoglobulin

- CSF IgG can arise from:
  - Plasma cells within CSF "mostly"
  - The blood through BBB
- ↑ [IgG] and normal [Alb] of CSF suggests local production of IgG, e.g.,
  - Multiple sclerosis (MS)
  - Subacute sclerosing panencephalitis (SSPE)

CSF Proteins

What to do if ↑ CSF [protein] was detected?

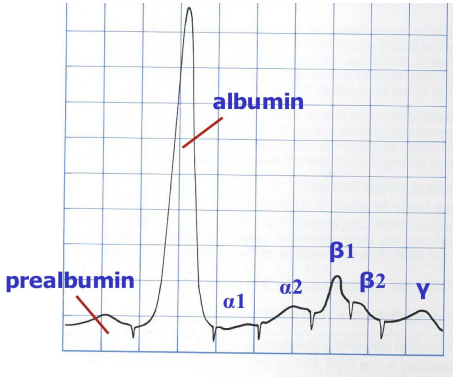
- Perform electrophoretic separation (separates proteins)
- If multiple banding (oligoclonal bands) of the γ-globulin is detected, the following differential Diagnosis is suspected:

MS | SSPE | Inflammatory diseases

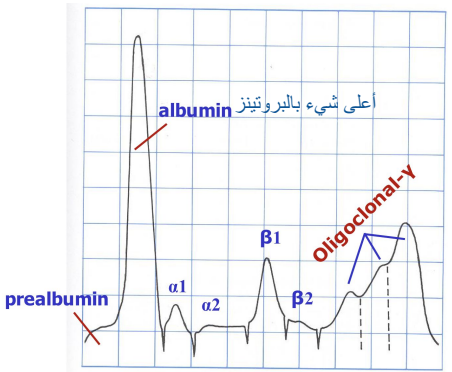
If the culture is normal and there's no bacterial or fungal meningitis, we'll look at the proteins, if the albumin is normal and the IgG is high we'll need further investigations (electrophoresis) for diagnosis.

CSF Electrophoresis

Normal Pattern



Oligoclonal Banding



- Oligoclonal "three" is present in Gamma region.

- If it's Monoclonal (one sharp) "in blood sample" Indication of multiple myeloma.

Other Chemical Components of CSF

- CSF [Calcium], [Potassium] & [Phosphates] are lower than their levels in the blood
- CSF [Chloride] & [Magnesium] are higher than their levels in the blood
- Abnormal CSF [Chloride], we always use chloride for differential diagnosis
    - Marked decrease in acute bacterial meningitis
      Decreased glucose
      Decreased chloride
      Increased protein
      = Bacterial meningitis
    - Slight decrease or normal in viral meningitis & brain tumors

No need to memorize all of them

Normal Composition of CSF

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Appearance	Clear ,Colorless
Lymphocytes	<5/mm^3
Polymorphs	Nil
pH	7.4
Total Volume	100 - 150 ml
Daily Secretion	450 - 500 ml
Specific Gravity	1.006 - 1.007
Protein	0.15 – 0.45 g/L

Glucose	50 - 80 mg/dL (2.8-4.2 mmol/L) (>50% plasma level)
Chloride	115 - 130 mmol /L
Calcium	1.0 - 1.40 mmol/L
Phosphorus	0.4 - 0.7 mmol/L
Magnesium	1.2 - 1.5 mmol/L
Potassium	2.6 - 3.0 mmol/L

Abnormal Findings of CSF in Some Pathological Conditions

Parameter	Condition		
	Bacterial Meningitis (pyogenic)	Tuberculous Meningitis	Viral Meningitis
Appearance	Often turbid	Often fibrin web	Usually clear
Predominant cell	Polymorphs	Mononuclear (lymphocytes)	Mononuclear (lymphocytes)
Cell count/mm3	90 - 1000+	10 - 1000	50 - 1000
Bacteria/virus	+ve smear & culture	Often none in smear	negative smear or culture
Protein (0.15 - 0.45 g/L)	> 1.5 (↑ ↑)	1-5 (↑ ↑)	<1 (Normal)
Glucose (2.8 - 4.2 mmol/L)	<1/2 plasma (↓ ↓)	<1/2 plasma (↓ ↓)	>1/2 plasma (Normal or slightly ↓)
Chlorides (115 - 130 mmol/L)	↓ ↓	↓ ↓	Normal or ↓

Otorrhea & Rhinorrhea

Otorrhea : leakage of CSF from the ear

Rhinorrhea : leakage of CSF into the nose

- Usually comes when the patient is traumatic.
- Test done by radiology (MRI) because it's much faster.

Take Home Messages

- CSF is formed in the choroid plexus
- It is essential for the physical protection of the CNS
- The physical & chemical analysis of CSF is essential for diagnosis of certain diseases

Summary

- CSF is formed by selective ultrafiltration and active secretion.
- Indications for laboratory investigation of CSF: CNS infection, demyelinating disease, CNS malignancy, hemorrhage in CNS.
- Contraindications: increased intracranial pressure, bleeding diathesis, infection at site of insertion of needle.
- Protein is high in bacterial and tuberculous meningitis, and normal in viral.
- Polymorphs are found in CSF in bacterial meningitis.
- Decreased glucose indicates: neoplasm, TB meningitis, bacterial meningitis.

MCQs:

1- Xanthochromia is the presence of what in CSF?

A- urea B- protein C - bacteria D- hemoglobin breakdown pigments

2- Protein is normal in:

A- viral meningitis B- Multiple Sclerosis C- bacterial meningitis D- tuberculous meningitis

3- Which substance is higher in CSF?

A- chloride B- Calcium C- potassium D-Sodium

4- which substance is lower in CSF?

A- calcium B- chloride C- magnesium D-Sodium

5- Increased igG and normal albumin indicates:

A- bacterial meningitis B- MS C- fungal meningitis D-viral meningitis

1- D
2- A
3- A
4- A
5- B

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Girls team

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