Biochemical examination of cerebrospinal fluid

General Medicine

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1. Cerebrospinal fluid

Cerebrospinal fluid (CSF, liquor cerebrospinalis) is a clear, colorless liquid. In comparison to blood plasma, the composition of CSF is qualitatively identical, but quantitatively different.

1.1. Origin, circulation and absorption of cerebrospinal fluid

The cerebrospinal fluid is secreted by the cells of choroid plexus and ependyme of cerebral ventricles (50 – 70 %). Another portion originates from ultrafiltration of blood plasma by choroid capillaries. The volume of CSF in an adult individual is about 120 – 180 ml. It is produced with the rate of about 500 – 600 ml per 24 hours. Secretion of cerebrospinal fluid continues even if its flow is obstructed, and then the CSF accumulates and intracranial pressure rises.

Location of the CSF is *intracerebral* (20 %) inside the two lateral ventricles, the third and the fourth ventricles and connections among them, and *extracerebral* (subarachnoid) (80 %) in the space between pia mater and arachnoidea on the surface of brain and spinal cord.

Circulation of CSF begins in the lateral ventricles, continues through the third and fourth ventricles; the CSF then flows on the brain hemispheres and terminates in the Pacchioni's granulations and sagittal sinus, where it is absorbed. A portion of CSF flows around the brain stem and spinal cord.

1.2. Function of cerebrospinal fluid

The CSF serves several functions:

- *Mechanical* – surrounds the brain and spinal cord and in this way protects them from shocks, changes in pressure and temperature.
- *Homeostatic* – provides an optimal medium for the CNS cells (stable ionic composition, pH and osmolarity).
- *Metabolic* – provides removal of catabolic waste products (e.g. lactate, CO_2) and supplies the brain cells with various bioactive substances.
- Contributes to *protection from pathogenic microorganisms*.

2. Blood-brain barrier

The composition of CSF is affected by a system of barriers. The term blood-brain barrier encompasses interfaces between the blood stream, brain and CSF, which allow passage of some substances in both ways or in one way only, while passage of some other compounds can be restricted. The blood-brain barrier provides an optimal medium for the brain function and enables supply of the brain with substances necessary for its metabolism.

We can distinguish *blood-brain, brain-CSF, and blood-CSF barriers*.

2.1. Blood-brain barrier

The blood-brain barrier in narrow sense forms the interface between brain capillaries and the brain tissue. It consists of a continuous *layer of brain capillary endothelium* from the blood side, *basal membrane*, and a *layer of astrocytes from the brain tissue side*. Unlike endothelium in other localisations, the brain endothelium lacks fenestrations and its cells are connected with tight junctions. The processes of astrocytes together with pericytes (microglia) are attached to the basal membrane (Fig. 1). The passage of substances from blood to brain occurs in dependence on their solubility in lipids, or is mediated by carrier systems. Water and fat-soluble substances, such as

ethanol, nicotine, and gases like O_2, CO_2, N_2O, get through the barrier easily. Important hydrophilic compounds, such as glucose and amino acids, are transported by means of specific carriers. Vesicular transport is very limited. The intact blood-brain barrier essentially prevents entry of macromolecules to the brain tissue. There is also an enzymatic component to the barrier, consisting of enzyme systems localised to the brain blood vessel wall, such as monoamine oxidases – enzymes degrading monoamines, and aminopeptidases – inactivating enkephalins.

Fig. 1: Blood-brain barrier

BLOOD

tight junction

endothelium

basal membrane

astrocytes

BRAIN
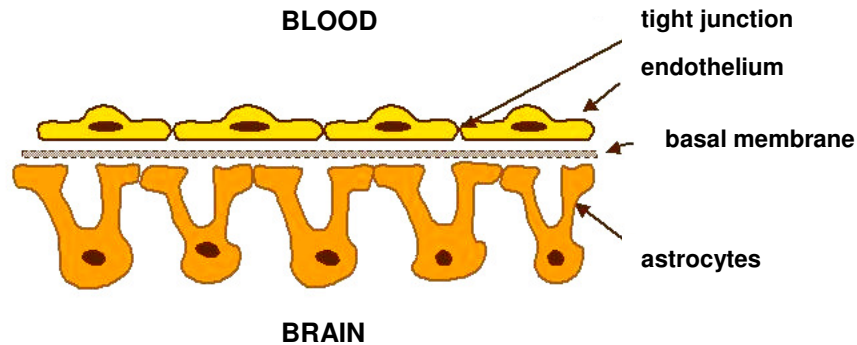
2.2. Blood-CSF barrier

The blood-CSF barrier separates blood from cerebrospinal fluid. It consists of ***epithelium of choroid plexus*** that secretes the CSF. The epithelial cells are connected with tight junctions. On the CSF side they form microvilli, which substantially increase the epithelium surface. In the choroid plexus a simple diffusion, facilitated diffusion and active transport to the CSF, but also transport from CSF to circulation, take place. The ***capillaries of pia mater*** represent another part of blood-CSF barrier; they possess fenestrations and resemble capillaries from other parts of the body (Fig. 2). The blood-CSF barrier is more permeable than the blood-brain barrier in other regions and enables certain entry of proteins from plasma to CSF by pinocytosis and specific carriers. A disorder in the blood-CSF barrier manifests as an increased protein concentration in the CSF (see below albumin and immunoglobulins in the CSF).

Fig. 2: Blood-CSF barrier

BLOOD

fenestration

endothelium

basal membrane

choroid epithelial cells

CSF

tight junction
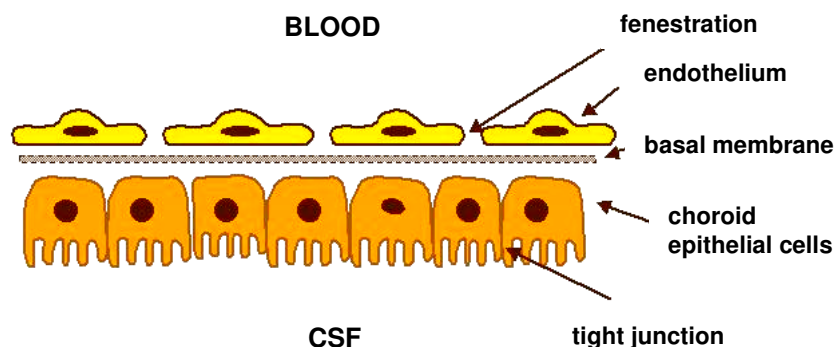
2.3. Brain-CSF barrier

The brain-CSF barrier consists of a layer of glial fibers on the brain surface, together with ependyme of cerebral ventricles. This interface is more permeable than the blood-CSF barrier. Passage of substances takes place through slits in the glial layer and among the ependymal cells. Particles of up to protein size can diffuse in both directions.

3. Examination of cerebrospinal fluid

Examination of CSF is one of basic approaches contributing to diagnostics of neurological disorders. The CSF is taken most often by lumbar puncture (3x5 ml, between L4-L5 or S1); the suboccipital approach is less common. The CSF sample must be delivered to the laboratory as soon as possible, because upon standing the cells break down, glucose concentration decreases while lactate increases.

The examination includes *assessment of physical properties* (color, turbidity), *chemical examination* (total protein, glucose, lactate, albumin, IgG, IgA, IgM and other proteins), *spectrophotometry and cytological examination*.

The *basic examination of CSF* consists of these analyses:
- assessment of CSF appearance;
- quantitative estimation of total protein;
- quantitative estimation of lactate;
- qualitative and quantitative cytological examination;
- spectrophotometry of CSF.

Further examination of CSF includes:
- estimation of IgG, IgA, IgM and albumin in serum and CSF with assessment of intrathecal synthesis of immunoglobulins and degree of blood-CSF barrier impairment;
- isoelectric focusing for detection of oligoclonal bands of IgG;
- some other examinations, such as measurement of other proteins in CSF and serum, special staining of cytological preparations.

The CSF is *examined especially in these diseases*:
- suspect acute neuroinfection;
- suspect subarachnoid bleeding;
- demyelinisation diseases;
- malign infiltration of meninges.

4. Physical examination of cerebrospinal fluid

4.1. Color

Under physiological condition the CSF is a clear colorless liquid. Any presence of colored substances in CSF is pathological. A color is most often caused by presence of hemoglobin, methemoglobin or bilirubin. Admixture of blood results in slight rose to red color, denoted as *erythrochromic (sanguinolent)* appearance of CSF. The blood can contaminate the CSF sample artificially due to damaged local blood vessels during the lumbar puncture. In this case, if the CSF is taken subsequently to three test tubes, the color tends to weaken from one tube to another. Also, the blood color can be removed by centrifugation of the CSF sample. In contrast, in intracranial bleeding the color of CSF should be the same in all test tubes, and should resist the centrifugation, although in a very fresh bleeding the supernatant can still be colorless. A yellow *xanthochromic* color of CSF is due to presence of bilirubin originating from catabolism of hemoglobin (older bleeding). The xanthochromy can persist up to 3 – 4 weeks since the bleeding episode (see below spectrophotometry of CSF). Presence of methemoglobin manifests as ochre yellow to brown color.

4.2. Turbidity

The CSF sample is cloudy usually due to presence of **leukocytes**, which appear in the CSF in **purulent neuroinfections**. Intensity of the turbidity is proportional to amount of leukocytes. **Presence of erythrocytes** can also manifest as turbidity.

5. Chemical examination of cerebrospinal fluid

5.1. Total protein in CSF

The CSF contains about 200-fold less protein than blood plasma. About **80 %** of the CSF proteins **come from plasma**. The entry of proteins to the CSF is affected by their molecular weight, charge, plasmatic concentration and condition of the blood-brain barrier. Larger molecules (e.g. IgM) travel more slowly than smaller ones (e.g. IgG, albumin). The remaining **20 % of proteins is produced intrathecally[1]** (e.g. part of immunoglobulins, β_2-microglobulin). Some plasmatic proteins are modified in the CSF areas (e.g. transferrin, prealbumin). In minimal amounts also **structural proteins** are found in the CSF.

From a clinical point of view, an increase in total protein in CSF, called **hyperproteinorachia**, is significant. It can be caused by the following mechanisms:

- **If the blood-CSF barrier is impaired**, passage of proteins to the CSF is pathologically high. An obstruction of CSF pathways results in a severe damage to the blood-CSF barrier downstream of the blockade and proteins from plasma enter the CSF (albumin as well as high-molecular-weight fibrinogen).
- **Intrathecal synthesis of immunoglobulins** in activation of immune system.
- **Abnormal spectrum of serum proteins** will project also to the CSF, for instance monoclonal gammapathy results in presence of the same immunoglobulins in CSF.
- **Elevation of structural proteins** due to injury of CNS tissues.
- **Tumor infiltration of meninges**

Estimation of total protein in CSF is useful mainly as a quickly accessible test providing basic information on the condition of blood-CSF barrier.

One of the recommended assays for quantitative estimation of total protein in CSF is the **reaction with pyrogallol red** (see the measurement of protein in urine).

A preliminary qualitative information on whether the CSF protein is increased can be provided by the **Pandy's reaction,** in which globulins and in part also albumin are denatured by the aqueous solution of phenol.

Physiological values:

Sp[2] - Total protein (proteinorachia) **0.20 – 0.45 g/l**

Pandy's reaction: negative (protein < 0.2 g/l)

5.2. Albumin in CSF

The entire albumin found in CSF has to come from blood, because albumin is not formed in the CNS. Rather, it is synthesized in the liver and enters the CSF via passage through blood-CSF barrier. Albumin represents about 57 % of total CSF protein. An **increased concentration of albumin in CSF** always means a disorder in blood-CSF barrier. For a more detailed evaluation of

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[1]Intrathecal synthesis means synthesis within CNS and structures filled with CSF.

[2] Sp – cerebrospinal fluid

the blood-CSF barrier condition an **albumin quotient Q_{alb}** is used. It takes into account concentration of albumin in CSF (Alb_{CSF}) and in serum (Alb_{serum}).

$$Q_{alb} = \frac{Alb_{CSF}}{Alb_{serum}}$$

The albumin quotient is used for:

- assessment of blood-CSF barrier impairment,
- calculation of intrathecal synthesis of immunoglobulins.

Pathological increased values of albumin quotient are found due to impaired blood-brain barrier, which may occur in inflammatory diseases of CNS (meningitis of various etiology), multiple sclerosis or an obstruction in the CSF pathways.

Albumin in the CSF is measured by **sensitive immunochemical assays** (immunoturbidimetry, immunonephelometry, ELISA).

Physiological values:

Sp-albumin: **120 – 300 mg/l**

Albumin quotient Q_{alb} depends on age:

up to 15 years of age $\leq \mathbf{5 \times 10^{-3}}$
up to 40 years of age $\leq \mathbf{6.5 \times 10^{-3}}$
up to 60 years of age $\leq \mathbf{8 \times 10^{-3}}$

5.3. Immunoglobulins in CSF

Immunoglobulins in CSF can either **come from blood**, or they are **produced intrathecally**. The intrathecal synthesis of antibodies is performed by perivascularly localised B lymphocytes that differentiate to plasmocytes. An increase in CSF concentration of immunoglobulins may be caused by a disorder of blood-CSF barrier, an increased intrathecal synthesis, an elevated immunoglobulin level in plasma, or impairment of CSF circulation. For this reason, a mere estimation of CSF concentration of immunoglobulins is usually insufficient as for differential diagnosis it is necessary to distinguish between intrathecal and plasmatic origin of immunoglobulins. Various indexes or graphs are employed for this purpose.

Demonstration of intrathecal synthesis of immunoglobulins

Immunoglobulin index

Preliminary information can be provided by the **immunoglobulin index**. It evaluates together immunoglobulin and albumin levels in the serum and CSF. For its calculation both analytes must be measured simultaneously in the serum and CSF. The calculation is based on relating a quotient for a particular immunoglobulin (IgG, IgA, IgM) to the albumin quotient.

$$IgG_{index} = \frac{Q_{IgG}}{Q_{albumin}} = \frac{IgG_{CSF}}{IgG_{serum}} \times \frac{Alb_{serum}}{Alb_{CSF}}$$

Reiber's diagram

The Reiber's diagram enables a rapid evaluation of intrathecal synthesis of immunoglobulin. The calculated Q_{IgG} is plotted against Q_{Alb} (Fig. 3) The position of the resulting value allows assessment both of the origin of immunoglobulins and condition of the blood-CSF barrier.

Fig. 3: Reiber's diagram
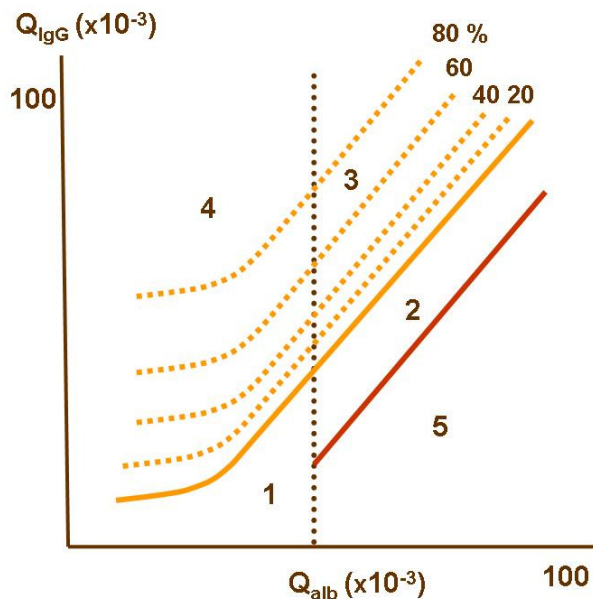
The Reiber's diagram is divided to 5 areas that correspond to the following findings:

1. normal condition

2. isolated blood-CSF barrier disorder without local synthesis of Ig

3. blood-CSF barrier disorder together with intrathecal synthesis of Ig

4. isolated intrathecal synthesis of Ig without blood-CSF barrier disorder

5. region of analytical errors

The transition between local synthesis of immunoglobulins and their passive entry is marked with the thick yellow line. Values above this line mean an intrathecal synthesis whose degree can be read from % values associated with the dotted lines.

The particular immunoglobulin classes are estimated by ***sensitive immunochemical assays*** such as immunoturbidimetry, immunonephelometry, and ELISA.

Physiological values:

Concentration of immunoglobulins:

Sp-IgG	**12 – 40 mg/l**
Sp-IgM	**0.2 – 1.2 mg/l**
Sp-IgA	**0.2 – 2.1 mg/l**

Evaluation of immunoglobulin index:

|		
IgG_{index}	**< 0.5**	**does not suggest intrathecal synthesis of IgG**
IgG_{index}	**0.5 – 0.75**	**does not exclude intrathecal synthesis of IgG**
IgG_{index}	**> 0.75**	**suggests intrathecal synthesis of IgG**

5.4. Oligoclonal immunoglobulins in CSF

The most sensitive technique for demonstration of intrathecal synthesis of antibodies is estimation of *oligoclonal immunoglobulins* by means of *isoelectric focusing[3]* followed by *staining*, *immunofixation* or *immunoblotting*. Physiologically, immunoglobulins both in serum and CSF are polyclonal, which reflects heterogeneity of individual antibodies produced in response to various antigens encountered during the whole lifetime. It is assumed that under conditions activating intrathecal synthesis of immunoglobulins, only a limited number of B lymphocytes enter the brain following activation with an antigen (certain microorganism or an autoantigen) and differentiate into plasmatic cells secreting antibodies. Therefore, heterogeneity of intrathecally made antibodies is limited, i.e. they are oligoclonal, which is seen on isoelectric focusing as isolated bands, not apparent in analysis of serum. Accordingly, it is necessary to analyze simultaneously immunoglobulins both in CSF and in serum. For evaluation, presence or absence of identical bands of IgG in CSF and serum is compared; while number and position of bands is insignificant for differential diagnosis.

Five different types of electrophoreograms can be described (Fig. 4):
Type 1)   both serum and CSF contain *only polyclonal IgG* - normal finding;
Type 2)   *oligoclonal bands only in CSF* - local synthesis of IgG (e.g. in multiple sclerosis[4])
Type 3)   *oligoclonal bands in CSF and further oligoclonal bands that are both in CSF and serum* - local synthesis of IgG and production of antibodies in the whole organism (e.g. chronic infection of CNS, multiple sclerosis;
Type 4)   *identical oligoclonal bands in serum and CSF* ("mirror image" of bands in serum and CSF) - antibodies penetrate from blood to CSF, systemic immune activation without local synthesis of IgG in the CNS;
Type 5)   *paraprotein pattern* - identical monoclonal bands both in serum and CSF in a short region of pH gradient, it indicates presence of monoclonal paraprotein in CSF of serum origin (myeloma, monoclonal gammapathy).

Fig. 4: Basic types of isoelectrophoreograms

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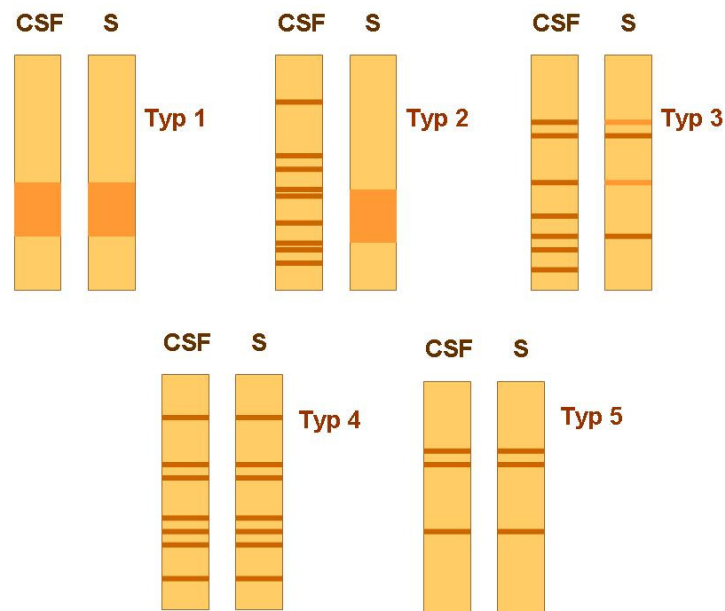
[3] Isoelectric focusing is an electrophoretic technique that employs a pH gradient and separates proteins on the basis of their isoelectric points
[4] Multiple sclerosis (sclerosis multiplex) is a severe chronic disease of CNS, in which demyelinisation (loss of myelin of nervous fibers) occurs due to an autoimmune process. In dependence on localization of the pathological changes various neurological symptoms arise, such as disorders of walk, perception and speech.

5.5. Glucose in CSF

Glucose is the main energy source for the nervous tissue and its uptake to the brain is facilitated by transport systems in the choroid plexus. Concentration of glucose in the CSF is given by capacity of the transport systems, utilization in the nervous tissue and extent of reabsorption in the CSF. Concentration of glucose in the CSF - **glycorachia** follows concentration of glucose in blood. Therefore, in order to assess glycorachia it is necessary to estimate both serum and CSF concentrations and calculate their ratio Q_{glu}, in the same manner as in examination of albumin and immunoglobulins:

$$Q_{glu} = \frac{Glu_{CSF}}{Glu_{serum}}$$

Under physiological condition the ratio between glycorachia and glycemia is approximately 0.6, values below 0.45 are considered pathological.

Elevated glycorachia is found in diabetics. For diseases of the nervous system rather decreased values of **glycorachia - hypoglycorachia** (if hypoglycemia is excluded) are significant. They in general occur in CSF containing high numbers of cells. Hypoglycorachia is found in **bacterial meningitis**, where it is explained by consumption of glucose both by bacteria and leukocytes ($Q_{glu}<$ 0.4). It can fall to zero values. Successful treatment returns glycorachia to normal values. Another cause of decreased concentration of glucose in CSF can be a **tumor disease of CNS**, where glucose is utilized by the tumor cells, and **brain ischemia**, where lack of oxygen limits aerobic glycolysis and in order to produce equivalent energy by anaerobic glycolysis more glucose is needed. In **subarachnoid bleeding** the red blood cells are responsible for a high consumption of glucose.

Methods for measurement of glucose concentration in the CSF are analogous to glucose estimation in blood (plasma), i.e., the **glucose oxidase/peroxidase** or **hexokinase** methods can be used (see estimation of glucose in serum). If glucose cannot be measured within 30 minutes from sample collection, the CSF sample either must be kept on ice or sodium fluoride must be added, in order to prevent undesirable decrease in glucose due to glycolysis, which can take place in microorganisms, leukocytes or tumor cells that all may appear in CSF under pathological condition.

Physiological values: Sp-Glucose   **2.2 – 4.2 mmol/l**
Q_{glu} **0.6**

5.6. Lactate in CSF

Lactate originates from breakdown of glucose under anaerobic condition. Even healthy brain tissue forms certain amount of lactate that reflects brain metabolic activity. Lactate does not pass the blood-brain barrier and, unlike glucose, its **concentration is independent of its concentration in plasma**. The CSF levels of lactate and glucose tend to move in opposite directions.

Measurement of lactate in CSF is a more sensitive marker than estimation of glucose. Lactate is an important parameter that helps to distinguish between meningitis of bacterial or viral origin. **Elevated lactate in bacterial meningitis** is due to anaerobic glycolysis of bacteria and to a lesser extent, also of leukocytes. Effective therapy normalizes the lactate levels. All **disorders of brain blood supply** (e.g. anoxia, hypoxia in stroke episodes) bring about increased anaerobic metabolism of glucose and are accompanied with increased lactate levels. In subarachnoid bleeding the elevation of lactate is caused by erythrocytes that obtain energy also from anaerobic glycolysis (red blood cells lack mitochondria). Next, lactate also rises in malign infiltration of meninges and in some metabolic diseases, such as mitochondrial encephalomyopathies.

Lactate in CSF is estimated by an enzymatic spectrophotometric method based on the Warburg optical test.

Physiological values: Sp - lactate **1.2 – 2.1 mmol/l**

5.7. Chlorides in CSF

Concentration of chlorides in CSF is usually about 124 mmol/l. A decrease below 100 mmol/l together with low glucose suggests a tuberculosis or mycotic infection of the CNS.

6. Spectrophotometry of cerebrospinal fluid

Spectrophotometry of CSF is used in diagnostics of brain stroke, especially in cases of suspect *bleeding to subarachnoid space.* It is important mainly in the types of brain hemorrhage that are difficult to see by imaging methods. In particular it is valuable in early stages of the disease. It provides information on time period since the bleeding episode, as well as whether the bleeding has been protracted or recurrent. Spectrophotometric examination of CSF makes use of different maxims in the visible region for *oxyhemoglobin* (at 415 nm), *methemoglobin* (at 405 nm) and *bilirubin* (at 420 − 460 nm).

At the beginning of brain hemorrhage the CSF contains mostly oxyhemoglobin, in the later stages spectrophotometry yields a summation spectra of oxyhemoglobin/methemoglobin and bilirubin. The rate of hemoglobin degradation to bilirubin displays a high individual variability, but isolated bilirubin xanthochromia in general does not appear earlier than 5 days after bleeding.

Spectrophotometry of CSF is performed on a scanning spectrophotometer in the wavelength range 370 − 600 nm. It is recommended to centrifuge the CSF sample within one hour since its collection.

Evaluation:

Physiological trace

Spectrophotometric trace of normal CSF is flat or slightly rising in the direction from 600 nm to 370 nm. The absorbance values in the visible region are less than 0.02.

Pathological traces

- **Detection of oxyhemoglobin**

    Erythrocytes that appear in the brain ventricles or subarachnoid space start to undergo hemolysis about 2 hours later and the released hemoglobin gives rise to absorption maxims typical for oxyhemoglobin. The presence of oxyhemoglobin in CSF manifests as a big maximum at 415 nm and two minor peaks at 540 and 577 nm. Its detection in CSF is a sign of *recent brain hemorrhage*. Its concentration peaks around 4 − 5 days; disappears after 7 − 10 days (Fig. 5). The same trace can however be obtained also in case of artificial contamination of CSF with blood, if the CSF sample is not centrifuged early after collection.

- **Detection of methemoglobin**

    Presence of methemoglobin results from fairly *long-lasting changes of hemoglobin*. Maximum at 415 nm is blue-shifted to 406 nm. Methemoglobin is found as a component of complex summation traces where absorbances of particular pigments overlap. It can be differentiated by addition of KCN: if methemoglobin is present, cyanmethemoglobin appears with an absorption maximum at 419 nm, if methemoglobin is absent, this change does not occur. Demonstration of methemoglobin together with oxyhemoglobin proves that presence of blood in CSF is caused by brain hemorrhage, rather than by an artificial contamination during lumbar puncture.

Fig. 5: Spectrophotometric trace of oxyhemoglobin (e.g. recent subarachnoid hemorrhage)
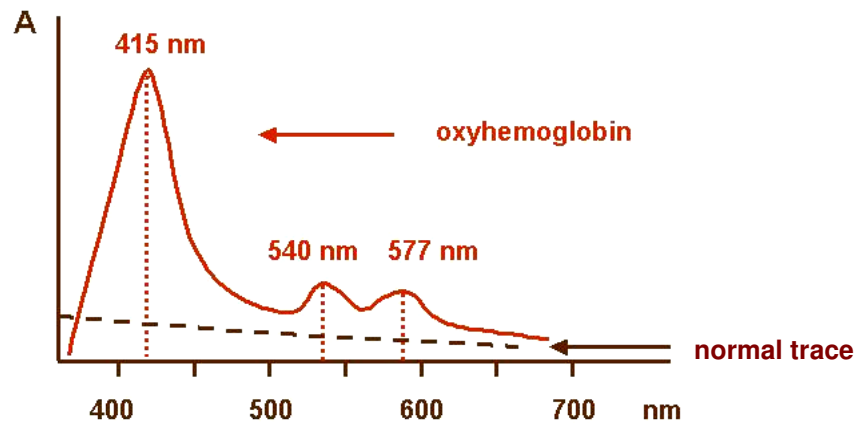
- **Detection of bilirubin**

Presence of bilirubin indicates an ***older bleeding to CSF pathways***, where bilirubin is formed as a product of degradation of hemoglobin released from hemolysed red blood cells. The hemolysis of red blood cells yields **non-conjugated bilirubin** with absorption maximum at 460 nm (so called long bilirubin). It appears in the CSF about $10 - 12$ hours after bleeding, maximum is recorded the third day, and it persists $3 - 4$ weeks.

A typical spectrophotometric trace confirming the subarachnoid hemorrhage displays a spectrum of oxyhemoglobin with the main peak at 415 nm, which on its shoulder bears another broad peak of bilirubin (Fig. 6). Gradually, as the hemolysis of red blood cells continues, the ratio of oxyhemoglobin to bilirubin decreases with time. Bilirubin in CSF can later become conjugated with free fatty acids and amino acids. The conjugated bilirubin has its spectral maximum shifted to about 420 nm (so called short bilirubin). The spectrum of isolated bilirubin cannot be observed earlier than on the 5th day after subarachnoid bleeding (Fig. 7).

There is also a possibility of passage of bilirubin from serum, through immature blood-brain barrier, which physiologically occurs in the newborn, or through a damaged blood-brain barrier in adults with concurrent high serum bilirubin. Conjugated bilirubin in CSF is most often of serum origin.

Fig. 6: Summation spectrophotometric trace of oxyhemoglobin and bilirubin (e.g. older subarachnoid hemorrhage - conversion of hemoglobin to bilirubin)
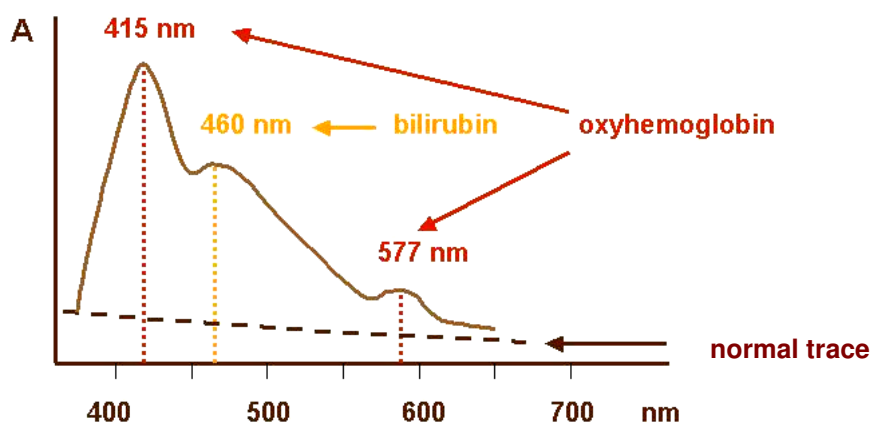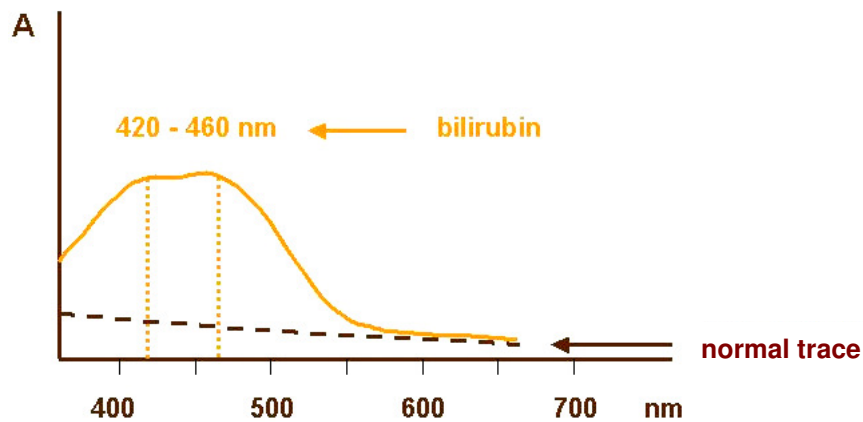
Fig. 7: Spectrophotometric trace of bilirubin (late stage of subarachnoid hemorrhage)

7. Cytological examination of cerebrospinal fluid

Cytological examination is part of basic examination of CSF, contributing to diagnostics of neuroinfections, bleeding to CNS, autoimmune diseases and tumors. It encompasses *quantitative cytology*, which estimates number of cellular elements, and *qualitative cytology*, which focuses on differentiation of various types of cells in the CSF and their numbers.

The cells are counted in the Fuchs-Rosenthal chamber, which has volume approximately 3 mm^3. That is why the results are expressed as fractions n/3. Erythrocytes are counted in native preparation, whereas for the other elements a staining is used.

In the CSF of an adult person up to 10/3 (3 cells per 1 μl) is found; values 11 – 15/3 are considered as borderline. The normal number of cells is denoted as *oligocytosis,* in cases of elevated cell numbers we talk about *pleocytosis.*

In the qualitative evaluation, normal CSF contains only lymphocytes (60 – 80 %) and monocytes (20 – 40 %), rarely some ependymal or choroid plexus cells can occur as well. Presence of red blood cells can be due to artificial injury to a blood vessel during lumbar puncture, or it can indicate a hemorrhage to the liquor pathways. Presence of other cells (granulocytes, activated lymphocytes, plasmatic cells, activated monocytes, tumor cells) is also a sign of pathological process in the CNS.

Some types of pathological CSF findings

Pleocytosis
   a) *Monocytic*
      Monocytic cells prevail and presence of their activated forms is increased. They represent a non-specific reaction to previous irritation of the nervous system (e.g. ischemia of CNS, terminal stage of inflammation with 'cleaning reaction', condition after CNS angiography).

   b) *Granulocytic*
      A marked increase in *neutrophilic granulocytes* (thousands to tens of thousands) is a hallmark of *purulent (bacterial) inflammations*. Dominance of eosinophils occurs in allergic reactions or certain neuroinfections (parasitic, mycotic).

   c) *Lymphocytic*
      Pleocytosis with majority of lymphocytes including their activated forms is indicative of *non-purulent inflammatory disease of viral origin*, but can also be seen in some bacterial neuroinfections.

Pathological oligocytosis (total number of elements is within normal range, but the spectrum of cells is pathological)

a) *Monocytic*
   Displays a dominance of monocytes and relatively increased occurrence of their activated forms. This **non-specific finding** can accompany for instance bleeding to the CSF pathways, when macrophages with ingested erythrocytes can be seen, or a terminal stage of an inflammation.

b) *Granulocytic*
   Granulocytic oligocytosis with majority of neutrophils is a common finding in **starting purulent as well as non-purulent neuroinfection**.

c) *Lymfocytic*
   Characteristic by dominance of lymphocytes with relatively increased occurrence of their activated forms. Presence of plasmatic cells suggests an intrathecal synthesis of antibodies. This is typical for **chronic neuroinfections and multiple sclerosis.**

Tumorous pleocytosis or oligocytosis: Tumor elements in the CSF come from tumors localized close to the CSF pathways or from malign infiltration of the meninges.

CSF syndromes

Interpretation of number of cells in CSF together with total CSF protein allows description of the following syndromes:

   Syndrom of proteinocytological dissociation – increased concentration of total protein (hyperproteinorachia) and normal number of elements (oligocytosis) – finding typical for blockade of CSF pathways e.g. by tumor, sometimes seen in multiple sclerosis and terminal phase of inflammation.

   Syndrom of proteinocytological association – increased concentration of total protein (hyperproteinorachia) and high number of elements (pleocytosis). Typically occurs in neuroinfections.

   Syndrom of cytoprotein dissociation – increased number of elements (pleocytosis) and normal protein (normoproteinorachia) – common finding in the initial phase of inflammation.

Differential diagnosis of typical CSF findings in some common infectious diseases of CNS:

	Number of cells and type	Total protein	Glucose	Chlorides	Cultivation
Acute bacterial meningitis	500-20,000/µl (neutrophils)	↑↑	↓ to ↓↓	normal	+
Acute viral meningitis	50-1,000/µl (lymphocytes, monocytes)	(↑)	(↓)	normal	(+)
Chronic CNS infection	↑↑ (lymphocytes, monocytes)	↑↑	↓↓	normal	
TBC	50-1,000/µl (monocytes, neutrophils)	↑↑	↓↓	↓	+
Viral encephalitis	5-100/µl (monocytes)	(↑)	normal	normal	-

(According to: Lobovská, A.: *Infekční nemoci*. Praha, Karolinum 2002, s. 36)