Proteins in cerebrospinal fluid

Pathological changes in proteinorachia:

From a clinical point of view, the increased concentration of total protein in cerebrospinal fluid, so-called **hyperproteinorachia**, which can be caused by several mechanisms, is important:

- When *the blood-brain barrier is broken*, a larger amount of protein penetrates pathologically into the cerebrospinal fluid. When the cerebrospinal fluid pathways are blocked, a severe blood-brain barrier breakage occurs and plasma proteins (albumin and high-molecular-weight fibrinogen) enter the fluid.
- *Intrathecal synthesis of immunoglobulins* when the immune system is activated.
- *The abnormal composition of plasma proteins* is reflected in the composition of cerebrospinal fluid proteins, eg monoclonal gammopathy is manifested by the presence of the same immunoglobulins in cerebrospinal fluid.
- *Increased structural proteins* in CNS tissue damage.
- *Tumor infiltration* of the meninges.

The determination of total protein in cerebrospinal fluid is used primarily as a rapidly feasible examination, which provides basic information about the state of the blood-brain barrier.

Methods for determination of protein in cerebrospinal fluid:

- One of the recommended methods for the quantitative determination of total protein in cerebrospinal fluid is *the reaction with pyrogallol red.*
- As a guide, a qualitatively increased amount of protein in the cerebrospinal fluid can be demonstrated by the *Pandy reaction*, in which globulins and partly also albumin are denatured with an aqueous phenol solution.

Reference values:

- Sp-Total protein (proteinorachia): **0,20–0,45 g/l**
- Pandy reaction: **negative** < 0,2 g/l of protein

Albumin in cerebrospinal fluid

Albumin in cerebrospinal fluid always comes from the blood, because it is not formed in the CNS. Its synthesis takes place in the liver and enters the cerebrospinal fluid by crossing the blood-brain barrier. Albumin accounts for about 57 % of the total protein in CSF. Elevated cerebrospinal fluid albumin levels are always a sign of a blood-brain barrier disorder.

For a more accurate assessment of the barrier condition, the so-called ***albumin quotient*** Qalb is used, which takes into account the concentration of albumin in cerebrospinal fluid (AlbCSF) and serum (Albserum):

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

Albumin quotient is used:

- To assess the degree of involvement of the blood-brain barrier;
- For the calculation of intrathecal immunoglobulin synthesis.

Pathological values of albumin quotient:

- An increase in Qalb is found in a damaged blood-brain barrier, which we encounter in inflammatory diseases of the CNS (meningitis of various origins), multiple sclerosis or obstruction in the cerebrospinal fluid.

Methods for determination of albumin:

- Albumin is determined in the CSF by sensitive immunochemical methods (immunoturbidimetry, immunonephelometry, ELISA).

Reference values:

- Sp-Albumin: **120–300 mg/l**
- Albumin quotient – Q_{alb} (depends on age):

  up to 15 years: ≤ $\mathbf{5\times10^{-3}}$
  up to 40 years: ≤ $\mathbf{6{,}5\times10^{-3}}$
  up to 60 years: ≤ $\mathbf{8\times10^{-3}}$

Immunoglobulins in cerebrospinal fluid

Immunoglobulins in cerebrospinal fluid can either come from the blood or arise *intrathecally*. Intrathecal synthesis of immunoglobulins takes place in perivascularly deposited B-lymphocytes, which differentiate into plasma cells.

Pathological changes in immunoglobulin concentration:

The increase in the concentration of immunoglobulins in cerebrospinal fluid may be due to:

- Blood-brain barrier disorder;
- Increased intrathecal synthesis;
- Increased serum immunoglobulin levels;
- Cerebrospinal fluid circulation disorder.

Methods for determination of immunoglobulins:

Individual classes of immunoglobulins are determined by more sensitive immunochemical methods such as immunoturbidimetry, immunonephelometry and ELISA.

Reference values:

- Immunoglobulin concentrations in cerebrospinal fluid:

  Sp-IgG: **12,0–40,0 mg/l**
  Sp-IgM: **0,2–1,2 mg/l**
  Sp-IgA: **0,2–2,1 mg/l**

Demonstration of intrathecal immunoglobulin production

Determination of the concentration of immunoglobulins in cerebrospinal fluid alone is insufficient, as it is necessary to distinguish the intrathecal or blood origin of immunoglobulins for differential diagnostic purposes. For this, the calculation of various indices, equations or evaluations using graphs is used.

Immunoglobulin index

- *The immunoglobulin index* provides us with indicative information. It evaluates immunoglobulins and albumin in serum and in cerebrospinal fluid. To calculate it, it is necessary to determine the concentrations of both analytes in the cerebrospinal fluid and at the same time in the serum. It is calculated on the basis of the quotient of the relevant immunoglobulin (IgG, IgA, IgM) and the albumin quotient.

$$IgG_{index} = \frac{Q_{IgG}}{Q_{alb}}$$

$$IgG_{index} = \frac{IgG_{CSF}/IgG_{sérum}}{Alb_{CSF}/Alb_{sérum}}$$

Reference values:

- Immunoglobulin index IgG:

  IgG index: **< 0,5 does not indicate intrathecal IgG synthesis**
  IgG index: **0,5–0,75 does not rule out intrathecal IgG synthesis**
  IgG index: **> 0,75 indicates intrathecal IgG synthesis**

Reiber diagram

Reiber diagram allows rapid demonstration of intrathecal immunoglobulin synthesis. The calculated values of QAlb and QIgG are output to it. According to the location of the plotted value in the graph, the origin of immunoglobulins and the disorder of the blood-brain barrier can be determined.

Evaluation:

Reiber diagram (picture 3) is divided into **5 regions**, that define the findings:

- **Region 1** – normal finding;
- **Region 2** – an isolated disorder of the blood-brain barrier without local synthesis of Ig;
- **Region 3** – blood-brain disorder together with intrathecal Ig synthesis region 3;
- **Region 4** – isolated intrathecal Ig synthesis without blood-brain barrier disorder;
- **Region 5** – an area of analytical errors.

The boundary between local immunoglobulin synthesis and their passive transfer is shown by the blue line. Values above this line indicate intrathecal synthesis and the range is indicated by a dashed line and expressed as a percentage. A vertical dashed line separates the normal and disrupted hematoliquor barrier.

🔎 *For more information see Reiber diagram.*

Oligoclonal immunoglobulins in cerebrospinal fluid

The most sensitive method for detecting intrathecal antibody synthesis is the determination of oligoclonal immunoglobulins by isoelectric focusing followed by staining or immunofixation or immunoblotting.

Physiologically, immunoglobulins in serum and cerebrospinal fluid are polyclonal in nature and express the heterogeneity of individual antibodies produced in response to a variety of antigens encountered by an individual.

It is believed that only a limited number of B-lymphocytes enters the CNS, which, upon activation by an antigen (eg, a particular microorganism or autoantigen), differentiate into antibody-secreting plasma cells. Intrathecally produced antibodies show only limited (oligoclonal) heterogeneity, which in isoelectric focusing appears as isolated bands that are not apparent in the serum analysis. This implies the need to perform cerebrospinal fluid and serum immunoglobulin analysis at the same time. The presence or absence of identical IgG bands in serum and fluid is compared; the number and location of the strips have no differential diagnostic significance.

Evaluation:

Five different types of isoelectrophoregrams are described (picture 4):

Type 1 – either in serum and in cerebrospinal fluid only polyclonal IgG are presented – normal finding;

Type 2 – oligoclonal bands only in cerebrospinal fluid - local IgG synthesis (eg: multiple sclerosis);

Type 3 – oligoclonal bands in cerebrospinal fluid and other oligoclonal bands in cerebrospinal fluid and serum - local IgG synthesis and antibody production in the body (eg chronic CNS infection, multiple sclerosis);

Type 4 – identical oligoclonal bands in serum and fluid (so-called "mirror" image of bands in serum and cerebrospinal fluid - antibodies penetrate from the blood into the cerebrospinal fluid) - systemic immune activation without local IgG synthesis in the CNS;

Type 5 – identical monoclonal bands in serum and fluid in a short section of the pH gradient, it is the presence of a monoclonal paraprotein in cerebrospinal fluid of serum origin (myeloma, monoclonal gammopathy) – paraprotein image.

Links

- ws:Bílkoviny v mozkomíšním moku

Related articles

- Cerebrospinal fluid
- Biochemical examination of cerebrospinal fluid
- Cerebrospinal fluid spectrophotometry
- Cerebrospinal fluid cytology
- cerebrospinal fluid syndromes

External links

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