Hormones in cerebrospinal fluid after introduction of shunt to patients with hydrocephalus as possible predictors of the further disease development

Richard Hampl, Lucie Sosvorová, Milan Mohapl, Marie Bičíková

Institute of Endocrinology, Prague
Dpt Neurosurgery, Central Military Hospital, Prague
Hydrocephalus - definition

- **Hydrocephalus** belongs to severe brain diseases. It is generally accepted that it is a consequence of disbalance between formation and outflow of cerebrospinal fluid (CSF), formed in cells constituting plexus choroideus and circulating among brain chambers. CSF flows slowly towards subarachnoid space and is finally absorbed by venous sini.

- CSF is then accumulated in brain, where it squeezes and distorts soft brain tissues. As much as 500 ml/day CSF is formed in comparison to 150 ml in healthy subject, so that its turnover is about three times lower.
CSF and ISF in brain form a functional unit


Interstitial fluid (ISF) and CSF are formed by water filtration across walls of arterial capillars in CNS, while osmolytes from plasma are retained on the “sieve”, resulting in osmotic counterpressure, which supports absorption of ISF/CSF water to venous capillaries and postcapillary venules
Hydrocephalus - classification

- We usually distinguish hydrocephalus **acquired** and inborn (congenital).

- According to functions we distinguish two major types of hydrocephalus in adults: **obstructive** and **hyporesorption** (non-obstructive).

- **Obstructive form** is caused by obstruction preventing CSF from flowing into the subarachnoid space.

- **Hyporesorption form** is caused by impaired resorption of CSF to circulation.

- **Hyporesorption** hydrocephalus can be further divided to **hypertensive** and **normotensive**, typical for elder patients.
Diagnostics of acquired hydrocephalus

- Diagnosis is based first of all on imaging methods – sonography, computer tomography and magnetic resonance, enabling visualization of pathological changes in brain including eventual obstruction.

- Biochemical tests: important for prediction of further disease development.
Treatment of acquired hydrocephalus

• **Conservative**
  – Treatment by drugs decreasing formation of cerebrospinal fluid as e.g. acetazolamide or furosemide may temporarily mitigate disease symptoms and postpone operation

• **Surgical**
  – Introduction of a shunt
Shunt and further development of the disease

- Shunt is a tube connecting the ventricles of the brain to an alternative drainage site, usually the abdominal cavity. A shunt contains a one-way valve to prevent reverse flow of the fluid and enables to collect CSF for laboratory testing.

- The patient’s condition is usually improved and he or she is sent out home in a relatively very good state. Unfortunately the effect of the operation is not durable, the percentage of patients in which the improvement is recorded sinks to 64% after 3 months from the operation, and within 3 years to only 26%, while many of them develop dementia, mostly of Alzheimer’s type.
Ventriculo-peritoneal shunt between brain ventricles (chambers) and abdominal cavity
Composition of CSF from patient with hydrocephalus

- Low molecular compounds penetrating haematoencephalic barrier
  - nutrients,
  - substrates and intermediates of carbohydrate or lipid metabolism
  - amino acids and their metabolites
  - low molecular hormones (thyroid hormones, steroids, catecholamines)
  - some metabolites of arachidonic acid, especially 8-isoprostane – marker of oxidative stress, 9-hydroxyoctadecanoic acid, a product of LDL oxidation
  - some low molecular growth factors or interleukines

- Proteins – about 1% of the concentration occurring in plasma; it is enabled by the fact that several areas of the brain have "windows" or sections that do not have tight junctions
  - Immunoglobulins
  - Typical markers: leucine rich alpha-2 glycoprotein (LRG), alpha1-antichymotrypsin, apolipoprotein D, apolipoprotein J, haptoglobin alpha 1, serum albumin, alpha-1-microglobulin/bikunin
  - Characteristic protein markers of AD: vascular endothelial factor (VEGF), glial fibrilar acidic protein (GFAP), tau-proteins and their products (total tau protein, hyperphosphorylated tau protein), beta-amyloid and its precursor and fragments
Protein markers in CSF – possible prediction of the disease development?

- Concentration of amyloid beta (1-42) in CSF below 180 pg/ml, and
- Total concentration of tau protein below 767 pg/ml,

may predict development without deterioration 6 years after operation with acceptable sensitivity (80%) and specificity (82.4%)

Neuroactive steroids in CSF as potential markers of further development of the disease after introduction of shunt

**Steroids**
- Corticosteroids: glucocorticoids and mineralocorticoids
- DHEA/S and its precursor and metabolites (pregnenolone, pregS, 7-oxygenated metabolites)
- 5-Alphsa-saturated progesterone metabolites (e.g. Allopregnanolone)
- Estradiol

**Effects**
- Glycoregulation, immunosuppressive effects, regulation of hydrodynamic and osmotic homeostasis
- Immunoprotective, modulators of neurotransmitter receptors (GABA\(_A\)-R, NMDA-R, sigma-R), neuroprotective
- Modulators of GABA\(_A\)-R
- Neuroprotective
Corticosteroids in CSF and importance of 11beta-HSD

- The effect of corticoids via mineralocorticoid receptors consists in regulation of active sodium transport through Na+/K+ ATPase on the membrane of cells forming choroid plexus and thus maintaining osmotic homeostasis in brain chambers.
- Concentration of cortisol in circulation as well as in CSF is about by three orders of magnitude higher than aldosterone and since its affinity to mineralocorticoid receptors is only about ten times lower, cortisol acts as a mineralocorticoid.
- The balance between biologically active cortisol and inactive cortisone is provided by an enzyme 11beta-hydroxysteroid dehydrogenase (11beta-HSD), existing in two isotypes:
  - Type 1 acts as a reductase: by increasing actual (in situ) cortisol concentration
  - Type 2 on the other hand acts as an oxidase, by decreasing actual cortisol concentration

Both types were found in epithelial cells of choroid plexus.
- The cells constituting choroid plexus in brain are embryonally as well as functionally related to cells of neuroepithelial layer of ciliary body of the eye, where also 11beta-hydroxysteroid dehydrogenase is present.
Determination of cortisol/cortisone ratio in CSF reflects 11beta-HSD activity

• **Method:**
  – Extraction of CSF (1 ml), HPLC with prednisolone as an internal standard, u.v. detection at 245 nm
  – Method parameters: detection limit 0.5-1 nmol/l, repeatability: intraasay c.v. 3.7 and 7.6 for cortisol and cortisone, respectively
  – Values found: cortisol 10 – 30 nmol/l, cortisone 1 -15 nmol/l

• **Preliminary results:**
  – In 9 out of 10 so far investigated patients in which improvement of the state was recorded after 1 month from introduction of shunt the cortisol level sank and the ratio cortisol/cortisone decreased
Cortisol/cortisone ratio in CSF before and 1 month after shunt implementation
Suggested steroids and other analytes in CSF, successfully used as biomarkers for diagnosis of Alzheimer’s disease

**Analyte**
- DHEA and DHEAS
- Pregnenolone sulfate
- 7-Oxygenonated DHEA metabolites
- 16alpha-hydroxy DHEA
- Homocysteine
- Selected cytokines

**Reason**
- Altered levels in AD
- DHEA/S precursor
- Neuro- and immuno-protective, decreased in AD
- Potential antagonist of 7-oxygenated DHEA metabolites
- Significantly increased in AD
- Analogy to AD
Based on our recent experience with investigation of biochemical markers in CSF in Alzheimer’s dementia, we suggest that in patients with hydrocephalus, who later develop mental disorders, the changes of the above mentioned neurosteroids and homocysteine may appear, along with changes of cytokine composition and the cortisol/cortisone ratio.