Algorithm of CSF Diagnostics

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Modern and effective approach to CSF diagnostics: Multilevel model

LEVEL I.

Basic spectrum of lab examinations (locally performed urgent examinations)

LEVEL II.

Examinations performed in a specialised CSF laboratory (extended and specialised CSF diagnostics)

LEVEL I.

= basic prompt information regarding:

- Presence and type of basic pathological process in CSF
- Entering indications of specialised examinations for „Level II“
- Examinations from „Level I“ will be incorporated into the final complex laboratory report

Consecutive examinations in specialised CSF laboratory Topelex LEVEL II:

COMPLEX, MULTIDISCIPLINARY EXAMINATIONS:

A) Extended qualitative CSF cytology

B) CSF Proteinogram

-CSF barrier function, Immunoglobulins inc. IEF (OCB), structural proteins…

C) Immunological markers

- *Acute-phase proteins, cytokines, auto-antibodies*

D) Proof of microbial agents

-Specific antibodies, PCR …

COMPLEX INTERPRETATION OF LAB. RESULTS

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A) Extended CSF cytology

Transport of CSF cytological slides for consecutive 2nd reading, eventually specialised staining in laboratory Topelex…

Leading expert for CSF cytology:
Prof. Jaroslava Dušková, MD, PhD, FIAC

B) CSF Proteinology

Blood- CSF barrier function (Q Alb)
Immunoglobulins IgG, IgM, IgA, FLC

- **Calculation of i.t. synthesis rate…**
- **IEF /OCB of IgG, IgM, IgA, FLC kappa, lambda**

Structural proteins of CNS = identification of brain damage…

S100, NSE, Tau, 14-3-3, MBP, BTP…

AD: CSF triplet *Tau / P- Tau / AB*
CJD: *14-3-3 … NSE, Tau*
CSF leak: *Beta- Trace Protein*
Demyelination: *MBP*
Neural damage: *NSE*
Glial marker, melanom: *S100*

IsoElectric Focusing - IEF

Detection of OligoClonal Bands - OCB…

The most sensitive laboratory method:
Immunoblotting- IgG, IgA, IgM, FLC kappa, lambda

Results of the laboratory study in the file of 25.402 CSF:

samples with negative IgG:

IgM OCBs in CSF 17,88%
IgA OCBs in CSF 17,79%
FLC K OCBs in CSF 4,97%
FLC L OCBs in CSF 7,16%

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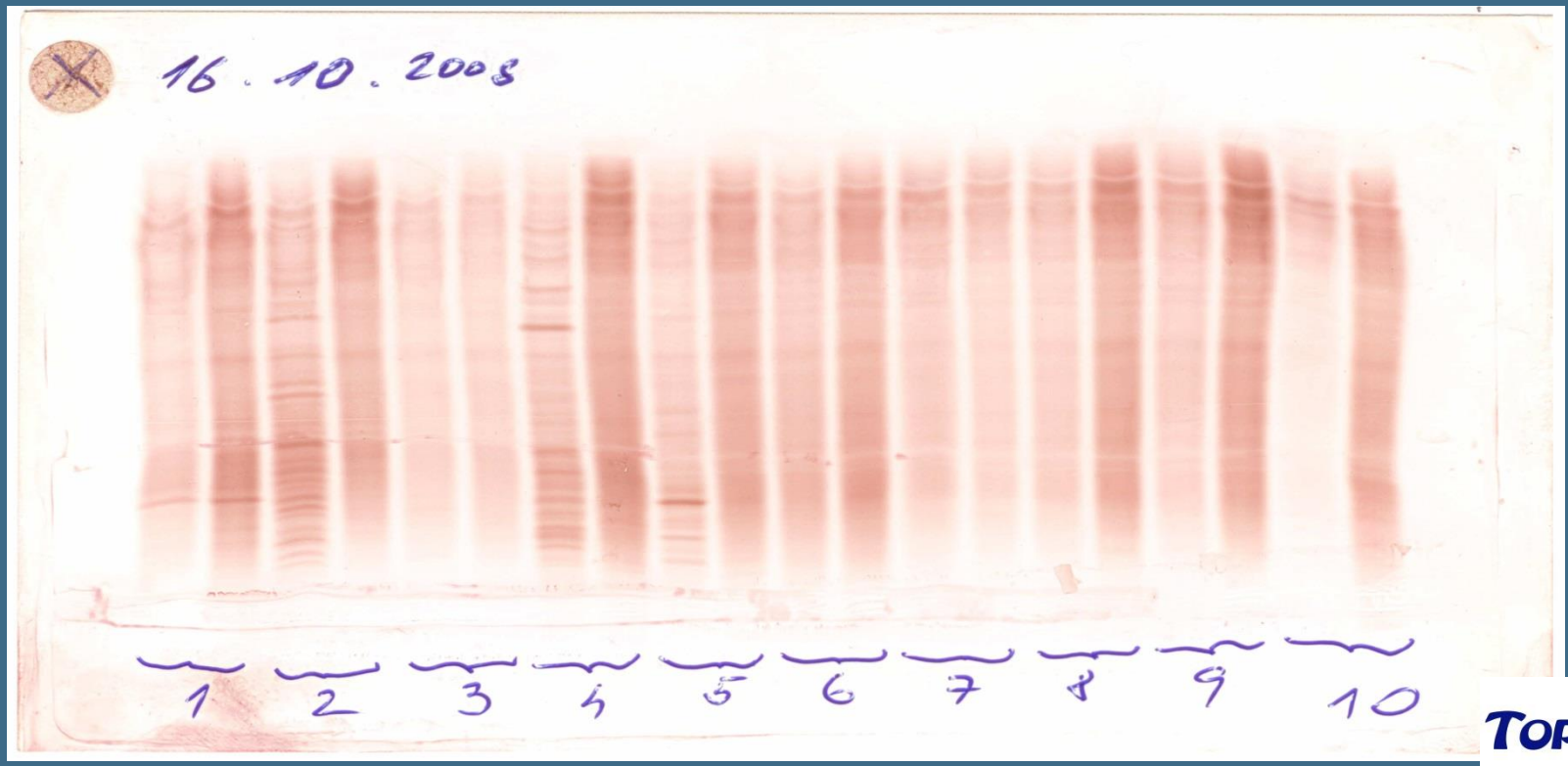
IEF

- I. Normal finding
- II. Intrathecal synthesis *(MS)*
- III. „More than pattern“ *(MS)*
- IV. Mirror pattern
- V. Monoclonal gamapathy



C) Immunological markers in CSF

Humoral inflammatory markers

- Differential diagnosis of infectious inflammation, activity of the inflammatory process

IL 6, IL1 – basic anti-inflammatory cytokines

IL 8 – chemokine

IL 10- anti-inflammatory cytokine

CXCL 13- neuroborreliosis

Acute-phase proteins: CRP, BMG, AAG, transferrin, prealbumin, haptoglobin …

Neural auto-antibodies

- Onconeural – paraneoplastic sy

- CLASSIC – intracellular Ag
  - Hu/ANNA-1, Ri, Yo, Ma2, amphiphysin…
- NEW - Membrane and receptor Ag
  - VGKC (LGI1, caspr-2), AMPA1, AMPA2, NMDAR, GABAB …

–Autoimmunne diseases

AQP 4 / *NMOSD ….(diff. Dg. Anti-* MOG, MBP)

GAG, MAG / *Inflammatory neuropathies*

Disorders of NM transmission (*MG, LEMS):* Titin, SOX1

D) Indirect detection of microbial agents in CSF- specific antibodies

- **! 2-step algorithm!**
- **Quantitative** determination by ELISA method NECESSARY to evaluate simultaneously in CSF+ Blood for i.t. synthesis calculation (Antibody Index- AI)
- **Qualitative** confirmation of the specificity: Western Blot- WB
- **Gold standard:**
  Borrelia, Treponema Pallidum, TBE…

Determination of intrathecal antibody synthesis

Calculation of Antibody Index (AI):

$$Antibody\_index = \frac{Q(IgX)_{SPEC}}{Q(IgX)_{TOTAL}}$$

Modification according to the Reiber‘s formula:

$Q(IgX)_{TOTAL} > Q_{lim(IgX)}$, inserting Q_{lim}

$$Q_{\lim(IgG)} = 0{,}93 * \sqrt{(Q_{alb})^2 + 6 * 10^{-6}} - 1{,}7 * 10^{-3}$$

$$Q_{\lim(IgM)} = 0{,}67 * \sqrt{(Q_{alb})^2 + 120 * 10^{-6}} - 7{,}1 * 10^{-3}$$

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D) Direct detection of microbial agents in CSF – PCR

! Preferred in acute phase !

Methodology of choice for diagnostics of infectious agents:

I) Before antibody production

!!! Herpetic viruses

!!! JC virus in immunosuppressed patients in suspected PML

II) Insufficient or hardly detectable antibody production

Borrelia, MEK *in early stage*

Enteroviruses

M. tuberculosis

Chlamydia, Mycoplasma, HHV6 …etc.

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Differrential Diagnostics in CSF

Inflammatory diseases of CNS/PNS
- infectious x autoimmune (MS !)

Tumorous impairment of NS
- infiltration of NS x Paraneoplastic NS

Destruction of CNS tissue
- neurodegenerative processes, dementia (CJD, AD)

Hemorrhage into CSF areas

CSF leak - BTP

Adequately indicated spectrum of CSF markers

+

Erudite and complex interpretation

= Highly Specialised CSF Laboratory !!!

Up to date approach to CSF diagnostics

- Urgent basic examinations- LEVEL I
- LEVEL II - Specialised CSF laboratory
- Mutual Communication clinician <-> laboratory
- Adequately indicated spectrum of CSF markers
- Erudite and complex interpretation of CSF finding

= correct, timely diagnosis

+ effective and economic therapy