

Interpretation of CSF Quantities with the Knowledge-Based System Pro.M.D.-Cerebrospinal Fluid Diagnostics*

Interpretation von Meßgrößen in der Liquoranalytik mit dem wissensbasierten System Pro.M.D.-Liquordiagnostik

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Summary: The clinical diagnosis of neurological diseases can be supported by the use of instructive, case-related reports for interpretation of CSF quantities. By using the knowledge-based system Pro.M.D.-cerebrospinal fluid diagnostics the process of clinical diagnosis can be optimized and standardized, as far as sensible. With the presentation of an exemplary case, the main features of the system are demonstrated.

Keywords: Expert Systems; Diagnosis, Computer-Assisted; Cerebrospinal Fluid.

Zusammenfassung: Mit Hilfe einer individuellen fallbezogenen Befunderstellung in der Liquoranalytik kann ein Beitrag zur Beantwortung differentialdiagnostischer Fragestellungen bei neurologischen Erkrankungen geleistet werden. Wie anhand eines Fallbeispiels gezeigt wird, ist es mit Unterstützung durch das wissensbasierte System Pro.M.D.-Liquordiagnostik möglich, den Befundungsprozeß zu verbessern und, soweit sinnvoll, zu standardisieren.

Schlüsselwörter: Expertensysteme; Diagnose, Computer-unterstützte; Liquor cerebrospinalis.

Analysis of cerebrospinal fluid is established for the early diagnosis of neurological diseases and differential diagnostic assessment [1-5]. Pathobiochemical characterization and interpretation of complex patterns in cerebrospinal fluid diagnostics require experience and special practical knowledge [6]. Furthermore the often demanded creation of case-related reports is a time-consuming procedure [7].

With the following example we want to demonstrate the optimization and standardization in the process of clinical diagnosis by the use of the knowledge-

based system Pro.M.D.-cerebrospinal fluid diagnostics.

Materials and methods

The knowledge-based system Pro.M.D.-cerebrospinal fluid diagnostics consists of two parts: the Pro.M.D. inference engine and the medical knowledge base, which contains the rules required for the interpretation [7-12].

On the base of prior studies performed by *Zerbe* et al. the knowledge-based system was extended and modified [1,2]. It consists of one main- and four sub-data bases (external modularisation). Besides the external modularization every data base is arranged clearly in knowledge sections (internal modularization).

Results

Structure of the knowledge-based system for interpretation of CSF data

Table 1 shows quantities used in the knowledge-based system.

Table 1 Quantities used in the knowledge-based system

Time and location of puncture
Total cell count, differential cell count, activated B-lymphocytes
Red blood cell count, hemoglobin
Xanthochromia
Lactate in CSF
Total protein in CSF
Albumin in CSF and serum
IgG, IgA, IgM in CSF and serum
Oligoclonal IgG in CSF
Virus-specific antibodies to:
Herpes simplex virus, varicella-zoster virus, mumps virus, rubella virus, toxoplasma, cytomegalovirus, <i>Borrelia burgdorferi</i> , etc.

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The interpretative report created with the aid of the knowledge based system Pro.M.D-cerebrospinal fluid diagnostics consists of case-related modules.

By presenting an example kindly provided by Prof. Reiber (Neurochemisches Labor, University Göttingen) the leading features of these modules are demonstrated.

The report can be presented either in text or tabular/graphical form. The text form (fig. 1) will be taken as a base for further characterization.

◦ *Blood-CSF barrier*

The characterization of the blood-CSF barrier is based on the CSF/serum quotient of albumin.

The degree of the blood-CSF barrier dysfunction is age-dependently interpreted for both individuals older than 6 years (tab. 2), and those younger than 6 years.

Example: QAlb 66.2×10^{-3}

Report:

The elevation of the albumin quotient is consistent with an extreme blood-CSF barrier dysfunction.

◦ *Leukocytes in CSF*

Leukocyte count:

A leukocyte count > 30 cells/ μ l respectively 90/3 cells indicates the cellular stage of inflammation in the CNS and is described in consideration of its extent (tab. 3).

Example: Leukocyte count 82 cells/ μ l

Report:

The slight pleocytosis is consistent with a cellular immune response in the CNS.

◦ *Differential cell count*

A descriptive assessment of differential cell count will be given, if total cell count reveals a value > 30 cells/ μ l respectively 90/3 cells (tab. 4).

Example: The differential cell count is represented in table 5.

Report:

The differential cell count indicates a lymphocytosis with 93% lymphocytes.

◦ *Activated B-lymphocytes*

The presence of activated B-lymphocytes $> 0.1\%$ of lymphocytes indicates the cellular stage of inflammation in the central nervous system and will be mentioned in an appropriate way in the report.

◦ *Red blood cell count*

Elevated values for total protein, IgG, IgA, IgM due to artificial blood admixture to CSF are corrected in consideration of red blood cell count as shown in the following equation [5]:

$$Y' = Y - Z/V * X$$

Y' = corrected concentration of protein in mg/l

X = concentration of protein in serum in mg/l

Y = concentration of protein in CSF in mg/l

V = red blood cell count in peripheral blood / μ l

Z = red blood cell count in CSF / μ l

Elevated values for total white cell count in the CSF due to artificial blood admixture are corrected in a similar way. The total white cell count is decreased by 1 leucocyte / μ l per 1000 erythrocytes/ μ l CSF.

◦ *Lactate in CSF*

Elevated values of lactate in CSF are described as shown in tab. 6.

Table 2 Characterization of the blood-CSF barrier for individuals older than 6 years

QAlb	> age-dependent limit	$< 10 \times 10^{-3}$	moderate dysfunction
	$> 10 \times 10^{-3}$	$< 20 \times 10^{-3}$	slight dysfunction
	$> 20 \times 10^{-3}$	$< 50 \times 10^{-3}$	severe dysfunction
	$> 50 \times 10^{-3}$	$< 15 \times 10^{-3}$	extreme dysfunction

Table 3 Ranges of pleocytosis

Leukocyte count	> 30 cells/ μ l and < 300 cells/ μ l	slight elevation
	> 300 cells/ μ l	severe elevation

Table 4 Descriptive assessment of differential cell count

Granulocytosis	$> 50\%$ granulocytes
Lymphocytosis	$> 85\%$ lymphocytes
Monocytosis	$> 40\%$ monocytes
Mixed pleocytosis	Granulocytes, lymphocytes, monocytes elevated in equal amounts

Table 5 Differential cell count of the example case

Leukocyte count	82 cells/ μ l
Lymphocytes	93%
Monocytes	6%
Plasmacytes	1%

Table 6 Characterization of ranges for lactate

Lactate in CSF	> 2.2 mmol/l	slight elevation
	> 3.5 mmol/l	severe elevation

Nonstandard abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; Pro.M.D., Prolog-System (supporting) Medical Diagnostics; Q, quotient.

Institute	19.04.1995
Clinic.....	Tel.
	rft/950419t
To	
Clinic	
Name of patient	::: r40
Date of birth	::: 01.01.53
Age of patient	::: 42.3 years

C S F - R e p o r t

Total cell count	::: 82 cells/ μ l
Lymphocytes	::: 93 %
Monocytes	::: 6 %
Plasmacytes	::: 1 %
Lactate(CSF)	::: 3.4 mmol/l
Total protein in CSF	::: 4087.0 mg/l (450)
Albumin in CSF	::: 2620.0 mg/l (340)
IgG in CSF	::: 663.0 mg/l (40)
IgA in CSF	::: 181.3 mg/l (6)
IgM in CSF	::: 34.5 mg/l (0.8)
Albumin in serum	::: 39.6 g/l (35-55)
IgG in serum	::: 8.8 g/l (8-18)
IgA in Serum	::: 1.8 g/l (0.9-4.5)
IgM in serum	::: 0.7 g/l (0.6-2.5)

oligoclonal IgG in CSF ::: positive

The concentration of lactate in CSF revealing a value of 3.4 mmol/l is slightly elevated.

The slight pleocytosis is consistent with a cellular immune response in the CNS. The differential cell count indicates a lymphocytosis with 93% lymphocytes.

The elevated IgA quotient, the elevated IgM quotient, the elevated IgG quotient and the detection of oligoclonal bands in CSF are consistent with a local, inflammatory process in the CNS. The elevation of the albumin quotient is consistent with an extreme blood-CSF barrier dysfunction.

Graphical evaluation of the CSF/Serum quotients for albumin (QA1b = 66.2) and IgG (QIgG = 75.3) in the CSF/serum quotient diagram by Reiber is consistent with an extreme blood-CSF barrier dysfunction plus an intrathecal IgG synthesis in the CNS.

For IgA (QIgA = 100.7) and IgM (QIgM = 47.9) an intrathecal synthesis in the CNS is indicated.

52% of IgA, 21% of IgM and 21% of IgG measured in CSF are synthesized intrathecally.

These findings are consistent with a dominant intrathecal synthesis of IgA in a three class humoral reaction and an extreme blood-CSF barrier dysfunction.

Signature

Figure 1 Text form of Pro.M.D.-CSF report

Example: Lactate in CSF 3.4 mmol/l

Report:

The concentration of lactate in CSF revealing a value of 3.4 mmol/l is slightly elevated.

◦ *Calculation of CSF/serum quotients for IgG, IgA and IgM*

The calculations of CSF/serum quotients for IgG, IgA and IgM are based on the equations of Reiber [4,5,13,14]. After numerical evaluation the interpretations of these data are specified in the report.

Example: Values of albumin, IgG, IgA and IgM in CSF are represented in table 7.

Report:

The elevated IgA quotient, the elevated IgM quotient and the elevated IgG quotient are consistent with a local, inflammatory process in the CNS.

◦ *Oligoclonal IgG*

If oligoclonal bands are detected in the CSF, they will be mentioned in an appropriate way in the report.

Report:

The elevated IgA quotient, the elevated IgM quotient, the elevated IgG quotient and the detection of oligoclonal bands in CSF are consistent with a local inflammatory process in the CNS.

◦ *Calculation of intrathecal IgG-, IgA- and IgM-synthesis*

The calculations of intrathecal IgG-, IgA- and IgM-synthesis are based on the equations of Reiber [4,5,13,14]. If numerical evaluation reveals significant intrathecal synthesis of immunoglobulins (i.e. > 10%), it will be mentioned in an appropriate way in the report.

◦ *Calculation of specific antibody indices*

In consideration of the statistical discrimination line QIgX(Lim) or the QIgG of the patient the specific antibody indices for mumps virus, rubella virus, varicella-zoster virus, *Borrelia burgdorferi* etc. are calculated on the base of the Reiber equations [15, 16].

◦ *Assessment*

After characterisation of basic CSF variables a descriptive assessment of CSF/serum quotients for albumin, IgG, IgA and IgM based on the CSF/serum quotient diagram by Reiber is given.

Report:

Graphical evaluation of the CSF/serum quotients for albumin (QAlb = 66.2) and IgG (QIgG = 75.3) in the CSF/serum quotient diagram by Reiber is consistent with an extreme blood-CSF barrier dysfunction and an intrathecal IgG synthesis in the CNS.

For IgA (QIgA = 100.7) and IgM (QIgM = 47.9) an intrathecal synthesis in CNS is indicated.

In a final, summarized assessment the intrathecal fraction of each class of immunoglobulins and the blood-CSF barrier function is described.

Report:

52% of IgA, 21% of IgM and 21% of IgG measured in CSF are synthesized intrathecally.

These findings are consistent with a dominant intrathecal synthesis of IgA in a three-class humoral reaction and an extreme blood-CSF barrier dysfunction.

◦ *Tabular/graphical report*

In addition to the detailed type of report a more aggregated type can be selected.

On the base of the evaluation graph of Reiber [17] (fig. 2) measured and calculated CSF and serum values are presented. In a final, summarized assessment CSF findings are characterized by a combination of 6 descriptive terms.

With the aid of the above mentioned rules the condition of every term is checked by the knowledge-based system. If the condition is true, the term will be marked with X.

The embedding of a graph in the report will be supported in a future version under MS-Windows.

◦ *Hints at diagnosis and plausibility*

In rare or interesting case constellations hints at diagnosis and plausibility are given at a second report page (fig. 3). These hints are intended for laboratory use only and can be used as a basis for clinical consultation. Fig. 4 reveals an assortment of supplementary diagnostic hints [18].

◦ *Connection to the laboratory computer system*

The knowledge-based system Pro.M.D. CSF diagnostics is operated on IBM-compatible Personal Computers using the operating systems MS-DOS or MS-Windows.

The Personal Computer can be connected to the laboratory computer system like analyzing equipment. With the aid of the laboratory computer system requests can be transferred directly to the

Table 7 Values of albumin, IgG, IgA and IgM in CSF of the example case

Albumin in CSF	2620.0 mg/l	Albumin in serum	39.6 g/l	QAlb	66.2×10^{-3}
IgG in CSF	63.0 mg/l	IgG in serum	8.8 g/l	QIgG	75.3×10^{-3}
IgA in CSF	181.3 mg/l	IgA in serum	1.8 g/l	QIgA	100.7×10^{-3}
IgM in CSF	34.5 mg/l	IgM in serum	0.7 g/l	QIgM	47.9×10^{-3}

Institute....
Clinic.....

19.04.1995
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To
Clinic

Name of patient ::: r40
Date of birth ::: 01.01.53
Age of patient ::: 42.3 years

C S F - R e p o r t

Appearance: clear () cloudy () bloody () xanth. ()

Location of puncture: LP Amount: Hb:

Cells:
Total cell count: **82 cells/µl** Erythrocytes:

93 % 6 % 1 %
Lymphoc. Monoc. Granuloc. Plasmac.

Activ. B-lymphocytes:

Lactate (CSF): **3.4 mmol/l**

Proteins	CSF (mg/l)	serum (g/l)	Q(CSF/ser) * 0.001	locale synthesis
Tot.Prot.	4087.0			
Albumin	2620.0	39.6	66.2	
IgG	663.0	8.8	75.3	21 %
IgA	181.3	1.8	100.7	52 %
IgM	34.5	0.7	47.9	21 %

Oligoclonale IgG in CSF: **positive**

Specific antibodies:

HSV-AI =	Rubella-AI	=
VZV-AI =	Toxopl.-AI	=
CMV-AI =	Borrel.-AI(IgG)	=
Mumps-AI =	Borrel.-AI(IgM)	=

Reference values for specific antibody indices:
Synthesis in CNS: AI > 1.4

Assessment:

Normal CSF assessment () Normal CSF protein assessment ()
Blood-CSF barrier dysfunction(X) Cell count elevated (X)
Inflammatory process in CNS (X) Spec. Antibody synthesis in CNS ()

Signature

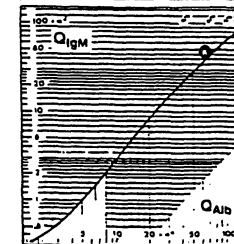
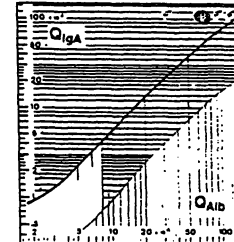
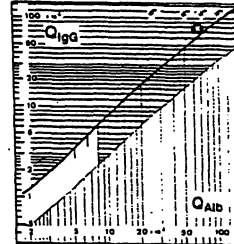


Figure 2 Tabular/graphical form of Pro.M.D.-CSF report

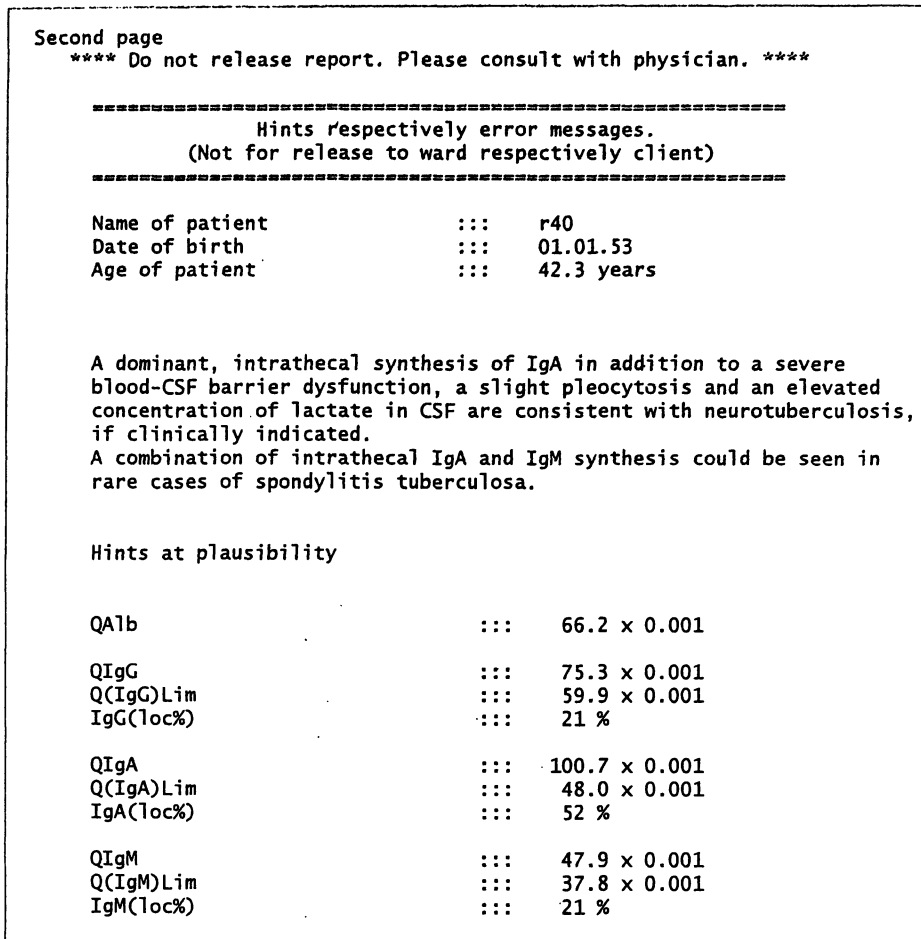


Figure 3 Hints at diagnosis and plausibility for laboratory use only

knowledge-based system [19]. After interpretation of CSF-findings, reports can be printed directly.

From 1991 to 1995 more than 1000 reports of CSF findings were created in the above mentioned way by the aid of the knowledge-based system Pro.M.D. CSF diagnostics.

Discussion

The intention in developing the knowledge-based system Pro.M.D. CSF diagnostics was to fulfill the often demanded improvement of reports on special findings in laboratory medicine [7]. The complex patterns in cerebrospinal fluid diagnostics particularly require further pathobiochemical characterisation and interpretation [6]. This characterisation and interpretation in the way of an individual case related report is a time-

consuming procedure and therefore not performed in the required extent [7,12].

This expenditure of time and work can be reduced by the use of a knowledge-based system, as shown by various applications [20]. On the basis of an experience of more than 1000 reports the system is well established and it is planned to start clinical evaluation [20-22].

With the aid of the knowledge-based system, the particularity of reports can be modified and adapted to the extent of personal knowledge of different clients [23]. Considering our own experience, the more detailed, textual report is suited to the client who is not so familiar in CSF diagnostics and is by this way introduced into terminology of CSF analytics.

On the other hand the tabular/graphical report allows the more experienced client to grasp essential information at a glance. Furthermore, it is planned to reduce the amount of data without loss of information by use of suited graphs that emphasize essential facts.

Diagnostical hints

Hint at neuroborreliosis

A dominant intrathecal synthesis of IgM in a three class humoral reaction in addition to lymphocytosis and severe blood-CSF barrier dysfunction i.e. reduced CSF flow rate, are typical for neuroborreliosis.

This pattern of three Ig-class reaction with predominance of IgM, blood-CSF barrier dysfunction and lymphocytosis in addition to detection of IgM-containing activated B lymphocytes reveals a diagnostic specificity of 96% and a diagnostic sensitivity of 70%.

Along with the detection of intrathecal *Borrelia burgdorferi*-specific antibody synthesis diagnostic sensitivity is enhanced up to 80%.

Hint at multiple sclerosis

Constant intrathecal IgG-synthesis in addition to normal or moderate reduced CSF flow rate and a normal cell count displays a distinctive pattern of CSF diagnostics in multiple sclerosis.

Along with a dominant intrathecal synthesis of IgG an intrathecal IgM-synthesis could be seen in 25-50% of MS patients.

Intrathecal synthesis of IgG is detected in 70% of MS patients by calculation of CSF/serum quotients while it is detected in 98% of MS patients by isoelectric focusing of oligoclonal IgG. Local synthesis of antibodies to measles virus (60%) and/or rubella virus (50%) and/or VZV (59%) could be found frequently in the CSF of MS patients. A combination of these local syntheses could be seen in 94% of MS patients.

Hint at VZV-ganglionitis

An isolated synthesis of VZV-specific antibodies in the CNS is consistent with a VZV-ganglionitis, if the clinical status matches the suspicion.

VZV-ganglionitis is characterized by moderate or slight blood-CSF barrier dysfunction and a cell count between normal or slight pleocytosis (1-260 cells/ μ l). The most characteristic sign is an elevated VZV antibody index due to local antibody synthesis in the CNS.

The VZV antibody index is more sensitive than detection of an intrathecal synthesis of IgG by isoelectric focusing of oligoclonal IgG or by calculation of CSF/serum quotients.

An elevated VZV antibody index is seen up to two years after convalescence and therefore not considered as an indicator for acute disease.

Hint at neurotuberculosis

A dominant, intrathecal synthesis of IgA in addition to a severe blood-CSF barrier dysfunction, a slight pleocytosis and an elevated concentration of lactate in CSF is consistent with neurotuberculosis, if clinically indicated.

A combination of intrathecal IgA and IgM synthesis could be seen in rare cases of spondylitis tuberculosa.

Figure 4 Assortment of diagnostical hints [18]), which are given in rare or interesting cases on a second page

Embedding of graphs, data import, creation and verifying of report suggestions and release of reports will be improved by the meanwhile possible implementation into Pro.M.D. for ACCESS and the availability of a database.

Finally it should be noted that every created report suggestion has to be controlled by a person who is experienced and responsible for interpretation of CSF findings [7].

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