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WHO Collaborating Centre for Quality Assurance
and Standardization in Laboratory Medicine

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27.3.09

Konsens Ergebnis

Empfehlungen zur Sicherung der Qualität in der Liquoranalytik

Auf der INSTAND-Veranstaltung : „Ringversuch Liquoranalytik- Seminar für Teilnehmer“ am 27.3.09 in Düsseldorf wurde von 120 Teilnehmern dem folgenden Konsens zugestimmt. Die einzelnen Punkte stellen auch die Konsequenzen einer umfangreich begründeten Darstellung der Probleme mit der Qualität der Liquoranalytik im Ringversuch und der alltäglichen Analytik dar. Der wesentliche Hintergrund ist aber eine am Patientenwohl orientierte Qualität für die ein umfassendes „quality assessment“ (s. engl. Anlage) nötig ist. Dazu gehört es auch eigenständig Verfahrensprotokolle zu verändern, was von manchen Teilnehmern mit Verweis auf die Akkreditierung ihrer Labors irrtümlicherweise als nicht erlaubt bezeichnet wurde. Dieser Beitrag soll dazu helfen bei Bedarf (im Interesse des Patienten , nicht des Verfahrensherstellers) ein modifiziertes Protokoll zu erstellen und zu dokumentieren. Als Beispiel einer Lösung des Problems der fehlenden adäquaten Kontrollproben für die Liquoranalytik, ist ein Protokoll des Neurochemischen Labors in Göttingen angehängt.

Serumwerte im Liquor RV:

Die zulässige Abweichung vom Zielwert für die Serumwerte von Alb, IgG, IgA, IgM wird den nach RiliBÄK zulässigen Abweichungen der Liquorwerte dieser Proteine gleichgestellt.

Kontroll-Proben für die Liquoranalytik:

Da es keine kommerziellen Kontrollen im Normalbereich für Liquorproteine gibt, werden entweder verdünnte kommerzielle Kontrollproben (Liquor oder Serum) eingesetzt oder In-house-Pools aliquotiert eingefroren und täglich aufgetaut eingesetzt. (z.B. wie umseitiges Beispiel)

Interne QC

Als Bestandteil der internen QC wird empfohlen zusätzlich zu Liquor und Serum Kontrolle den Liquor-Serum Quotienten zu errechnen und zu dokumentieren.

Testkontrolle und Reagenzien Kontrolle

Die eigenständige Überprüfung bei neuen Tests oder Reagenzien Chargen sollte bezüglich der Tauglichkeit für die Liquoranalytik grundsätzlich in jedem Labor durchgeführt werden. Dazu wird eine seriell verdünnte Serumprobe über den gesamten Messbereich einer Standardkurve als Liquor probe gemessen (s. umseitige Beschreibung).



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Wissensbasierte Änderung der Firmenprotokolle

Die offensichtlichen Fehleinschätzungen bei den Testentwicklungen sollten nicht nur bei den Firmen reklamiert werden, sondern wenn über Jahre keine Veränderung erzielt wird im Interesse einer Patienten-orientierten Qualitätssicherung auch selbständig verändert werden.

Dazu gehört z.B.

Liquorverdünnung im Beckman-Coulter Protokoll für IgA : 1:1 statt 1:8

Serumverdünnung im Siemens-Behring Protokoll für den Liquortest 1:400 statt 1:2000

Umgang mit vom Benutzer nicht behebbaren Verfahrens-Fehlern

Siemens Nephelometer: Ungeeigneter Kurvenfit (logit-log) führt bei niedrigen Konzentrationen zur Täuschung über die Vertrauenswürdigkeit einer neuen Kalibration.

Vorläufige Abhilfe: siehe obiges Verfahren zur Testkontrolle mit geeigneten Kontrollen für den relevanten Messbereich. Gegebenenfalls Wiederholung der Kalibration.

Beckman Nephelometer: Die Standardkurve ist im unteren Messbereich nicht richtig. Kurzfristige Abhilfe: IgM-Werte im Liquor < 0.5 mg/l werden nicht bewertet da zu hohe, falsch pathologische Interpretationen der Quotienten möglich sind.



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ANHANG 1

Interne Qualitätskontrolle im Liquor (Neurochemisches Labor Göttingen)

Solange keine kommerziellen Kontrollproben in der Liquoranalytik verfügbar sind, die den relevanten Normalbereich für IgA (1-3 mg/L), IgM (0,5- 1,5 mg/L) und IgG (10-30mg/L) abdecken, kann in Kombination mit den RilibÄK relevanten Vorschriften, ein eigener Liquorpool hilfreich sein. Dieser Pool sollte nach filtrieren und aliquotieren in ca 100 Einzelproben eingefroren aufbewahrt werden.

Bei jeder (täglich) neuen Messreihe sollte ein neues Aliquot dieses Liquorpools (normal) mit einer zertifizierten Serum-Kontrollprobe (verdünnt) zusammen im Liquor-Assay (im benachbarten Messbereich der Standardkurve) gemessen werden. Dokumentiert werden die von Tag zu Tag Werte von Serum, Liquor und der daraus berechnete Quotient. Die Richtigkeit wird durch die Serumwerte kontrolliert, die Messbereichsbezogene Präzision durch den Liquorpool und die Kalibrierungsunabhängige Präzision durch den Quotienten.

Die Messung eines normalen und eines pathologisch hohen Liquorwertes macht nur Sinn wenn diese Proben auf der Standardkurve den oberen und unteren Bereich kontrollieren, d.h. mit derselben Geräte-(default-) Verdünnung gemessen werden können. (Kontrolle der Verdünnungsechtheit der Standardkurve = repräsentative Steigung der Kurve).

Dieses Verfahren ist geeignet die im Ringversuch (INSTAND) beobachteten Probleme zu erkennen: Einzelne Assays die keine verdünnungsechte Standardkurve anbieten lieferten in niedrigen Konzentrations-Bereichen der Standardkurve zu hohe Patienten-Werte und in den hohen Konzentrationsbereichen der Standardkurve zu niedrige Patienten-Werte. Nur in den mittleren Bereichen der Standardkurve gemessene Werte waren dann richtig. Mit jeder höheren Geräteverdünnung bei wesentlich höheren Probenkonzentrationen wird dieser Vorgang erneut beobachtet (zu hoch, richtig, zu niedrig). Die Kontrolle der Standardkurve muss also bei derselben default- Verdünnung gemacht werden.

Kontrolle nach Neu-Kalibration oder bei Chargenwechsel der Reagenzien

Da der unterste Standardkurvenwert bei der Siemens –Behring Nephelometrie von Kalibration zu Kalibration unabhängig von der Restkurve stark variiert, macht es Sinn nach jeder Kalibration ein Probenpaar wie z.B. bei IgM mit der Konzentration 2mg/l und daraus gewonnen 0,2 mg/l gleichzeitig zu bestimmen. Bei zu hoher Abweichung der Relation der Ergebnisse der beiden Proben (Faktor 10) kann dann die Kalibration wiederholt werden.



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ANHANG 2

20 Quality assessment in the CSF laboratory

H. Reiber (In: Wildemann et al, Laboratory Diagnosis in Neurology, ThiemeVerlag, 2009.)

20.1 Quality assessment in laboratory medicine

Accuracy and precision in laboratory medicine are kept on a high level controlled mainly by the following activities:

- Internal quality control (QC)
- External quality assurance (EQA)
- Knowledge based interpretation concepts. In CSF analysis this is the integrating CSF data report (Chap 19).
- Laboratory protocols (laboratory accreditation)

Internal quality control (QC)

QC is part of the daily analysis protocol using certified commercial control samples for assurance of accuracy in a single analytical series and of precision calculated from a series of daily control values. The mean of these data measured between two calibrations of an analyzer may be used to control the calibration dependent variation of accuracy .

External quality assurance (EQA)

EQA is a major attempt to improve the quality standards in laboratory medicine and to keep interlaboratory variation low. Many national and international institutions have defined rules and regulations and also organize meetings (links in INSTAND e.V.). There may be 1-2 official assessors per country which offer surveys. In Germany INSTAND (s. INSTAND e.V.) is one of two institutions for quality assurance working from mandatory guidelines defined by the German Federal Medical Association (BÄK, 2008 and Table 20.1). The following description of EQA for CSF analysis is based on the development of INSTAND with the German society of CSF analysis and clinical Neurochemistry (www.dgln.de) as an implicit consensus of 400 participating laboratories from Germany and twelve different European countries (Reiber 1995, Reiber and Uhr 2003).

Interpretation concepts and the quality of information

As a generally accepted definition (ISO15189) of the EQA we find:

“ External quality assessment programmes should , as far as possible, provide clinically relevant challenges that mimic patient samples and have the effect of checking the entire examination process, including pre- and post-analytical procedures.”

It is not only about finding the adequate samples for a survey, which might be demanding, EQA is also considering the postanalytical procedures, i.e. the data handling and interpretation.

General guidelines (BÄK 2008) regulate quality of results (mostly numbers for absolute concentrations in a sample), but have problems with very particular rules for quality of information or do not consider them at all. But this is the relevant issue for the patient.



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Laboratory accreditation

The accreditation of a laboratory by an accreditation body is a big business driven by competing laboratories. This cost and time consuming activity leads to a tremendous consumption of time for documentation of everything and is, compared to the other activities, of questionable relevance for quality of information provided to the medical doctor.

20.2 Special features for quality of CSF protein analysis

1. The CSF/serum quotient of serum proteins in CSF, a mathematically normalized CSF concentration, is based on a natural, biological relation.

Most proteins in CSF are blood-derived. As shown in Chapter 1-3 the CSF concentration of a serum protein is modulated by its serum concentration (and the CSF flow rate). So the CSF/Serum quotients represents a normalized CSF concentration, i.e. a value independent of the varying concentration in blood. This is the reason why CSF/serum concentration quotients of serum proteins, which represent a biologically founded entity, are different from any other calculated ratio in clinical chemistry, e.g. the percentage of albumin in total protein calculated from serum electrophoresis.

The CSF/serum quotient has a smaller *biological* variability than the absolute CSF concentration and offers therefore a more sensitive and specific reference value for the discrimination of a brain-derived pathological fraction from normal blood-derived fraction in CSF.

2. The CSF/serum quotient is a method-independent value if derived after paired protein analysis in CSF and (appropriately diluted) serum samples.

If CSF and serum samples are analysed in the same analytical run compared to analysis with reference to two different calibration curves (and by this way different accuracies) also the CV is smaller (Andersson et al., 1994).

But, a basic precondition must be fulfilled for these statements: The calibration curve must give concentration independent accuracy. This is controlled by measuring a serially diluted serum sample with dilutions covering the complete analytical range of the corresponding calibration curve. The quotient is independent of absolute accuracy of CSF and serum concentration values, i.e., a method and calibrator independent value.

3. CSF flow-related, i.e. barrier function (QA_{lb})- related interpretations of Ig-quotients are most specific for detection of an intrathecal Ig fraction in CSF (referred to a hyperbolic discrimination function in quotient diagrams).

In contrast to the linear IgG Index or linear functions with many false positive interpretations (Reiber et al 2001) the hyperbolic discrimination line is an empirically and theoretically founded function (chapter 2).

4. The age-related evaluation of the QA_{lb} to detect a barrier dysfunction must take into account different reference values for ventricular, cisternal or lumbar CSF.

5. The integrating CSF data report (chap 19) is part of a quality assessment by plausibility controls for the quality of results and of information.

The physiological connection between different parameters analysed in CSF allows a particular plausibility control of the value of a single analyte if data of a single patient are reported in a combined "integrating" data report (Chap 19). This is an improvement for quality of results. And, with the disease-related data patterns in an integrated report (chap 19) we get in addition an improvement of information quality, eventually in case of contradictions, also indicating problems in the analytical results.



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20.3 Internal Quality Control for CSF proteins (TP, Albumin, IgG, IgA, IgM)

CSF assays must take into account the low protein concentrations in normal CSF and the large variation of concentrations in case of intrathecal synthesis, 10-100fold larger than in pathological serum. This is the basic demand to industrial development to allow a sufficiently high sensitivity and a reasonable protocol for change of the default dilution to avoid extreme positions on the calibration curve. These aspects are the main problems of immunochemical nephelometry leading to concentration-dependent differences between different analysis methods (Reiber et al 2009). The individual laboratory must control this by the internal quality control.

The use of an integrating CSF data report (chap 19 and 20.2) for reporting laboratory data to the medical doctor is a basic part of the quality assessment in the CSF laboratory: It improves quality control by plausibility control in the context of a disease specific data pattern. Analytical data discrepancies (Chapt. 21) or discrepancies between suggested diagnosis and analytical results (Chapt 19) may lead to a repetition or extension of analysis.

Precision.

For interassay precision CSF and serum control samples are measured with each analytical run and documented together with the CSF/serum quotients. Variation and trends between two calibrations can be read directly from the charts or by statistics calculation.

Accuracy.

The accuracy control of absolute values is ensured by two certified reference serum samples (normal range and pathological range), and two CSF samples in the upper and lower range of the calibration curve. The control samples can be measured alternating in different analytical runs. A calibration dependent variability is recognized from mean values of the precision controls.

With each new assay or a new batch of reagents the laboratory ensures the method-independent accuracy of the paired CSF and serum analysis: A serum control sample is serially diluted down to CSF concentrations with dilutions covering the complete analytical range of the corresponding calibration curve in the CSF assay.

Control material for CSF analysis

Certified control samples for proteins in serum are used as available from commercial sources.

But, up to now (2009) there is no certified commercial protein control available suited for normal CSF protein concentration (in particular for IgA and IgM) as the concentrations of analytes in commercial control samples are too high. This leads to serious control problems (Reiber et al 2009) and makes the following particular proposals necessary:

Diluted control serum may be used (1 : 200 to 1 : 2000, depending on the analyte) and stored frozen in aliquots. In combination with a certified reference serum sample, an in-house CSF pool may also be used with sample aliquots stored at 4°C, provided an antimicrobial agent has been added for stabilization (e.g., NaAzid).

A suitable control sample for normal CSF should yield (Andersson et al, 1994):

IgM values between 0.5 and 1.5 mg/L

IgA values between 1.0 and 3.0 mg/L

IgG values between 10 and 30 mg/L

Albumin values between 100 und 300 mg/L.



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20.4. The CSF Survey of INSTAND

Already 20 years ago the CSF survey of INSTAND in Germany (s.INSTAND eV) established a qualitative, information-oriented evaluation in addition to a single result control. This EQA concept (Reiber 1995) takes the post analytical part , the data interpretation as an aspect of a general quality assessment, serious. With this kind of training program for interpretation of CSF data, participants also improved their awareness for methodological discrepancies.

20.4.1 External Quality Control for CSF proteins (TP, Albumin, IgG,, IgA, IgM)

The survey for these combined analytes contains three levels:

CSF survey: 1. Evaluation of Information quality.

With the five aspects in chap 20.2 , based on the interpretation of the CSF/serum quotients in the quotient diagrams (chap19) the participants in the CSF survey (Reiber 1995) have to judge:

- Barrier function, normal or pathological
- Intrathecal IgG-,and/or IgA- and/or IgM- synthesis, detectable or absent
- Inflammatory process in CNS, detectable or absent

The certificate (Reiber 1995) documents, as primary result the correct patient-oriented interpretation of the data.

CSF survey: 2. Evaluation of CSF/serum quotients

Regarding quantitative results we refer with priority to the CSF/serum quotients as the specific feature for quality of CSF analysis (chap 20.2) and judge(Reiber, 1995).:

- Accuracy of CSF serum quotients and deviation from target value (Table 20.1)
- A possibly serious deviation in the accuracy of a quotient is commented by pointing to the source of deviation in the absolute value of the analyte (CSF or serum or both)

CSF survey: 3. Evaluation as independent values in CSF and serum

- Absolute values in CSF and serum are individually certified to meet the RILIBÄK specifications (BÄK, 2008) with the new permissible borders in Table 20.1.

Target value, consensus value of the group after subtraction of the outliers, CV of the interlaboratory variation and the individual deviation of the participants value from target value are reported, including a graphical demonstration of the participants position in the group performance in quotient diagrams. This established protocol was reported earlier (Reiber 1995). Numerical statistics and method related performance are reported to the participants in a summarizing letter, recent examples of which can be obtained from the website of INSTAND (www.instandev.de , English, EQAS, Reports, Category: Cerebrospinal fluid analysis).

This evaluation protocol was enabled by the knowledge based software of A.Wormek (www.wormek.com).

CSF survey: Total Protein

Total protein in CSF has lost its diagnostic relevance , but offers a plausibility control for the correct analysis of albumin (<85%of TP) or helps to find suitable predilutions in the automated analysis of single proteins. The evaluation of the absolute value is sufficient, serum analysis is redundant to albumin analysis for QAlb. Samples of one normal and one pathological total protein concentration in



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the CSF pool are tested. The method-related evaluation shows large differences of the medians between methods which led to an improvement of the calibrator from one manufacturer (reports 2006-2009 in www.instandev.de , English, EQAS, Reports, Category: Cerebrospinal fluid analysis).

20.4.2 CSF survey: Specific antibodies in CSF and serum

Like with total immunoglobulins , the detection of specific antibodies in CSF and serum by evaluating the CSF/serum quotients is better than the evaluation of absolute values. Titers are not suitable for CSF analysis.

As a basic challenge for the standard microbiological laboratory we have to regard the low concentration of the antibodies in blood, frequently below the cut off for a systemic infection in blood. Accurate analysis of serum antibody concentrations, also below the cut off value, are the challenge for the usual methods used in serology: In this case of a CSF related serum analysis the usual report in serology for such a case with a comment like "blood-titer is negative" is obviously not helpful at all.

In the CSF survey where the calculated antibody indices (Chapter 5.4.6) are interpreted, only the Q_{Spec} has an impact on the result because the IgG and albumin values are passed on to the participants in advance to ensure that uniform IgG values serve as a basis for calculating the Antibody Index (Quality control of IgG analysis is carried out separately). The mean coefficient of variation for Q_{Spec} is 5–10%, whereas the mean coefficients of variation for total AI values (including the imprecision for IgG analysis) is 16%. For a correct result participants also have to calculate and choose the relevant reference quotient Q_{IgG} or Q_{Ilg} (IgG).

The AI values are evaluated regarding deviation from target values and certified as right /wrong.

Additionally the participants interpretations are compared with the correct interpretation which contains the following spectrum of options:

- Normal AI values
- Intrathecal antibody synthesis with specification of the antibody species that is pathologically increased
- Chronic inflammation (when certain combinations of antibodies are increased, like MR MZ or RZ in the MRZ antibody response, Chapt. 19.3)
- Implausible data combination (a single value with AI < 0.5 among other different, normal values).

20.4.3 CSF survey: Oligoclonal IgG

The collection of samples which suit for the control of oligoclonal IgG in the CSF survey is a challenge, as these samples can not be obtained from pooled CSF, rather need to be from a single patient. To collect the volume necessary for a group of 200 participants in the INSTAND survey this is only possible from patients with a ventricle catheter in a neurosurgical intensive care unit. Multiple lumbar punctures are comparably rare, but with predilution of the samples occasionally it is possible to recruit samples in this way.

The bands in paired CSF and serum sample are evaluated according to the international criteria (Andersson et al., 1994) (see also Fig. 4.13, Chapter 4.2.6):

- No oligoclonal IgG detectable by IEF
- Oligoclonal IgG in the CSF (intrathecal synthesis)
- Oligoclonal IgG in the CSF, additional identical bands in both CSF and serum (intrathecal synthesis)
- Identical bands in both CSF and serum, no isolated oligoclonal IgG in the CSF (no intrathecal synthesis)
- Monoclonal IgG in both CSF and serum (paraprotein, no intrathecal synthesis).



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20.4.4 Method-related versus Patient-related evaluation in surveys.

The evaluation of participants data in a survey refers to target values (defined for cases of analytes with a reference method, like for glucose or total protein in serum) or assigned values (defined for analytes without a reference method). The assigned values for nephelometric analysis in the CSF survey are detected by two laboratories with Beckman- and two with Behring- nephelometers by tenfold interassay analysis each. The mean in each group is eventually corrected by the consensus value of the group (For detailed procedures see website of INSTAND). Occasionally the method-related evaluation shows concentration dependant discrepancies which do not allow a common evaluation of all participants. In reality these discrepancies are a problem for the patients diagnosis and eventually with consequences for the therapy. In particular the aspects in chapt.20.2 clearly show that these problems in protein analysis could be avoided by the manufacturer (Reiber et al 2009) and in any case must be controlled by each single laboratory (chapt 20.3.). It is a proposal from some EQA authorities that the assigned values for data control could be found as the median in a group with the same method. Under these aspects the survey is not testing the real accuracy of reported results with serious consequences for the patients: In particular in the decision range between normal and pathological values this concept supports false positive or false negative interpretations, which finally must lead to wrong information for the medical doctor (Reiber et al 2009). This discussion is actually also lead for the Antibody Index (AI) of microorganism-specific antibodies. For the viral antibody assays it is easier to find a method-independent common target value for the AI than for the bacterial antibodies with a much larger variation of coating antigens in the different ELISAs. With the introduction of the ViSE antigen in most borrelia antibody assays the large variation of the group-related target values for the Borrelia-AI diminished as shown in the reports for CSF surveys of neuroborreliosis 2007-2009 (see www.instandev.de, English, EQAS, Reports, Category: Cerebrospinal fluid analysis).

It must become the target for the manufacturers to evaluate and adapt new assays sufficiently to allow a patient-related accuracy instead of a relative, method-related result. To allow the highest quality of information is the responsibility of the manufacturers but the users in the laboratories are responsible for the decision of choosing an assay found reliable by the own testing.

20.5 CSF survey: Lactate, glucose and surrogate markers

Glucose and lactate concentrations in CSF are of similar size and there are no different matrix effects in the assays. This allows the usual survey conditions for serum to be applied to CSF samples.

Surrogate marker proteins for differential diagnosis of dementia. The increasing spectrum of surrogate markers with a large variation of laboratory dependent reference values and tremendous pre-analytical problems need urgent a quality control scheme. A first approach is made for a new survey (Lewczuk et al 2006) to be launched by INSTAND in the near future.

20.6 CSF Cytology- Quality control and Interpretation Training

The internal and external quality controls for CSF cytology are very demanding. The excellent training program founded by E. Linke (Linke et al., 2005) in Stadtroda, Germany, is unique in the world. This event is organized under the name "*Ringversuch vor Ort*" (On-site survey); it offers regularly education and, at the same time, examination of each participant on four cytological CSF preparations. The written exam is then certified by INSTAND e.V. This survey is performed by a reviewer of the DGLN confirmed by the board of INSTAND.



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Table 20.1 Permissible maximum deviation from target value in CSF Survey.

Values for analytes 1-7 according to (BÄK 2008). Values for quotients 8-11

represent an experience based consensus value from INSTAND survey participants

No.	Analyte	Permissible deviation in the CSF survey	Range of application
1	Albumin	23%	20-1000 mg/l
2	Total Protein	23%	10-2000 mg/l
3	Glucose	18%	1.1-17 mmol/l
4	Immunoglobulin A	27%	2-40 mg/l
5	Immunoglobulin G	20%	15-500 mg/l
6	Immunoglobulin M	33%	1-30 mg/l
7	Lactate	20%	1.1-11 mmol/l
8	Q_{Alb}	30%	$0.6-750 \times 10^{-3}$
9	Q_{IgA}	30%	$0.6-750 \times 10^{-3}$
10	Q_{IgG}	30%	$0.6-750 \times 10^{-3}$
11	Q_{IgM}	30%	$0.6-750 \times 10^{-3}$