GUIDELINES

S1 guidelines “lumbar puncture and cerebrospinal fluid analysis” (abridged and translated version)

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Abstract

Introduction: Cerebrospinal fluid (CSF) analysis is important for detecting inflammation of the nervous system and the meninges, bleeding in the area of the subarachnoid space that may not be visualized by imaging, and the spread of malignant diseases to the CSF space. In the diagnosis and differential diagnosis of neurodegenerative diseases, the importance of CSF analysis is increasing. Measuring the opening pressure of CSF in idiopathic intracranial hypertension and at spinal tap in normal pressure hydrocephalus constitute diagnostic examination procedures with therapeutic benefits.

Recommendations (most important 3-5 recommendations on a glimpse):

1. The indications and contraindications must be checked before lumbar puncture (LP) is performed, and sampling CSF requires the consent of the patient.
2. Puncture with an atraumatic needle is associated with a lower incidence of postpuncture discomfort. The frequency of postpuncture syndrome correlates inversely with age and body mass index, and it is more common in women and patients with a history of headache. The sharp needle is preferably used in older or obese patients, also in punctures expected to be difficult.
3. In order to avoid repeating LP, a sufficient quantity of CSF (at least 10 ml) should be collected. The CSF sample and the serum sample taken at the same time should be sent to a specialized laboratory immediately so that the emergency and basic CSF analysis program can be carried out within 2 h.
4. The indication for LP in anticoagulant therapy should always be decided on an individual basis. The risk of interrupting anticoagulant therapy must be weighed against the increased bleeding risk of LP with anticoagulant therapy.
5. As a quality assurance measure in CSF analysis, it is recommended that all cytological, clinical-chemical, and microbiological findings are combined in an integrated summary report and evaluated by an expert in CSF analysis.

(Continued on next page)
Conclusions: In view of the importance and developments in CSF analysis, the S1 guideline “Lumbar puncture and cerebrospinal fluid analysis” was recently prepared by the German Society for CSF analysis and clinical neurochemistry (DGLN) and published in German in accordance with the guidelines of the AWMF (https://www.awmf.org). /uploads/tx_szeitleitlinien/030-1411_S1_Lumbalpunktion_und_Liquordiagnostik_2019-08.pdf). The present article is an abridged translation of the above cited guideline. The guideline has been jointly edited by the DGLN and DGN.

Introduction
The present article is an abridged translation of the guideline recently published online (https://www.awmf.org/uploads/tx_szeitleitlinien/030-1411_S1_Lumbalpunktion_und_Liquordiagnostik_2019-08.pdf). This guideline contains basic recommendations concerning practical procedures for CSF space puncture, in particular with regard to indications and possible contraindications, information and consent, selection of the puncture needle, procedure in patients treated with anticoagulants, and thrombocytic function inhibitors, sample collection, treatment, and analysis as well as for compiling findings. The long version deals in detail with individual clinical presentations which had to be shortened for reasons of space in the present guideline. The structure, table of contents, and basic features are presented here.

Diagnostic lumbar puncture

Indications
Apart from a brain biopsy, CSF analysis is the only procedure that can detect inflammation in the CSF or the central nervous system. Therefore, meningitis, encephalitis, myelitis, radiculitis, and (poly)neuritis in acute or chronic form constitute core indications for lumbar puncture (LP) (Table 1). CSF analysis is playing an increasingly important role in neurodegenerative diseases, especially for dementia and differential diagnoses. Detecting malignant cells in the CSF confirms the diagnosis of a meningeosis carcinomatosa or lymphomatosa. The detection of blood and its degradation products in the CSF can confirm the diagnosis of subarachnoid hemorrhage even if the diagnosis cannot be made by cranial CT. LPs for relief in normal pressure hydrocephalus or idiopathic intracranial hypertension represent a special case. In children under 18 years of age, fever of unknown cause was the most frequent indication for LP at 20%, in adult patients headache at 39% [45, 179].

Contraindications

Increased intracranial pressure
Before electively collecting CSF, the presence of clinical CSF pressure signs must be ruled out. Cranial imaging (CCT, cMRT) prior to LP is needed in special cases (clinical evidence of increased cerebral pressure, focal neurological deficits, first epileptic seizure, vigilance disorder, or history of immunosuppression), but is not necessary in the absence of clinical signs of increased cerebral pressure.

The removal of CSF in cases of increased cerebrospinal pressure can lead to an entrapment of neuronal structures due to axial displacement of the brain and may be fatal. Examination of the ocular fundus by ophtalmoscopy is less sensitive than cross-sectional imaging as a congestive papilla may be absent despite increased intracranial pressure. The presence of a congestive papilla in the case of idiopathic intracranial hypertension does not represent a contraindication for a relief puncture.

Tendency to bleed
A platelet count below 50,000/μL, a quick test below 50%, an INR of more than 1.8, and a clearly pathologically activated partial thromboplastin time (aPTT) are considered contraindications for LP. When in doubt, the platelet aggregation time can be determined by apparatus or the

Table 1 Indications for the diagnostic LP under consideration of the contraindications (see below)

| Suspected condition                                      |
|---------------------------------------------------------|
| ...Meningitis                                           |
| ...Encephalitis                                         |
| ...Myelitis                                             |
| ...Neuroborreliosis                                     |
| ...Neurotuberculosis                                    |
| ...Polyradiculoneuritis Guillaín-Barré                  |
| ...Chronic inflammatory demyelinating polyneuropathy    |
| ...Encephalomyelitis disseminata                        |
| ...Neuromyelitis optica spectrum disorder               |
| ...Neurosarcoidosis                                     |
| ...Neurolupus                                           |
| ...Subarachnoidal hemorrhage                            |
| ...Meningiosis carcinomatosa                             |
| ...Meningiosis lymphomatosa                              |
| ...Idiopathic intracranial hypertension                 |
| ...Normal pressure hydrocephalus                        |

Differential diagnosis of the following core symptoms:
-Headache
-Dementia syndrome
-Sepsis with unknown focus of infection
bleeding time can be clinically determined by a scratch test.

Thrombocytopenia below 50,000/µL is a relative contraindication and thrombocytopenia below 10,000/µL an absolute contraindication. In the case of thrombocyte counts below 10,000/µL, thrombocytes should always be substituted prior to LP. In the range between 10,000 and 50,000/µL an increased complication rate is to be expected. The decision for thrombocyte substitution must be made individually.

Therapeutically induced coagulation disorders should - if medically justifiable - be stopped before the procedure, and their effect should be eliminated by medication if necessary (Table 2).

Patients anticoagulated with Phenprocoumon or other coumarin derivatives should be transitionally switched to heparin, as this can be antagonized more rapidly. At this point we would like to refer to the S1 guideline of the DEGAM (German Society for General Medicine and Family Medicine) on the subject of bridging (AWMF 053/027 [111, 122]). In emergencies, an attempt to normalize the blood coagulation can be undertaken by substituting coagulation factors. This also applies to individuals with a disease-related lack of clotting factors.

For the use of NOAK (new oral [or non-vitamin K-dependent] anticoagulants) such as dabigatran, rivaroxaban, apixaban, and edoxaban for the prophylaxis or therapy of thromboembolic events no systematic studies are available. Initial recommendations [39] consider emergency punctures under therapy in vital indications. Elective punctures of the CSF space should be carried out - if medically justifiable - after interrupting the NOAK according to the respective half-life, considering renal function, in particular for dabigatran (usually 2-3 days, for dabigatran and GFR [glomerular filtration rate] below 50 ml/min >3 days). For the treatment of life-threatening bleeding, idarucizumab is available in Germany as a specific antidote that antagonizes the effects of the thrombin inhibitor dabigatran by picking up the Fab antibody fragment (Fab: “fragment antigen binding”).

Andexanet alfa has already been approved and is available as an antidote for bleeding caused by Factor Xa inhibitors. Approval was granted in the first half of 2019 in Germany. If discontinuation of NOAK is associated with increased thromboembolic risk, conversion to heparin (bridging) is recommended [39, 111].

A case of a bleeding complication after LP under a double platelet inhibition with ASS (acetylsalicylic acid) and clopidogrel has been reported [137]. Systematic studies on the frequency of bleeding complications after LP in patients with dual thrombocyte aggregation inhibition (dTAH) are missing, however. For individuals with dTAH and planned LP in emergency indications and high thrombotic risk, the LP should be carried out while maintaining the dTAH according to a recommended procedure [39]. In the case of elective LP and high thrombotic risk a delay of the LP should be considered. For low thrombotic risk, elective LP is postponed 1 week after discontinuing clopidogrel under aspirin monotherapy.

ASS does not need to be discontinued for LP.

**Infection in the course of the puncture pathway**

Both superficial and deep inflammation of the skin or subcutis, but also inflammation of the muscle in the area of the puncture site represent a contraindication for LP.

**Lack of consent for emergency indications**

In emergency situations (for example, acute bacterial meningitis is clinically suspected), which cannot be delayed, the LP can also be carried out without a declaration of consent from patients who are unable to consent. It is recommended to document this consideration in written form.

**Pregnancy**

The benefit of the diagnostic measure must be weighed against the additional risk of inducing premature labor. In cases of idiopathic intracranial hypertension (IIH), relief punctures with reduction in visual acuity are among the therapeutic options available, even during pregnancy [78, 166].

**Implementation**

**Informing the patient**

Outside the scope of individual case decisions (e.g., emergency indication for patients who are not capable of giving consent), a patient who is capable of giving consent or the legal representative of a patient who is not capable of giving consent is required for LP. The information should always be provided in written form and patients should be

| Thrombocyte count /µL | Procedure for a planned LP |
|-----------------------|-----------------------------|
| > 50,000              | If there are no other contraindications. |
| 10,000–50,000         | Relative contraindication. An increased risk of bleeding is to be expected. Substitute thrombocytes if necessary. |
| < 10,000              | Absolute contraindication. Thrombocyte substitution before LP mandatory. |
given sufficient time for reflection. The procedure differs depending on the indication for the puncture and is also dependent on the patient’s level of consciousness. If an appropriate reflection period cannot be adhered to for clinical reasons, this must be noted separately. In this case, the physician performing the procedure must also document the indication. The patient can waive a further reflection period in written form.

The information for the patient should include the following:

- Information about risk and benefit.
- Adverse consequences if LP is not carried out, depending on the respective suspected diagnosis.
- Identification of alternative diagnostic methods.
- Explanation of the technical aspects of the puncture:
  - Procedure of the examination.
  - Possibility of local anesthesia. If a local anesthetic is used, possible hypersensitivity reactions must always be pointed out.
- Indications of possible adverse effects.

It should also be pointed out that patients may need to be hospitalized and the inpatient stay extended if side effects develop. In exceptional cases it may be necessary to perform a second puncture (with blood patch); in very rare cases, surgical measures may be necessary to treat complications (e.g., subdural hematoma).

If a suboccipital puncture is to be performed, additional reference to this should be made:

- Possible occurrence of a centrally caused circulatory or respiratory disorder
- Possible occurrence of suboccipital hemorrhage with atypical course of an arterial vessel (owing to this complication the suboccipital puncture approach is no longer routinely carried out)
- Information on suboccipital puncture should include the alternative of other puncture routes

For purposes of clarification, ready-made information sheets are commercially available.

The LP can be performed in an outpatient or inpatient setting after the patient has been informed in detail about benefits, procedures, and risks and after the patient has provided documented consent. In addition to the severity of the clinical presentation, patient-related factors such as age, weight, comorbidities, and coagulation status; organizational aspects such as the availability of the examination procedure; further CSF analysis; and the patient’s wishes also play a role in deciding whether the LP should be performed in an outpatient or inpatient setting. In advance, it must be checked whether special precautions must be taken to ensure that the CSF is properly processed, e.g., information about the laboratory or the laboratory courier in order to guarantee a prompt cell count or cytological processing. Preanalytics also play a role, for example, when CSF samples need to be freshly stained for microscopy. The container in which the CSF is collected and stored also affects the results: Proteins that tend to form aggregates, for example, amyloid-β1-42, are particularly highly absorbed by certain tube materials such as glass or polystyrene, resulting in false-positive results in Alzheimer’s disease diagnostics [42]. The use of polypropylene tubes is therefore recommended. It should also be noted that the sample containers selected should be made of the same material, at least within one center, from LP to laboratory analysis (including for aliquoting, biobanking, etc.).

As a rule, CSF is drawn by LP. The selection of the puncture needle depends on the anatomical conditions and the experience of the examiner. If possible, an atraumatic puncture needle should be used in order to minimize postpuncture syndrome [128]. A sharp needle is preferred in older or obese patients, also for expected difficult punctures, if necessary, and as a rule for measuring pressure and for attempted drainage.

**Technical implementation of the LP**

**General information**

The puncture should be performed by or under the supervision of an experienced physician. Standards for disinfection and hygiene must be met [147]. These include:

- The physician must wear sterile gloves.
- A sterile drape or cover must be used.
- The skin must be locally disinfected using a sterile swab and include at least one preliminary cleansing step. The exposure time of the disinfectant as specified by the manufacturer must be considered.
- Suitable measures should be taken to prevent contamination of the cannula. These include:
  - Handling under sterile conditions
  - Avoidance of contact with the patient’s clothing or exam table cover.

In the literature, the need for wearing a face mask while performing an LP has been the subject of controversy [10, 56, 121, 155]. Prospective studies to address this question have not been carried out, but numerous case reports of iatrogenically induced meningitis have been published. Molecular genetics investigations have proven that the infection was caused by microbes found in the oral cavity of the physicians [177]. These case reports indicate that the incidence of iatrogenic infections increases with the injection of diagnostic (myelography) or therapeutics (chemotherapy, local anesthesia). In such
cases the KRINKO (Commission for hospital hygiene and infection prevention) recommends more intensive preventive measures such as the use of mouth-nose masks by the physician and the assisting personnel.

From a pathogenetic point of view, an iatrogenic infection appears more likely if the physician has a respiratory infection and if talking while performing an LP [10].

Overall, the risk of iatrogenic infection in diagnostic punctures is low. Nevertheless, a face mask should be worn under the following conditions:

- Presence of a respiratory infection in the physician, the assisting staff, or the patient
- Injections into the CSF space
- LP under training conditions (accompanied by explanations or instructions).
- Implementation of further diagnostic measures (e.g., CSF pressure measurement) with increased time expenditure.
- Suspicion of an aerogenic infection (e.g., meningococcal meningitis) of the patient for self-protection.
- In all other cases, consideration should be given to whether the physician should also wear a face mask as little effort is involved and the potential benefit is substantial.

**Local anesthesia**

Decisions concerning local anesthesia must be made individually, but it is not generally recommended. If necessary, about 2 ml of a 1-2% lidocaine solution should be given for local anesthesia and it should be administered close to the skin surface. Puncture of the spinal canal must be avoided.

**CSF pressure measurement**

If an indication to measure CSF opening pressure is given, it should be measured, before a CSF sample is drawn. CSF pressure must be measured with the patient in the horizontal recumbent position. If this is not initially possible, LP can first be performed with the patient in a sitting position, but the CSF pressure must still be measured with the patient lying down. It is also important to ensure that the environment is sterile.

The reference values for CSF pressure with the patient lying down are as follows:

100-250 mmH₂O (2.5 and 97.5 percentiles [188]). The CSF pressure is dependent on the BMI [188]. Pulsations of 2-5 mm, in lying position of 4-10 mm, occur synchronously with the pulse.

To assure quality standards in CSF analysis, a standardized amount of CSF should be collected (10-15 ml) as a concentration gradient of CSF protein develops (the protein concentration is higher in the first fraction of CSF taken than in the last fraction [145, 167]. The quantity of the extracted CSF has no influence on whether postpunctural headache symptoms develop [100]. In individual cases (tuberculosis symptoms develop [100]. In individual cases (tuberculosis diagnosis, FACS analysis (FACS: fluorescence-activated cell sorting)) up to 30 ml CSF can be drawn without increasing the risk of complications [124].

The CSF sample should subsequently be collected in 3 different tubes if the first CSF sample contains blood in order to distinguish artificial contamination from pathological bleeding [124].

**Puncture site**

The LP is performed between the 3rd and 5th lumbar vertebral body (LWB). A puncture above LWB 2/3 should be avoided due to anatomical conditions (the conus medullaris extends to LWB 1/2 in 94% of the cases).

Spinal tap can be performed with the patient either lying or sitting. For CSF pressure measurement see the section above. During LP a kyphosis of the lower spine is desirable. It is preferable to perform LP with the patient in a sitting position if CSF pressure is not measured and the patient is awake and cooperative. This is more comfortable (faster and more accurate) as the anatomical situation of the spine is clearer.

Suboccipital puncture should only be performed in exceptional cases, when in emergency situations no CSF can be obtained by LP, or pathologically anatomical conditions (e.g., local abscess) represent a contraindication for LP.

**Risks, side effects, and complications**

Frequent side effects (> 3%) include:

- Local pain at the puncture site
- Acute transient lumbar radicular irritation symptoms
- Light bleeding locally
- Postpuncture syndrome

A postpuncture syndrome is an orthostatic headache, which can occur after LP especially if performed in an upright position. It may be accompanied by nausea, vomiting, and sensitivity to light [37]. For treatment of postpuncture headache, we refer to the AWMF S1 guideline 030/113 “Diagnostics and Therapy of the postpuncture and spontaneous CSF negative pressure syndrome” [36].

In a case series at a hospital in rural Congo, 307 consecutive patients with LP were treated with a complication rate of 7.5%, namely, headaches, back pain, and confusion. All side effects were transient in nature, and no permanent damage was observed [125].

Rare complications (< 3%) include:

- Infection of the injection canal
Circulatory reactions, which can be as serious as syncope

In individual cases the following complications have been reported:

- Bleeding with neurological deficits, mainly when LP was performed despite contraindications or if vascular anomalies were present
- Subdural hematomas
- Cranial nerve palsies
- Migraine attacks
- Epileptic seizures
- Entrapment syndromes, mainly when contraindications were disregarded

**Reporting**

All findings of the CSF analysis, including inspection, cell count, cytology, immunocytochemistry if necessary, and ranging from protein analytics to microbiological findings, should be presented in an integrated report that is summarized and checked for plausibility. The following chapters give general (Section Basic cerebrospinal fluid diagnostic testing) and specific (Sections Infectious inflammatory diseases, Non-Infectious inflammatory diseases, Degenerative Disorders, Vascular diseases, Neoplastic diseases, Other) guidance on how summary reports should be prepared.

**Basic cerebrospinal fluid diagnostic testing**
CSF analysis requires an assessment of all individual findings that should be summarized in an integrated, overall report so as to present findings that are reliable and diagnostically meaningful.

It is important to specify a meaningful question.

By applying an integrated diagnostic strategy, on the one hand, typical disease patterns can be identified and, on the other, plausibility checks can help avoid analytical errors (Fig. 1).

CSF examination consists of a three-step process (Table 3).

The reference ranges for routine parameters [140, 173] are summarized in Table 4.

### Cytology

Normal CSF contains less than 5/μL of nucleated cells composed of lymphocytes and monocytes in a ratio of 2:1 to 3:1 [191]. If CSF contains blood (artificial or subarachnoid hemorrhage), the erythrocytes are counted and reported

### Table 3 Steps of CSF analysis

| Analytical step       | Parameters                                           | Indication/Remarks                                      |
|-----------------------|------------------------------------------------------|--------------------------------------------------------|
| Emergency analysis    | Appearance (if contaminated with blood, 3-tubes test), cell count, total protein, lactate | Acute inflammation, bacterial or viral, cerebral bleeding (SAH, ICH) |
| Basic analysis        | Quotients Albumin, IgG, IgA, IgM, and oligoclonal bands | Intrathecal inflammation, Blood-CSF barrier function   |
|                       | Differential cell count                              | Differentiation of inflammation, bleeding, and neoplastic involvement |
|                       | Gram staining and culture                             | Pathogen detection (bacteria, fungi)                    |
| Extended analysis     | Pathogen-specific antibody (Antibody index)          | Infection or autoimmune disease                        |
|                       | CNS-specific proteins                                 | Neurodegenerative diseases (AD, CJD, ALS, Narcolepsy, etc.) |
|                       | Immune cytology, tumor markers                        | Tumor: confirmation and subtyping                      |
|                       | Antigen detection                                     | Pathogen detection (bacteria, fungi)                    |
|                       | PCR                                                  | Standard for viruses and Tbc, some other bacteria and parasites* |

* e.g., if findings from staining and antigen detection are negative

### Table 4 Reference ranges for routine parameters

| Parameter             | Method                                              | Reference range                                           |
|-----------------------|-----------------------------------------------------|----------------------------------------------------------|
| Appearance            | Inspection                                          | clear, colorless                                         |
| Cell count (Leukocytes/μL) | Manual evaluation by light microscopy, Fuchs-Rosenthal chamber | < 5                                                      |
| Differential cytology staining | Manual evaluation by light microscopy, Pappenheim staining | Lymphomonocytic (ratio 2:1 bis 3:1)                      |
| Total protein (mg/L)  | Nephelometry/Turbidimetry                           | < 500                                                    |
| L-Lactate (mmol/L)    | Enzymatic                                           | 0.9 – 2.7 (age dependent) [102]                          |
| Glucose (L/S)         | Enzymatic                                           | > 0.50                                                  |
| Albumin (L/5x10⁻³)    | Nephelometry                                        | < 5 - 10 (age dependent)                                 |
| Ig-Synthesis in CNS   | Nephelometry                                        | Not detectable                                           |
| Pathogens             | Gram staining, culture, light microscopy, PCR, antigen detection | Not detectable                                           |
| Pathogen-specific antibody (intrathecal synthesis) | Enzyme immunoassays                                 | Not detectable                                           |
| Brain-specific proteins (pg/mL) | Enzyme immunoassays                                 | Tau-Protein (< 450)                                      |
|                       |                                                     | Phospho-Tau (< 60)                                       |
|                       |                                                     | Abeta1-42 (> 550)                                        |
|                       |                                                     | (Laboratory- and assay dependent ranges)                 |
|                       |                                                     | Abeta1-42/Abeta1-40-Quotient (> 0,1)                      |

L/S = CSF/Serum quotient
separately [172]. Differential cytology by microscopy should be performed thoroughly at each puncture regardless of the total cell count. Automated cell counting and cell differentiation machines should be avoided in CSF analysis as the findings are not reliable [191].

**Quantitative evaluation of intrathecally produced immunoglobulins**

In order to be able to establish whether immunoglobulins or pathogen-specific antibodies are being produced intrathecally, CSF and blood need to be examined in parallel as the largest protein fractions in the CSF originate from the blood. These CSF-blood quotients are related to the individual blood-CSF barrier function (albumin-CSF/serum quotient, QAlb) [140, 173].

Albumin serves as a reference protein for the blood-CSF barrier as it originates exclusively from the blood. A corresponding graphic representation of the quotients was established by Reiber and Felgenhauer (Fig. 2) [145, 175].

Further advantages are that the quotient diagram can also be extended to IgA and IgM diagrams, so that three immunoglobulin classes can be evaluated in parallel, which increases the diagnostic significance of these parameters (see also Fig. 1 [175]).

**Oligoclonal IgG bands**

Oligoclonal IgG bands (OCB) occur nonspecifically in subacute and chronic inflammatory diseases of the CNS. OCB are more sensitive than quantitative quotient diagrams to detect intrathecal IgG production. An OCB pattern is present when at least two CSF-specific bands are detected (Figs. 3 and 4) [140, 173].

**Infectious inflammatory diseases**

**Bacterial meningitis**

If bacterial meningitis is suspected clinically, CSF analysis is necessary. With regard to the clinical presentation and therapy, reference is made to the AWMF guideline 030/089 “Outpatient acquired bacterial meningitis.”
Fig. 3 IgG band patterns. Five different patterns can be found, with patterns 2 and 3 indicating intrathecal synthesis, as shown in Fig. 3: Type 1: Normal finding. Type 2: Isolated OCB in the CSF. Type 3: Identical OCB in cerebrospinal fluid and serum, additionally isolated OCB in the CSF. Type 4: OCB with identical (mirror image) distribution in the CSF and serum. Type 5: Monoclonal bands (usually identical distribution in the CSF and serum) as an indication of systemic gammopathy [51].

Fig. 4 IgG band patterns illustrated graphically. Abbrev.: CSF, cerebrospinal fluid; Ser, serum; Poly, polyclonal; Oli, oligoclonal; Mono, monoclonal [7].
Table 5  Overview of diagnostically relevant routine parameters in acute bacterial meningitis (BM) and frequency of "typical" and "atypical" changes depending on the bacterial pathogen

| Parameter                              | Diagnostic (first) LP | Remarks / Special features |
|----------------------------------------|-----------------------|----------------------------|
| Cell count (CC) / μL                  | typical "CC ≥1000: ca. 80% Mean (SD): 7753 (14736) CC 100—999: 14% CC < 100: 7% | [16] Cave „purulent BM”: do not discontinue antibiotic treatment when CC is low, but CSF lactate or protein values are high! |
|                                        | Mean (SD): 7753 (14736) CC 100—999: 14% CC < 100: 7% | |
|                                        | CC > 999: 75.8-78% CC < 100: 17-19.3% CC < 10: 5% | [17, 136] (n = 153) [24]; |
|                                        | Cave "apurulent BM": do not discontinue antibiotic treatment when CC is low, but CSF lactate or protein values are high! | |
| S. pneumoniae                         | Median (IQR): 1842 (291–4419) CC > 999: 75.8-78% CC < 100: 17-19.3% CC < 10: 5% | |
|                                        | Cave "apurulent BM": do not discontinue antibiotic treatment when CC is low, but CSF lactate or protein values are high! | |
| N. meningitidis                       | Median (IQR): 5328 (1590–12,433) CC > 999: 80-82% CC 100–999: 6.5-11%; CC < 100: 9-11.6% initial CSF normal: 1.7% (CC ≤5/μL, TP ≤0.50 g/l und Glucose ratio CSF / blood ≥0.40) | [68] (n = 258) [24]; |
| L. monocytogenes                      | Median (IQR): 680 (291–1545) CC < 100: 1% | |
| H. influenzae b                       | Median (Min-Max): 1470 (0–11,400) CC > 999: 92.9%; CC 100–999: 7%; CC < 100: 0% | [14] (n = 11) |
| B-streptococci                        | Median (Min-Max): 1230 (0-80,000) CC "normal": 6% | [57] (n = 242) |
| Newborn meningitis                    | CC ≤ 3: 10% | [54] |
| Differential Cell count               | `typical =" granulocytic | |
| S. pneumoniae                         | ≤20% Granulocytes: 5.9% | [24] |
| N. meningitidis                       | ≤20% Granulocytes: 8.2% | [24] |
| L. monocytogenes                      | ≤50% Granulocytes: 26% | [99] |
| H. influenzae b                       | ≤20% Granulocytes: 4.3% | [24] |
| B-Streptococcus                       | Median (Min-Max): 87 (0-100) % | [57] |
| Total protein (TP) in mg/l            | "typical "TP > 1000 Mean (SD): 4900 (4500) | [16] |
| S. pneumoniae                         | Median (IQR): 2700 mg/l (1400–5800) | [136] |
| N. meningitidis                       | Median (IQR): 4500 mg/l (2200–7000) | [68] |
| L. monocytogenes                      | Median (IQR): 2500 mg/l (1760–3650) | [99] |
| H. influenzae b                       | Median: 1800 mg/l | [14] (n = 11) |
| B-streptococci                        | Median (Min-Max): 2480 mg/l (200-16,000) | [57] |
| Newborn meningitis                    | TP < 400: 0% TP 410-1200: 24% TP > 1200: 76% | [54] |
| Lactate (mmol/L)                      | "typical "Lactate ≥3.5 l diverging reference ranges, recommended cut-off: 3.9 mmol/L (≥35 mg/dl) Man (SD): 16.51 (6.1) Median (IQR): 9.9 (6.8-12.9) mmol/L | [1, 97, 152] |
| DD bacterial versus viral meningitis  | Lactate as sensitive differentiation criterion (Meta-analysis: [79, 152]) Sensitivity untreated BM: 98% Sensitivity after preantibiosis: 49% | Cave: Lactate increase also found in status epilepticus, cerebral infarction, ICB, Tumor, Herpes encephalitis [152] |
| Macroscopy / Gram staining            | positive 63-72% no preantibiosis: 63% with preantibiosis: 62% | [24] (n = 667); [130] |
| S. pneumoniae                         | positive: 85.2% | [24] (n = 162) |
| N. meningitidis                       | positive: 72.5-89% | [24] (n = 356) [68]; (n = 244) |
and the “ESCMID guideline: diagnosis and treatment of acute bacterial meningitis” [17]. If cerebral imaging is necessary before LP is performed or if the LP is delayed, e.g., by cerebral imaging, empirical antibiotic therapy should be started beforehand. Antibiotic treatment reduces the sensitivity of methods for detecting bacterial pathogens. For this reason, blood cultures should always be obtained before antibiotics are administered [17, 67].

The “typical” CSF constellation of bacterial meningitis with granulocytic pleocytosis > 1000 cells/µL, total protein > 1000 mg/l and lactate > 3.5 mmol/L is present in approx. 80% of cases. Depending on the pathogen, however, “atypical” findings can be seen in up to 25% of cases (see Table 5). If bacterial meningitis is not yet treated with antibiotics, an increased lactate value in the CSF is more sensitive than the cell count. Antibiotic therapy should still be administered when cell counts are low, but lactate or protein values are high in the CSF, however. Here, the possibility of “apurulent meningitis” must be considered.

Owing to currently available multiplex systems for nucleic acid amplification, the most frequently observed meningitis and encephalitis pathogens can be rapidly investigated in a CSF sample. The pathogen-specific results are highly consistent with those gained by using standard methods. However, standard methods should still be applied since 6 to 25% of the pathogens causing bacterial meningitis are different from those detected in the test systems. The pathogens to be expected depend on the age of the patients and predisposing factors.

Table 6 shows the frequencies of the pathogens underlying acute bacterial meningitis in Europe as a function of age [8, 14, 23, 43, 55, 59, 61, 76, 105, 132].

**Neuroborreliosis**

CSF analysis is essential to determine whether the nervous system is involved in infection with Borrelia species (AWMF S3 guideline Neuroborreliose 030/071, [144]). The diagnosis may be certain, probable, or possible according to the diagnostic criteria. Re-infection with Borrelia is possible, especially in exposed persons such as forest workers or hunters. Neuroborreliosis is thought of as an acute disease which is curable, not as a chronic disease.
In general, CSF cell count varies from 50 to 500 cells/μL, mostly lymphocytes and plasma cells. The high percentage of plasma cells sometimes makes it difficult to distinguish between meningiosis lymphomatosa and neuroborreliosis [195]. Intrathecally produced IgM in early or IgG in late disease are generally found, as are oligoclonal bands on IEF [38]. PCR and other methods of detecting antigens are of little value in diagnosing neuroborreliosis as their sensitivity in CSF and other bodily fluids is low [3]. Therefore, antibody detection by ELISA and Western blot represent key techniques here [126]. Intrathecal production of specific borrelia antibodies (borrelia AI > 1.5) confirms an acute or previously acquired neuroborreliosis. In early neuroborreliosis, the chemokine CXCL13 may be of value as high levels may be seen in the CSF of untreated patients with neuroborreliosis when antibody titers have not yet risen [149].

Since intrathecally produced borrelia antibodies may persist lifelong, re-infection may be difficult to detect. The diagnosis can be made in patients with typical symptoms, elevated cell count consisting mainly of lymphocytes and plasma cells, blood-brain barrier dysfunction, and elevated CXCL13.

Lymphocyte transformation test (LTT) and PCR in serum or blood are not recommended for diagnosing neuroborreliosis (Table 7).

### Neurosyphilis

The diagnosis of neurosyphilis is confirmed when an intrathecal antibody synthesis against *Treponema pallidum* (Tp) is detected. The specific antibody index (AI) against *Treponema pallidum* is calculated as the ratio between Tp antibodies in CSF and serum divided by the ratio of all IgG antibodies in CSF and serum.

\[
Tp \text{ IG} \text{G AI} = \frac{Tp \text{ IgG CSF} \times \text{IgG serum}}{\text{IgG CSF} \times Tp \text{ IgG serum}}
\]

Mostly, TPPA and FTA antibody titers are used to calculate the AI, which normally should be 1 in absence of neurosyphilis. In Titer-based calculation, an AI of 3 or more is positive. If an IgG-EIA technique referring to a standard curve is used, AI values of 1.5 and above are positive and confirm the diagnosis of neurosyphilis. Highly sensitive EIA may also detect a positive IgM-AI of 1.5 and above.

A positive AI does not distinguish between acute or recent infection. A positive AI against *Tp* may persist lifelong. For assessment of acute infections, a combined evaluation of typical clinical symptoms, CSF findings as well as serological analysis including Tp, IgG immunoassay, IgG immunoblot, IgM immunoassay, IgM immunoblot, FTA abs-IgM, VDRL, and FTA Ak- IgM are recommended. In CSF, an elevated cell count of up to 100 cells/μL, predominantly lymphocytes, a disrupted blood-CSF barrier, and CXCL13 may indicate acute infection [34]. For further details, see also the AWMF guidelines “Neurosyphilis” 030/101 [184] and Diagnostik und Therapie der Neurosyphilis (059/002) [40].

If AI results are inconclusive, immunoblotting techniques may be of certain value. CSF and serum should be blotted simultaneously. If Tp-specific bands such as

| Table 7 CSF findings in patients with neuroborreliosis |
|----------------------------------|-----------------|-----------------|------------------|
| Parameter                        | Diagnostic LP   | LP after initiating antibiotic treatment | Remarks                     |
| Cell count                       | ≤ 4/μL: 0%      | normalized      | Increase may indicate reinfection |
|                                 | 5-30/μL: 1%     |                 |                               |
|                                 | > 30/μL: 99%    |                 |                               |
| Cell type                        | lymphocytes:    | normalized      |                               |
|                                 | activated lymphocytes or plasma cells: up to 20% |                 |                               |
| Albumin ratio                    | < 8 × 10⁻³: 1%  | normalized      |                               |
|                                 | 8-32 × 10⁻³: 99%|                 |                               |
| Quantitative IgG, IgA, and IgM synthesis | IgM > 0%: 70%   | May persist for years |                               |
|                                 | IgG > 0%: 20%   |                 |                               |
|                                 | IgA > 0%: 1%    |                 |                               |
| OCBs                             | positive in 70% of neuroborreliosis patients | May persist for years | Differentiational diagnosis for multiple sclerosis is necessary |
| Borrelia AI ≥ 1.5                | positive in > 80% | May persist for years | Not suitable in suspected reinfection |
| Borrelia PCR in CSF              | Positive in 10-30% | Negative after appropriate antibiotic treatment |                               |
| Lactate                          | < 3.5 mmol/L: 95% | Normalized after antibiotic treatment |                               |
|                                 | > 3.5 mmol/L: 5% |                 |                               |
| CXCL13                           | Sensitivity 80 - 100% | Not specific, elevated in CNS lymphoma and inflammation |                               |

*Note: Table 7 reflects the CSF findings in patients with neuroborreliosis.*
| Pathogen                          | Diagnostic method (1st choice) | Material                      | Diagnostic method (2nd Choice) | Material | Reference |
|----------------------------------|--------------------------------|-------------------------------|--------------------------------|----------|-----------|
| **Immunocompetent patients**     |                                |                               |                                |          |           |
| Enterovirus (Echo, Coxsackie A/B)| RT-PCR                          | CSF                           | Direct detection by electron microscopy | Stool    | [18, 198] |
| Flavivirus (FSME)                | Serology                        | Blood                         | RT-PCR (early Phase)           | CSF      | [72]      |
| Herpes simplex virus Type 1 & 2 | DNA-PCR                         | CSF                           | AI after 10-14 days             | CSF      | [63]      |
| Varicella zoster virus           | DNA-PCR                         | CSF                           | AI after 10-14 days             | CSF      | [104]     |
| **Immunocompromised patients**   |                                |                               |                                |          |           |
| Cytomegaly virus                 | DNA-PCR                         | CSF                           | AI after 10-14 days             | CSF      | [4, 19, 96] |
| Epstein-Barr virus               | DNA-PCR                         | CSF                           | AI after 10-14 days             | CSF      | [80]      |
| Human immune deficiency virus    | Serology                        | Blood                         | AI after 10-14 days             | CSF      | [5]       |
| John Cunningham virus            | DNA-PCR                         | CSF                           | AI after 10-14 days             | CSF      | [20]      |
| **Other viral CNS infections**   |                                |                               |                                |          |           |
| Adeno virus                      | DNA-PCR                         | CSF                           | Antigen detection              | CSF      | [28]      |
| Hanta virus                      | DNA-PCR                         | CSF                           | AI after 10-14 days             | CSF      | [178]     |
| Measles                          | Serology                        | Serum                         | AI after 10-14 days             | CSF      | [2]       |
| Mumps virus                      | Serology                        | Serum                         | AI after 10-14 days             | CSF      | [148]     |
| Polio virus                      | Serology                        | CSF                           | AI after 10-14 days             | CSF      | [69]      |
| Rabies virus                     | RT-PCR                          | CSF                           | Direct detection by electron microscopy | CSF      | [47]      |
| Rubella virus                    | Serology                        | Serum                         | AI after 10-14 days             | CSF      | [131]     |
| Zika virus                       | Serology                        | Serum                         | AI after 10-14 days             | CSF      | [168]     |
Tp47, Tp17, TmpA, or Tp15,5 stain more intensely in CSF than in serum, intrathecal antibody synthesis and CNS infection may be presumed [135].

Viral meningoencephalitis

– In up to 40-80% of the suspected cases of viral meningoencephalitis (ME), the underlying pathogens are not determined due to the broad spectrum of pathogens.

– In contrast to bacterial meningitis, patients with viral ME usually present 4-7 days after onset of the disease, so that the diagnostic LP is performed somewhat later. Reference should also be made here to the AWMF guidelines “Viral Meningoencephalitis” (030/100) [119] and “FSME” (030/035) [95].

– The cell count in the CSF usually shows a slight to moderate pleocytosis.

– In the early phase of infection, neutrophilic granulocytes can typically be detected in the cell samples, in addition to lymphocytes and monocytes.

– The most common pathogens are enteroviruses, followed by flavivirus and bunyavirus.

– Viral CNS infections with the herpes simplex group are of particular prognostic relevance.

– DNA amplification by PCR in the first 10-14 days with good sensitivity and specificity is mainly suitable to detect the causative pathogen.

– An important exception may be a negative HSV-PCR in the first 72 h after onset of symptoms: treatment should NOT be discontinued if herpes encephalitis is suspected clinically. In these cases, an MRI with typical changes in mesial temporal regions, analysis of CSF re-drawn 3 days later and positive HSV-AI in the CSF 10 to 14 days after onset of symptoms can be diagnostically helpful.

– Pathogen-specific antibody indices only become positive after about 10-14 days.

Depending on the constellation of findings (clinical findings, basic CSF findings, and suspected pathogens

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**Table 9** Typical CSF findings in acute and subacute phases of viral CNS infections

| Parameter               | Findings (diagnostic LP (days 1-7), before therapy) | Findings (follow-up LP (days > 10-14), during therapy) |
|-------------------------|-----------------------------------------------------|-------------------------------------------------------|
| CSF appearance          | clear                                               | clear                                                 |
| Cell count (Leukocytes/µL) | 5 – 1000                                           | << 1000                                              |
| Differential cell count | lymphomonocytic, in initial phase (days 1-3) small fraction of neutrophils | lymphomonocytic                                       |
| Albumin ratio (L/S × 10⁻³) | < 20                                               | < 10                                                  |
| Intrathecal Ig-Synthesis | No                                                  | Yes                                                   |
| Total protein (mg/L)    | < 1000                                              | < 1000                                               |
| Lactate (mmol/L)        | < 3.5                                               | < 3.5                                                 |
| PCR in CSF              | positive                                            | negative                                              |
| Antibody index          | Not detectable or < 1.5                             | > 1.4                                                 |

**Table 10** Overview of routine CSF parameters and approximate frequency of pathological results in PML

| Parameter                     | 1st diagnostic lumbar puncture for PML | Follow-up during therapy (IRIS) a | Comment                                                                 |
|-------------------------------|---------------------------------------|-----------------------------------|------------------------------------------------------------------------|
| Cell number                   | ≤ 4/µL: 85%                           | May increase during IRIS          | Also dependent on the underlying disease and treatment.                 |
|                               | ≥ 5 – ≤ 50/µL: 10%                    |                                   |                                                                        |
|                               | > 50/µL: 5%                           |                                   |                                                                        |
| Cell differentiation          | Normal or slightly activated.         |                                   | Also dependent on the underlying disease and treatment.                 |
|                               | Lympho-monocytic                      |                                   |                                                                        |
| Total protein/ Albumin quotient | Normal: 50%                           |                                   |                                                                        |
|                               | Slightly elevated: 30%                |                                   |                                                                        |
|                               | Severely elevated: 20%                |                                   |                                                                        |
| Quantitative IgG-, IgA-, IgM- synthesis | IgG > 0%: 25%                         |                                   | Is highly dependent on the underlying diseaseb                         |
|                               | IgA > 0%: 0%                          |                                   |                                                                        |
|                               | IgM > 0%: 0%                          |                                   |                                                                        |
| OCBs                          | 42% b                                |                                   | Highly dependent on the underlying diseaseb                            |
| JCPyV-PCR                     | Positive: 70-80%                      | May increase during IRIS before it normalizes | At first manifestation of PML: Sensitivity: 60-90% Specificity: 100% |

*Empirical values from own experience due to the lack of published systematic data

*bValue from a study with primarily HIV-PML patients. In particular, the natalizumab-PML cases will show an intrathecal immunoglobulin synthesis and oligoclonal bands corresponding to the underlying multiple sclerosis
(see also Table 8), virus PCR and/or virus AI (IgG and IgM) is selected to confirm the diagnosis (Table 9).

Progressive multifocal leukencephalopathy

CSF investigations are essential for diagnosing progressive multifocal leukencephalopathy (PML). The detection of JC polyomavirus (JCPyV) via PCR represents diagnostic proof of PML. However, it should be kept in mind that PCR is positive in only two thirds of cases at first LP. Thus, once PML is clinically suspected, LP needs to be repeated [110]. In some 20% of cases, the PCR remains negative even after repeated investigations of the CSF. If the clinical suspicion persists, intrathecal JCPyV-specific antibody production can be measured. An elevated antibody index (AI) suggests PML [183]. The AI remains elevated for months after the first manifestation. This investigation is limited, however, because the test can only be run at a few specialized laboratories.

The CSF cell count during PML is usually normal or only slightly elevated, usually below 20 cells/μL. To interpret CSF parameters, including cell counts and blood-CSF barrier dysfunction in PML, the underlying disease predisposing development of PML needs to be considered.

After treating the predisposing immune defect (e.g., combined antiretroviral therapy [cART] in HIV/AIDS patients or stopping medication in multiple sclerosis patients being treated with natalizumab), there may be an over-reacting immune reconstitution, known as IRIS (immune reconstitution inflammatory syndrome). During IRIS, the JCPyV copy number in the CSF may even rise, and the cell number and the blood-CSF barrier dysfunction, too. We refer here to the the AW MF guideline „viral meningoencephalitis” (030/100) [119] and „HIV-infection and antiretroviral therapy” (055/001) [32] (Tables 10 and 11).

Non-infectious inflammatory diseases

Multiple sclerosis

- CSF diagnosis appears to be useful and is indicated for all patients with, in particular, inflammatory CNS disease or MS.
- As a rule, a single CSF examination is sufficient for patients with suspected inflammatory CNS disease or MS. In differential diagnostically difficult cases, however, a CSF examination can be helpful in the course of the disease.
- If patients with inflammatory CNS disease or MS are diagnosed with CSF, cell count, differential cell count, glucose, lactate, quotient diagrams (albumin quotient, IgG, IgA, IgM), OCBs, as well as Lues and Borrelia antibodies should be determined [7, 145].
- Although the absence of intrathecal IgG synthesis (OKBs) does not rule out MS, it should give rise to a careful review of the diagnosis [120, 159].

### Table 11 Diagnostic criteria for PML (according to [20])

| Certainty of PML diagnosis | Clinical features | MRI | JCPyV-PCR |
|---------------------------|------------------|-----|-----------|
| Definite                  | +                | +   | +         |
| Probable                  | +                | -   | +         |
| Possible                  | +                | +   | -/ND      |
| Not PML                   | -                | -   | -         |

ND Not determined

### Table 12 Frequency of abnormal changes in routine CSF parameters in patients with multiple sclerosis [150]

| Parameter                        | Diagnostic LP          | Remarks                                      |
|----------------------------------|------------------------|----------------------------------------------|
| Cell count                       | ≤4/μL: 40%; 5-30/μL: 55%; >30/μL: 5% | Depends on LP and relapse time interval and on topography of lesion |
| Differential cell count          | lymphomonocytic: 100%; activated lymphocytes or plasma cells (< 5% of all cells): 50-60% |
| Albumin ratio                    | <8 × 10⁻³: 90%; 8-25 × 10⁻³: 10% | Depends on LP and relapse time interval and on topography of lesion |
| Intrathecal IgG, IgA, and IgM synthesis in Reiber diagrams | IgG > 0%: 72%; IgA > 0%: 8%; IgM > 0%: 20% | In clinically confirmed MS |
| OCB                              | CSF specific OCB (Type 2 oder 3 patterns): 88-98% |
| MRZ reaction                     | Measles: 78%; Rubella: 60%; Zoster: 55% | Positive in clinical definite MS, if AI > 1,4 for two of the viruses |

AI Antibody index, Ig Immunglobulin, MS Multiple sclerosis, OCB oligoclonal band
The MRZ reaction is the most specific laboratory parameter for MS and can be helpful in the differential diagnosis of MS [89].

According to the revised McDonald criteria of 2017, patients with a clinically isolated syndrome who meet the MRI criteria for spatial dissemination can be diagnosed with relapsing-remitting multiple sclerosis if isolated oligoclonal bands are detected in the CSF [169].

In up to 50% of all cases with negative, isolated OCBs in CSF in isoelectric focusing (IEF), intrathecal IgG synthesis can be detected by kappa free light chains, MRZ reaction, or nano-OCBs by capillary IEF [150] (Table 12).

Neurolupus

CSF analysis is of little help in diagnosing neurolupus. The diagnostic criteria for systemic lupus erythematosus according to the American College of Rheumatology and the presence of one of 19 well-defined neuropsychiatric syndromes are necessary to establish the diagnosis of neuropsychiatric lupus [6]. Each CSF parameter, such as cell count, albumin ratio, or intrathecal antibody production, may be normal or abnormal. The main advantage of CSF analysis in neurolupus is that a concomitant infection of the CNS can be detected, especially in immunocompromised patients.

Data on CSF findings in neurolupus are scarce. Pathological findings such as oligoclonal bands or

| Table 13 | Summary of relevant CSF findings in neuropsychiatric lupus |
| Parameter | Diagnostic LP | Follow-up LP (under immunosuppressive treatment) | Remarks |
| --- | --- | --- | --- |
| Cell count | 1-400/μL; in 30 to 44% of patients | | |
| Cell type | Lymphocytes, monocytes | | |
| Albumin ratio | < 8 × 10⁻³: 60% 8-25 × 10⁻³; 40% | | |
| Quantitative IgG-, IgA-, IgM-synthesis | IgG > 0%: 30% IgA > 0%: 13% IgM > 0%: 17% | | |
| OCB | Type 2 or 3: 30% | Change to type 1 or 4 possible | Intrathecal dsDNA antibodies in 20% |
| MRZ reaction | Measles: 30% Rubella: 30% Zoster: 40% | | |

| Table 14 | CSF findings in patients with neurosarcoidosis |
| Parameter | Diagnostic LP | Follow-up LP (under steroid treatment) | Remarks |
| --- | --- | --- | --- |
| Cell count | 0 to 575/μL; < 5/μL: 20% 5-30/μL: 30% > 30/μL: 50% | normalized | Higher cell counts in leptomeningeal forms |
| Cell type | Predominantly lymphocytes | Basophilic and eosinophilic granulocytes possible |
| CD4/CD8 ratio in CSF | No data available | | |
| Glucose ratio serum/CSF | < 0.4 in 50% | Glucose level may be reduced, but glucose ratio is more precise |
| Lactate in CSF | elevated | Few data | |
| Albumin ratio | 8-25 × 10⁻³; 25 up to 100% | Total protein is generally elevated, but albumin ratio is more precise |
| intrathecal IgG, IgA, and IgM-synthesis | 13 to 80% | Few data; intrathecal IgA production is seen |
| OCB | CSF-specific OCB (type 2 or 3): 0-70% | | |
| ACE in CSF | 20% | Genotype has an impact; thus sensitivity is low |
| soluble IL 2 receptor in CSF | elevated | Only in active disease and untreated patients |
Intrathecal antibody synthesis may return to normal during the course of the disease. This distinguishes neurolupus from MS, where CSF findings of chronic inflammation in general persist throughout the entire disease course, independent of treatment [66].

An intrathecal antibody synthesis against dsDNA antibodies is found in only 20% of neurolupus patients [146]. A polyspecific antibody synthesis, for example, intrathecal antibody synthesis against at least two antigens, represents an even rarer event (8.7%, [75]).

The presence of certain antibodies, for example, against anticardiolipin or ribosomal p-protein, as well as high interleukin-6 levels are thought to be associated with a higher risk of developing neuropsychiatric lupus, but data from the literature are divergent (Table 13).

**Polyradiculoneuritis: Guillain-Barré syndrome (GBS), Miller-fisher syndrome (MFS), and chronic inflammatory polyneuropathy (CIDP)**

A typical finding in certain diseases is high protein levels in the CSF in the absence of substantial pleocytosis (dissociation cytoalbuminique). CSF protein concentrations may reach 2000 mg/l, whereas the cell count usually does not exceed 10/μL. Disruption of the blood-CSF barrier is the main reason for elevated CSF protein [26]. Albumin ratio of CSF/serum as a measure of the blood-CSF barrier function up to 200 × 10^−3 may be seen, predominantly in the second to fourth week of the disease. It may take weeks and months for the values to return to normal, paralleling clinical recovery. The albumin ratio may be normal in the first week of the disease and requires that a second LP be performed later in the disease course. An intrathecal antibody synthesis or oligoclonal bands only in the CSF represent unusual findings in these medical conditions. In contrast, identical oligoclonal bands in serum and CSF are seen in up to 40% of patients and indicate systemic immune system activation.

Lymphocytes and monocytes are the main cell types found in CSF. Activated B cells or even plasma cells may be found. However, granulocytes or a cell count higher than 10/μL challenge the diagnosis.

In MFS antibodies against GQ1b are frequently found exclusively in serum, but not in the CSF. The ganglioside GQ1b is mainly expressed in eye muscles. In contrast to GBS, the CSF cell count and protein may be normal in MFS [197].

In CIDP, the cell count is normal in more than 90% of cases. Rarely, the cell count can reach 10/μL. A higher cell count should call the diagnosis into question [44]. CSF protein levels in general are elevated up to 6000 mg/l in CIDP. Likewise, the albumin ratio is elevated, too. Normal albumin ratio or oligoclonal bands may be found.

**Neurosarcoidosis**

Diagnosing cases of isolated neurosarcoidosis or neurosarcoidosis in patients presenting with initial neurological symptoms still represents a challenge. Isolated neurosarcoidosis may be seen in 10% of all sarcoidosis patients. Inflammatory signs of any kind in CSF are usually present. If findings from CSF analysis are completely normal, neurosarcoidosis is unlikely. However, other frequently affected organs, such as lung and skin, should be examined to search for typical signs of the disease. Appropriate techniques are CT-thorax, T4/T8 ratio from bronchoalveolar lavage, soluble interleukin-2 receptor in CSF, FDG positron emission tomography, and Gallium scintigraphy. Sometimes, a biopsy of affected brain tissue is required to establish the diagnosis. Diagnostic criteria have been established and recently confirmed [164, 196].

As only few cases of proven neurosarcoidosis have been reported, data on sensitivity and specificity of the various diagnostic procedures are scarce. The information gathered here is the result of several small case series. A systematic review of all published data from

| Table 15 CSF parameter of AE |
|--------------------------------|
| **Antigen** | **Pleocytosis in CSF (%)** | **Dysfunction of the blood/CSF barrier (%)** | **CSF-specific OCBs (%)** | **Detection of disease-specific antibody** | **References** |
| NMDAR | 70-90 | ~ 30 | 50-70 | (+) | + | [33, 81] |
| AMPAR | 50-70 | 40-60 | ~ 30 | +/(+) | + | [71, 93] |
| GABA(R) | 40-70 | 20-70 | 20-30 | + | + | [141, 158] |
| GABA(B) | 60-70 | 30-40 | 60 | + | + | [62, 70, 91, 134] |
| GlyR | 0-40 | ~ 50 | 20-30 | + | + | [29, 115] |
| LGI1 | 10-20 | 20-30 | < 10 | + | (+) | [52, 77, 82, 101, 156, 157] |
| CASPR2 | 30-70 | n.b. | ~ 40 | + | (+) | [22, 52, 94] |
| DPPX | 20-60 | ~ 30 | ~ 30 | + | + | [13, 65, 170] |
| IgLON5 | 0-30 | 30-50 | 0-70 | + | + | [53, 74, 151] |
| GAD65 | 0-20 | 10-30 | 0-70 | + | + | [15, 46, 73, 112] |
2013 produced heterogeneous findings for most CSF parameters [186] (Table 14).

**Autoimmune encephalitis and paraneoplastic neurological syndromes**

Autoimmune encephalitis (AE) and paraneoplastic neurological syndromes (PNS) include a heterogeneous group of autoimmune diseases affecting the central and/or peripheral nervous system that are characterized by anti-neuronal antibodies in the serum and/or CSF [118].

While CSF findings have been well described for AEs (for a comprehensive overview, see Table 15), little is known about CSF findings in PNS patients. So far, the largest study demonstrated increased cell numbers in the CSF in ~40% of the patients, increased total CSF protein in ~60-70% of the patients, or isolated cases of oligoclonal bands, indicating intrathecal IgG synthesis [143]. Approximately 5-10% of PNS patients displayed a normal CSF profile [143].

**Neuromyelitis optica spectrum disorders**

CSF analysis plays an important role in diagnosing NMOSD and - in addition to detecting IgG antibodies against the water channel protein aquaporin-4 (AQP4-IgG/AQP4-Ab) and magnetic resonance imaging - helps distinguish this rare disorder from multiple sclerosis (MS). This also applies to myelin-oligodendrocyte-glycoprotein

| Parameter | Relapse | Remission | Remarks |
|-----------|---------|-----------|---------|
| NMOSD with AQP4-IgG | | | |
| Cell count | > 4/μL: ca. 60 - 78% | Mostly normal (> 5/μL: 20%; > 100/μL: 0%) | Negative correlation between cell count and time (in days) since onset of relapse |
| Cell profile | - lymphocytes and monocytes (97% of cells) - neutrophils in 40-60% (rarely dominant cell population) - eosinophils in 10-15% - basophils in 2-4% - activated lymphocytes or plasma cells in up to 20% (up to approximately 15% of all cells) | Less pathologically altered to normalized | |
| Albumin quotient | Increased in 55% (mostly 8-25, rarely > 25) | | |
| Intrathecal IgG, IgA, IgM synthesis | QIgG > Qlim: 8% QIgA > Qlim: 6% QIgM > Qlim: 13% | 0% | |
| OCB | CSF-restricted OCB (type 2 or type 3): 20-30% | 9% | No significant difference between AQP4-IgG-positive and AQP4-IgG-negative patients |
| MRZ reaction | AI ≥1.5 for at least two of the viruses | Almost always negative | Almost always negative |
| Lactate | 43% | ~0% | |
| MOG-EM | | | |
| Cell count | ≤5/μL: 30-67% | | Pleocytosis more frequent in patients with myelitis as first manifestation |
| Cell profile | - lymphocytes and monocytes - plus neutrophils in 64% of cases with pleocytosis | | |
| Albumin quotient | >Qlim(Alb):32% | | |
| Intrathecal IgG, IgA, IgM synthesis | QIgG > Qlim: 7% | | |
| OCB | CSF-restricted OCB (type 2 or type 3): 6-22% | | |
| MRZ reaction | AI ≥1,5 | | Investigated in a small cohort only |

*In NMOSD with AQP4-IgG cell count, QAIb, QIgG, total protein, and lactate are more frequently increased and the increase is more pronounced in acute myelitis than in acute optic neuritis
(MOG) encephalomyelitis (MOG-EM), a novel entity associated with serum autoantibodies against MOG, which phenotypically overlaps with both NMOSD and MS or may present as acute demyelinating encephalomyelitis (ADEM) and encephalitis. The current diagnostic criteria, last revised in 2015, distinguish NMOSD with AQP4-IgG from NMOSD without AQP4-IgG [193] and, according to current evidence, a subgroup of AQP4-IgG seronegative NMOSD patients harbor serum antibodies against MOG (MOG-IgG/MOG-Ab) [88]. Both AQP4-IgG-seropositive NMOSD and MOG-IgG-seropositive encephalomyelitis follow a mostly relapsing-remitting disease course and - as humorally mediated autoimmune diseases - should be distinguished from MS in terms of pathogenesis, prognosis, and therapy. Rarely, antibodies targeting the astrocytic structural protein glial fibrillary astrocyte protein (GFAP) can be detected in the CSF of some patients presenting with symptoms of meningoencephalomyelitis [49, 92].

While the typical abnormalities of CSF cells and proteins generally remain relatively stable over the entire duration of the disease in MS, pathological findings in NMOSD can often only be detected during acute attacks (20-30%) [84–86]. This applies both to CSF cell count and CSF-specific oligoclonal bands (OCB) [7]. Intrathecal IgG synthesis as detectable by using quantitative methods is observed even less frequently than CSF-restricted OCB. The MRZ reaction is mostly negative. CSF cytology also helps to distinguish the two disorders as both neutrophils and eosinophils are often identified in NMOSD, yet are absent in MS. Occasionally, very high cell counts may mimic bacterial meningitis [87]. CSF lactate levels are increased in some cases, particularly in patients presenting with acute NMOSD myelitis. Notably, a normal CSF profile does not exclude a disorder prompted by AQP4-IgG or MOG-IgG. In MOG-EM CSF, cell and protein profiles appear to be similar to those found in NMOSD [90]. CSF abnormalities are currently being investigated in larger cohorts (Table 16).

**Degenerative disorders**

**Dementia**

In addition to anamnesis, clinical and neuropsychological examination, and cerebral imaging (described in detail in the S3 guideline “Dementia” (038/013) [35]), diagnostic testing of the CSF plays an important role in the differential diagnosis of dementia. In comparison to the criteria for diagnosing Alzheimer’s Disease (AD) published in 1984 [116], neurochemical dementia diagnostics (NDD) has developed from a purely negative to a positive diagnosis. On one hand, CSF diagnostic tests in dementia syndromes serve to exclude secondary causes of dementia (e.g., inflammatory or autoimmune causes, negative diagnosis); on the other hand, specific neuropathological correlates of the primary causes of dementia can be evaluated.

Primary neurodegenerative dementias include AD, the behavioral variant of frontotemporal dementia (bvFTD), primary progressive aphasia (PPA), which can be divided into the nonfluent-grammatical, semantic, and logopenic variants [60], corticobasal degeneration, as well as Lewy body or Parkinson’s dementia and Creutzfeldt-Jakob disease or prion diseases (see Table 17).

Currently, Amyloid-β-1-42 (Aβ1-42), Aβ42/40, Tau and Phospho-Tau-181 (pTau), and 14-3-3 protein and the PrPSc aggregation assay are considered clinically validated and established biomarkers ([31, 64, 114, 133, 154, 109]) and can be used mainly for positive diagnosis. However, for other primary dementias, such as PPA or DLB, there is a significant overlap of some biomarkers, especially Aβ1-42 and Tau [21]; thus, a purely neurochemical differentiation of the different etiologies based on these CSF biomarkers alone is insufficient.

Several studies have shown that the concentration ratio of Aβ1-42 to Aβ1-40 (Aβ1-42/1-40) [192] shows much better correlation with prognosis of the development of dementia, compares better with amyloid β-PET, and correlates better with postmortem validation than Aβ1-42. Therefore, it is recommended to use the Aβ42/40 ratio instead of Aβ1-42 alone [11, 12, 41, 106, 108, 129, 181].

### Relevant biomarkers

Routine performed basic CSF parameters: cell count, CSF differential cytology, glucose and lactate concentrations, quotient diagrams (Albumin, IgG, IgA, IgM - Quotients), and OCB by isoelectric focusing.

Specific parameters when AD is suspected: Aβ1-42, Aβ1-40, Tau, and pTau181.

Specific parameters when CJD is suspected: 14-3-3 protein, Tau, and PrPSc-aggregation assay (RT QuIC). If sporadic CJD is suspected, a stepwise approach is recommended for economic reasons, performing the PrPSc aggregation assay (RT QuIC) only when the 14-3-3 protein test is positive.

### Table 17 Expected patterns of the CSF biomarkers in different neurodegenerative disorders

|                  | Ab42 or Ab42/40 | Tau | pTau |
|------------------|-----------------|-----|------|
| Alzheimer’s disease | ↓               | ↑   | ↑    |
| Vascular Dementia     | ↔               | (↑) | (↑)  |
| bvFTD             | ↔               | (↑) | (↑)  |
| nf-avPPA          | ↔               | (↑) | (↑)  |
| svPPA             | ↔               |     |      |
| lvPPA             | ↓               | ↑   | ↑    |
| CBD               | ↔               | (↑) | (↑)  |
| DLB               | ↔               | (↑) | (↑)  |
To optimize a diagnosis-oriented interpretation as well as to enable inter-center comparison of the results, diagnosis-oriented interpretation algorithms are recommended, for example, the Erlangen Score (ES [107]).

The ES combines the results of the biomarkers of amyloidosis (Aβ1-42 and Aβ1-42/1-40) and the biomarkers of neurodegeneration (Tau and pTau) into a five-step ordinal scale. This is particularly relevant, as common reference values for AD biomarkers are currently unavailable. Each laboratory should develop and validate its own specific reference values, which should be continuously verified in quality control schemes.

Amyotrophic lateral sclerosis
In the basic CSF analysis, cell count, blood-CSF barrier function, and humoral signs of inflammation are usually normal [165]. Therefore, detection of neurofilaments in CSF and serum provides a useful biomarker for the early diagnosis and prognostic assessment of motoneuron diseases [27, 103, 160, 174, 176]. Currently, the light chain neurofilaments (Nf-L) and the phosphorylated heavy chain neurofilaments (pNf-H) can be determined in the CSF. For differential diagnosis of motoneuron disease, a diagnostic sensitivity of 77-83% and diagnostic specificity of 75-85% could be achieved [48, 162, 187]. Highly increased values could also be observed in CJD [161]. Similarly, good diagnostic values can also be achieved if Nf-L is measured in serum [176]. The commercially available SIMOA method (digital ELISA) is currently used to measure Nf-L in serum. Determining pNf-H in the blood with a conventional ELISA is clearly inferior to measuring Nf-L.

Normal pressure hydrocephalus
The CSF opening pressure is usually normal (< 20 cm H₂O) in normal pressure hydrocephalus (NPH). However, characteristic fluctuations develop over the long term (see AWMF guideline “normal pressure hydrocephalus” (030/063) [138]. Studies investigating the relevance of degeneration markers in the differential diagnosis for other dementia syndromes and gait disturbances are summarized in Table 18.

Chen et al. [30] conducted a meta-analysis of 10 studies with a total of 413 NPH patients, 186 Alzheimer’s patients, and 147 healthy controls. There was a significantly lower total-Tau and phospho-Tau in patients with NPH as compared to Alzheimer’s patients and healthy controls. NPH patients have significantly lower Aβ1-42 concentrations in the CSF than healthy controls and slightly higher Aβ1-42 levels than Alzheimer’s patients. Nevertheless, sensitivity and specificity are not high enough for reliable differentiation.

Vascular diseases
Subarachnoid hemorrhage
If a subarachnoid hemorrhage (SAH) is presumed according to clinical symptoms, but has not been proven by a CT or MRI scan, LP is necessary (see guidelines AWMF registration number: 30/073 [163, 172]). In emergency care, an evenly hemorrhagic CSF in a 3-tube test and xanthochromia of the CSF supernatant constitute leading signs.

Cytological detection of erythrophagocytosis (first, erythrocytes followed by siderophages) is most specific, also enabling chronological assessment (see Table 19). The high sensitivity of an increase in ferritin at a rather high specificity is suitable for excluding SAH [127]. A CSF that is not visibly hemorrhagic (erythrocytes < 1000/μL) does not exclude a SAH, particularly in cases of smaller or older hemorrhage. Both xanthochromia and erythrophagocytosis may still be lacking in acute cases (< 12 h; sometimes, ferritin may also begin to increase later.

| Table 19 Time course of various CSF alterations after SAH |
|----------------------------------|
| Time | Pleocytosis | Erythrocytes | Oxy – Hb | Erythrophages | Bilirubin | Siderophages | Ferritin | Bilirubin Crystals |
| < 12 h | +++ | + | + | + | +++ | + | ++ | (+) |
| 12 h – 3 d | ++ | + | +++ | + | ++ | + | ++ | + |
| >3d | + | + | + | ++ | +++ | +++ | +++ | ++ |

| Table 20 Immunological recognition of lymphoma cells in CSF |
|----------------------------------|
| B-NHL | T-NHL |
| Predominance of B cells | Strong deviation of CD4/CD8-ratio, High percentage of CD4⁺CD8⁻ cells |
| Light chain restriction (Monoclonality) | Loss of normally expressed antigens (e.g., CD7, CD5) |
| Lack of light chains | Isolated IgM production |
| Co-expression of immature or aberrant antigens on or in B cells (e.g. CD34, CD 10, CD 30, TdT, CD5) | Co-expression of immature or aberrant antigens on or in T cells (e.g. CD34, CD 10, CD 30, TdT, CD1a) |
Neoplastic diseases

Neoplastic meningitis

The gold standard for diagnosing neoplastic meningitis remains CSF analysis with cytomorphological examination, in some cases followed by immunophenotyping [191]. Despite the high sensitivity of MRI scans in cases of carcinoma and elevated CSF cell count, however, differentiated CSF analysis is still indispensable when cell count is normal or to confirm hematological neoplasia [83, 98, 123]. See also AWMF-guidelines "Brain metastases and neoplastic meningitis" (030/060) [185] and "Primary CNS lymphomas" (030/059) [153].

In contrast to CSF cytology, differentiating proteins does not provide a specific diagnosis; exceptionally, however, determining tumor markers may increase the sensitivity or specificity (e.g., CEA) [190]. As a rule, malignant cells in carcinomas can easily be recognized by experienced cytologists. A sensitivity of 70-80% is reached in the first LP [191], one of around 90% for acute leukemias accompanied by high cell counts. However, in other hematological neoplasias, it may be difficult to distinguish malignant cells from inflammatory alterations based on cytomorphology alone [139]. Therefore, in these cases, immunophenotyping may be helpful particularly in known neoplasias and their surface antigens, as well as detecting monoclonality in unclear lymphocytic CSF reactions. Again, atypical cells of unknown origin may be traced to a primary neoplasia by immunophenotyping.

It is of particular relevance to distinguish lymphomatous meningitis from inflammatory lymphocytic reactions [189]. The most important single analysis is the light chain ratio of B cells to detect monoclonality in the more frequent low-grade B-NHLs. Inflammatory CSF reactions as a rule contain only few B cells. A lymphomatous meningitis in low-grade, peripheral T-NHL is rare. A summary of different immunological signs of lymphoma cells in CSF is given in Table 20.

Others

CSF fistula

To confirm a CSF fistula, prostaglandin D synthetase (beta trace protein, BTP) or beta2 transferrin are measured. Both proteins are found in abundance in CSF, whereas concentrations in most other bodily fluids and tissue are very low. Levels above a given threshold indicate the presence of CSF. Under certain conditions, false-negative or -positive results may be obtained. In case of renal failure, for instance, BTP in other bodily fluids are higher than usual, leading to false-positive results [117]. If CSF leakage is proven by laboratory methods, it may be challenging to localize the leak. Imaging techniques such as cranial CT, cranial MRI, cisternography, or endoscopy with or without fluorescin are used [25, 180]. For details, see also AWMF guideline 039/93 "Algorithmen für die Durchführung radiologischer Untersuchungen der Kopf-Hals-Region". More details on how to deal with CSF leaks after LP (postpuncture syndrome) can be found in the AWMF guideline 030-113 "Diagnostik und Therapie des postpunktionellen und spontanen Liquorunterdruck-Syndroms".

Detection of glucose is of little value to prove or rule out CSF leakage [113]. Other CSF proteins such as cystatin C or transthyretin are less suitable for detecting CSF fistula (Table 21).

Idiopathic intracranial hypertension

For a diagnosis of idiopathic intracranial hypertension (IIH) biochemical and cytological CSF parameters must be normal. See also the AWMF guideline "idiopathic intracranial hypertension" (030/093) [194]. In contrast, signs of elevated intracranial pressure in the absence of focal neurological signs or other causes of increased intracranial pressure are obligatory [50]. LP should be performed with the patient in a lying position to measure the opening pressure [9]. Some authors propose different cut-off values for the opening pressure depending on the body weight:

| BMI < 30: >200 mmH2O |
|----------------------|
| BMI > 30: > 250 mmH2O |

These values are based on the CSF opening pressure and, thus, CSF for biochemical and cell analysis should be drawn

| Author | Subjects (n) | Population | Needle | Median | SD | Range | 2.5 | 97.5 |
|--------|--------------|------------|--------|--------|----|-------|-----|------|
| [58]   | 31           | Students, healthy | 22 und 26 G | 145 (22G); 157 (26G) | 37 (22G); 36 (26G) | 85 – 230 (22G); 80 – 240 (26G) | 40 (22G); 50 (26G) | 250 (22G); 260 (26G) |
| [188]  | 354          | Neurological diseases without increased intracranial pressure | 20 and 22 G, atraumatic | 170 | 90-280 | 100 | 250 |
after measuring the pressure. Pressure values taken after withdrawal of CSF are not reliable. The lowering of the CSF pressure depends on the rate of withdrawal. Withdrawal of 20 ml CSF lowers the pressure between 92 mm H₂O (5 ml/min) and 52 mm H₂O (1 ml/min). The needle caliber used for LP may also affect the opening pressure (Table 22).

If IIH is clinically suspected and no elevated pressure is measured on the initial LP, the pressure should be measured continuously to detect B and plateau waves [171, 182].

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Declarations
We note that these guidelines have not been peer reviewed by the journal as a regular research article. These recommendations have been approved by the Guideline Committee of the German Society of Neurology (DGN), the Executive Board of the DGN and other relevant scientific societies (DGLN) involved in the creation of the guideline.

Its German extended version is published on the websites of the societies involved and on the website of the AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; Collaboration of medical societies). Its importance in the field and its suitability for publication in Neurological Research and Practice has been evaluated and confirmed by an independent Neurological Research and Practice Editorial Board Member. No additional reviews have been solicited.

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All declarations of interest were reviewed by an anonymous, independent and knowledgeable conflict of interest officer of the DGN for potential thematically relevant interests. The information was reviewed with regard to an existing thematic reference, thematic relevance, type and intensity of the relationship and the absolute amount of remuneration.

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