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Z. S. POLIZOPOULOU (Ζ.Σ. ΠΟΛΥΖΟΠΟΥΛΟΥ)

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Cerebrospinal fluid analysis

Polizopoulou Z. S.

*Diagnostic Laboratory, Faculty of Veterinary Medicine,
Aristotle University of Thessaloniki, 54627 Thessaloniki, Greece*

Η ανάλυση του εγκεφαλονωτιαίου υγρού

Πολυζοπούλου Ζ. Σ.

*Διαγνωστικό Εργαστήριο, Τμήμα Κτηνιατρικής, Σχολή Επιστημών Υγείας,
Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, 54627 Θεσσαλονίκη*

ABSTRACT

The significance of cerebrospinal fluid (CSF) analysis has been compared to that of complete blood counts for systemic diseases. CSF changes generally follow specific patterns depending on the etiopathogenesis (inflammatory, metabolic, neoplastic) of neurological diseases, thus indicating which further diagnostic modalities should be applied. CSF collection requires operator skills and knowledge of sampling indications and contraindications. Analysis includes physical examination (colour, clarity, viscosity), cytological and biochemical analysis, microbiological and immunologic testing. Despite its limitations, CSF analysis is a useful diagnostic tool, in particular when results are interpreted in combination with historical information, clinical examination and the findings of clinicopathological and diagnostic imaging testing.

Keywords: cerebrospinal fluid, diagnosis, neurological diseases, animals

ΠΕΡΙΛΗΨΗ

Η ανάλυση του εγκεφαλονωτιαίου υγρού (ENY) είναι η σημαντικότερη εργαστηριακή εξέταση στη διαγνωστική διερεύνηση των παθήσεων του νευρικού συστήματος των ζώων, που ανάλογα με την αιτιολογία τους προκαλούν συνήθως συγκεκριμένου τύπου παθολογικές μεταβολές στη σύστασή του. Η δειγματοληψία του ENY γίνεται με ατλαντοϊνιακή ή οσφυϊκή παρακέντηση του υπαραχνοειδούς χώρου, με την προϋπόθεση ότι δεν υπάρχει οποιαδήποτε από τις γνωστές αντενδείξεις (αύξηση ενδοκρανικής πίεσης, αδυναμία χορήγησης γενικής αναισθησίας, απειρία εξεταστή). Η ανάλυση περιλαμβάνει την εκτίμηση των φυσικών χαρακτηριστικών (χρώμα, διαφάνεια, ιξώδες), την κυτταρολογική (ποσοτική και ποιοτική), τη βιοχημική (μέτρηση ολικών πρωτεϊνών και γλυκόζης), τη μικροβιολογική και τις ανοσολογικές εξετάσεις. Η διαγνωστική αξία των ευρημάτων της ανάλυσης του ENY ενισχύεται περαιτέρω αν συνδυαστεί με τα στοιχεία του ιστορικού, της κλινικής και της νευρολογικής εξέτασης και ιδιαίτερα με τα αποτελέσματα των ειδικών απεικονιστικών εξετάσεων.

Λέξεις ευρητηρίας: εγκεφαλονωτιαίο υγρό, διάγνωση, νοσήματα νευρικού συστήματος ζώων

Correspondence: Z. S. Polizopoulou
Diagnostic Laboratory, Faculty of Veterinary Medicine,
Aristotle University of Thessaloniki,
Stavrou Voutyra 11 54627 Thessaloniki, Greece
E-mail: poliz@vet.auth.gr

Αλληλογραφία: Ζ. Σ. Πολυζοπούλου
Διαγνωστικό Εργαστήριο, Τμήμα Κτηνιατρικής,
Σχολή Επιστημών Υγείας, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης,
Σταύρου Βουτυρά 11 54627 Θεσσαλονίκη
E-mail: poliz@vet.auth.gr

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INTRODUCTION

Cerebrospinal fluid (CSF) is a colorless, transparent fluid that surrounds the central nervous system (CNS) acting as a protective, nourishing and supporting agent (Chrisman, 1992). The clinical importance of CSF analysis has been compared to that of complete blood counts regarding the diagnostic investigation of systemic abnormalities. CSF changes tend to follow specific patterns associated with the pathophysiology of neurological diseases (inflammatory, metabolic, neoplastic) showing a satisfactory sensitivity in their detection but a low specificity, especially if a basic interpretation (total nucleated cell count and total protein estimation) is done (Vernau et al., 2008). Moreover, there are several neurological entities where no CSF abnormalities can be detected and this may be attributed to the location (proximity to the ventricular system and subarachnoid space) and severity of lesions (for example, meningeal versus intraparenchymal cerebral lesions) (Wamsley, 2013). CSF abnormalities may be masked by previous treatments, especially corticosteroids (Jamison and Lumsden, 1988). Given the aforementioned limitations, it is obvious that CSF analysis is a useful diagnostic tool only when its results are interpreted in combination with historical information, clinical examination and the findings of clinicopathological and diagnostic imaging testing (Vernau et al., 2008).

PHYSIOLOGY AND COMPOSITION OF CSF

CSF is produced mainly by selective blood plasma ultrafiltration and active (energy utilizing) transport from the ependymal lining of the choroid plexi in the lateral, 3rd and 4th ventricles. To a lesser degree, CSF is also produced from the leptomeningeal and brain tissue capillaries (De Lahunta and Glass, 2009). CSF then follows a caudal flow into the central canal of the spinal cord and through the brain tissue to the subarachnoid space, where it is reabsorbed into the venous circulation via the arachnoid villi (Wamsley, 2013).

The rate of CSF production is constant and varies depending on the animal species and physiologic conditions. Reported rates in the dog and cat are 0.047 and 0.017 ml/min, respectively and the entire volume of CSF is produced and absorbed 3 to 5 times per day (Vernau et al., 2008; De Lahunta and Glass, 2009). The rate of CSF production is not influenced by the arterial blood pressure but from blood osmotic pressure and therefore the intravenous administration of hypertonic solutions lowers CSF production (hence its clinical application in the treatment of cerebral edema) (De Lahunta and Glass, 2009).

The functions of CSF include physical support and protection of CNS tissue, removal of large protein molecules and cells (the "lymphatic" function of CSF), intracerebral transport of biologically active substances formed in the hypothalamus (among them thyrotropin, corticotropin, growth hormone and gonadotropin releasing hormones) and homeostasis control of CNS microenvironment (Di Terlizzi and Platt, 2006; Vernau et al., 2008).

Regarding its chemical composition (Table 1), compared to the blood plasma CSF contains more sodium, chloride and magnesium but less calcium and potassium. Its glucose content is 80% of the corresponding plasma concentration while its total protein is much lower than plasma and does not normally exceed 30 mg/100ml (Fishman, 1992; Kjeldsberg and Knight, 1993). Under normal conditions, the entrance of drugs and many other chemical substances produced in the body is prevented by several interfaces that isolate the brain from systemic circulation, such as the blood-brain, the blood-CSF and the CSF-brain barriers (De Lahunta and Glass, 2009). Serum proteins with a molecular weight in excess of 160,000 daltons are prevented to enter the CSF, unless the blood-brain barrier (BBB) is compromised. Nearly all protein types in normal CSF are derived from serum, with the exception of prealbumin, transferrin, beta and gamma trace proteins, tau protein, glial fibrillary acidic protein and myelin

Table 1. Normal cerebrospinal fluid analysis findings

Parameter	Findings
Colour and clarity	Clear and transparent
Total protein content	Cisternal tap: < 25 mg/100ml Lumbar tap: < 45 mg/100ml
Total cell count	Erythrocytes: 0/ μ l Leukocytes: < 5/ μ l
Differential cell count	Lymphocytes: 60-70% Monocytes: 30-40% Segmented white blood cells: <1%

basic protein which seem to be synthesized locally. Albumin, synthesized only in the liver, is the main CSF protein, whereas three major immunoglobulins (IgG, IgM and IgA) are also identified in normal animals (Fishman, 1992; Kjeldsberg and Knight, 1993). Several enzymes have been detected in the CSF of animals, their levels being however lower than the corresponding serum values. To date, none of these assays has proven to be of diagnostic significance in veterinary medicine (Fishman, 1992; Kjeldsberg and Knight, 1986).

Regarding its cellular composition, CSF is virtually devoid of erythrocytes and its total nucleated cell count (TNCC) is low (Table 1). Although controversies exist regarding the normal TNCC it is generally accepted that it should range from 0-2 cells/ μ l (in dogs and cats), with 3 cells/ μ l being marginally and ≥ 4 cells/ μ l definitely abnormal, respectively (Vernau et al., 2008). Normal CSF nucleated cells consist of small lymphocytes and monocytes. The latter are the dominant CSF type in dogs, cats and horses, while small lymphocytes predominate in cattle (Jamison and Lumsden, 1988; Rand et al., 1990; Welles et al., 1992; Furr and Bender, 1994). Occasionally, other cell types may be found in normal CSF including leptomeningeal, ependymal and choroid plexus cells, chondrocytes or bone marrow cells (in samples obtained via lumbar puncture) and

dermal squamous cells (Kjeldsberg and Knight, 1986; Cook and DeNicola, 1988; Christopher, 1992).

COLLECTION OF CSF

Indications for collection and analysis of CSF include suspicion for diffuse or multifocal intracranial disease, polyneuropathy and myelopathy (Chrisman, 1992; Sharp and Wheeler, 2004). This procedure is done with the animal under general anesthesia and this should be accounted for upon decision making as some patients may be at a greater risk of its complications (Sharp and Wheeler, 2004; Di Terlizzi and Platt, 2009). Except from the high risk of anesthetic complications further contraindications for CSF sampling include suspected increased intracranial pressure (ICP), active intracranial or intraspinal hemorrhage (unless myelography is to follow), suspicion of atlantoaxial subluxation (due to the danger associated with positioning) (Sharp and Wheeler, 2004). In these cases it is preferable to postpone CSF evaluation or select an advanced imaging modality (CT/MRI) in order to pursue diagnosis. It is recommended to collect CSF prior to certain diagnostic imaging techniques (myelography), as the injected contrast medium sometimes elicits a transient meningeal irritation (De Lahunta and Glass, 2009; Wamsley, 2013).



Figure 1. CSF collection from the cerebellomedullary cistern (cisterna magna). The large black dot on the right side indicates the occipital protuberance, the dotted line on the left delineates the transverse distance of the atlas wings and the X mark indicates the proposed centesis site.

CSF can be collected via subarachnoid space paracentesis at the cisterna magna (cerebelomedullary cistern) or the lumbar spine (L5-L6 in the dog or L6-L7 in cats). The former is the preferred collection site, as it allows the sampling of larger CSF volumes and is easier to perform (Vernau et al., 2008; Di Terlizzi and Platt, 2009). The animal is placed in lateral recumbency with the head and neck positioned near the edge of the table. The collection site clipped and surgically prepared. The neck of the animal is flexed at a 90° angle and the nose lifted to set the muzzle parallel to the table (Figure 1). Landmarks for needle insertion include the occipital protuberance and lateral wings of the atlas (C1) which form a triangle in the center of which lies the optimal paracentesis site (Figure 1). The spinal needle is advanced slowly and the stylet removed periodically to check for CSF flow. In case the needle contacts bone it should be removed and landmarks reevaluated. If CSF is grossly hemorrhagic, a few drops should be discarded to see whether it clears and then obtain a sample. If however blood appears in the needle hub the needle is discarded and the procedure has to be done from start (Chrisman, 1992).

CSF SAMPLE HANDLING

CSF is collected via free flow into a sterile plastic vial or by aspirating each drop that appears in the needle hub into a sterile syringe. Direct aspiration from the spinal needle is contraindicated. If the sample is grossly hemorrhagic then an aliquot should be transferred into an EDTA tube to avoid clotting, however if microbiologic testing is to be done plain transport tubes should be used. EDTA tubes are required if the samples are to be sent for polymerase chain reaction (PCR) evaluation (Di Terlizzi and Platt, 2009).

One milliliter of CSF per 5 kg of bodyweight (or in general 0.75-2 ml in total) is more than sufficient for several diagnostic tests (Carmichael, 1998). A small aliquot of the obtained sample must be saved separately in sterile plastic vials for microbiological testing (culture and sensitivity) if an infectious disorder is suspected. It has been anecdotally stated that cytological evaluation of CSF samples should be done within 30 minutes from collection, as subsequent cell degeneration associated with its low protein content (Cook and DeNicola, 1988; Oliver and Lorenz, 1993). More recent studies on the effects of time, composition and addition of stabilizing agents have concluded that CSF samples have to be processed as soon as possible, however delayed (from 4 up to 8 hours) analysis may not alter clinical interpretation significantly (Fry et al., 2006). Cell degeneration is evident first in the small mononuclear cell population, followed by the large mononuclear cells, neutrophils and finally eosinophils (Fry et al., 2006).

To improve the preservation and quality of cytological evaluation it is advised that CSF samples should be divided after collection. One aliquot should be saved for cytology and preserved either by refrigeration at 4°C, or by the addition of stabilizing agents such as 10% homologous serum from the patient, hetastarch solution (1:1 mixture) or 20% fetal bovine serum (Bienzle et al., 2000; Fry et al.,

2006). The second aliquot should be saved for total protein determination and marked accordingly as both the addition of homologous or fetal bovine serum artefactually raises the sample protein content (Wamsley, 2013).

CSF SAMPLE ANALYSIS

Gross appearance

Normal CSF is transparent and colorless and therefore any change affecting these characteristics is considered an abnormality. Pink or red discoloration indicate the presence of blood, either through a traumatic tap or very recent (within the past hours) subarachnoid hemorrhage. The latter is an uncommon cause of CSF red coloration because free erythrocytes start to degenerate within 1-4 hours in the subarachnoid space and fluid collection rarely coincides with their presence. In this case, sample centrifugation results in the formation of a erythrocyte “pellet” at the bottom of the tube while the supernatant remains clear (Cook and DeNicola, 1988). The presence of pink or reddish, “thread-like” swirls during CSF flow into the sampling vial suggest iatrogenic blood contamination (Levine and Levine, 2012).

Yellow and yellow-orange CSF discoloration (xanthochromia) is the result of hemoglobin degradation within the subarachnoid space or secondary to an increase of total protein concentration, hyperbilirubinemia, CNS neoplasia and inflammation (Kjeldsberg and Knight, 1986; Cook and DeNicola, 1988). In subarachnoid hemorrhage xanthochromia persists for 24 hours after the event and subsequently dissipates within the next 4-8 days, while erythrophagocytosis may also be detected in microscopic examination of the CSF sediment (Jamison and Lumsden, 1988; Levine and Levine, 2012).

Increased CSF turbidity is commonly attributed to marked (>500 cells/ μ L) pleocytosis, as mild to moderate increases in TNCC do not affect its clarity (Chrisman, 1992).

Total protein concentration

In health CSF total protein content is considerably lower compared to plasma or serum, due to the functions of the intact blood-brain barrier that prevents large size molecules from entering the subarachnoid space (Di Terlizzi and Platt, 2006). The reference intervals for normal CSF total protein content vary among diagnostic laboratories and also depend on the assay methodology applied (Levine and Levine, 2012). Furthermore, total protein concentration increases rostrally to caudally along the neuraxis (neuraxis concentration gradient) with lumbar taps yielding higher values than cisternal (Vernau et al., 2008) (Table 1). Accurate CSF protein measurement is done using special analytical methods (Coomassie blue, pyrogallol red, immunoturbidimetric assays) and diagnostic laboratories. The use of refractometers and urine dipstick readings is discouraged as they may yield inaccurate results (Vernau et al., 2008). Furthermore, urine dipsticks detect primarily albumin and not globulins, which are known to increase in inflammatory CNS disorders.

Nearly all of the proteins present in CSF are derived from plasma and albumin is the major (80-95%) protein type detected. Despite the low albumin content, CSF to serum albumin ratio (albumin quotient or index= CSF albumin / serum albumin) is kept constant and therefore its calculation could be useful in assessing the integrity of the blood-brain barrier (Di Terlizzi and Platt, 2009).

Other protein types that have been investigated for their diagnostic potential include myelin basic protein, associated with degenerative myelopathy (Oji et al., 2007), and C-reactive protein (CRP) which may help distinguishing bacterial and viral meningoencephalitis (Fishman, 1992).

Immunologic testing

The detection of antibodies against specific infectious agent is an additional diagnostic tool to be

used along with conventional CSF analysis and neuroimaging techniques. Gamma globulins present in CSF include IgG (the dominant fraction), IgM and IgA. Results should be interpreted bearing in mind the prevalence and exposure frequency of particular diseases and the antibody type (IgM, IgG) involved. IgM is mainly associated with recent infection while IgG with more chronic disease course (Levine and Levine, 2012). IgA increases both intrathecally and systemically in dogs with steroid responsive meningitis-arteritis (Tipold, 1995). CSF immunoglobulin content may be attributed to intrathecal synthesis (as in neurological disorders) or non-specific diffusion through the damaged BBB (Tipold et al., 1994). The IgG ratio of the serum to CSF immunoglobulin content (IgG index) and the antibody index may be useful for specific cases where there is a strong suspicion of infectious disease. The IgG index is calculated as follows: IgG in CSF : IgG in serum, divided by the albumin quotient of the same patient (Vernau et al. 2008).

In some cases assessment of CSF antibody titers for specific infectious diseases may be more useful than the relevant in serum, as they represent intrathecal production secondary to a local stimulus. On the other hand, disruption of the BBB, a common feature of several CNS inflammatory diseases, may result in CSF "contamination" and artefactual antibody titer elevation (Vernau et al., 2008; Di Terlizzi and Platt, 2009).

Polymerase chain reaction (PCR) testing may contribute to the diagnosis of infectious diseases, in particular when the isolation of organisms is not possible. Available PCR assays include canine distemper, feline leukemia and feline immunodeficiency virus, *Toxoplasma gondii*, *Neospora caninum*, *Ehrlichia canis*, *Borrelia burgdorferi*, *Bartonella spp.* infections.

Total nucleated cell count (TNCC)

Normal CSF cell count is very low (less than 5 nucleated cells/ μ l) and therefore it cannot be rou-

tinely measured by automated cell counters. Instead, a manual cell enumeration is done using a haemocytometer (Neubauer chamber), which is loaded on both sides with CSF and incubated for 5-10 minutes before cell counting. The TNCC is then calculated from the average of the two side counts using the equation [Number of cells x 10/9 = cells/ μ l].

Increased TNCC (pleocytosis) may be scored as mild (less than 25 cells/ μ l), moderate (26-100 cells/ μ l) and marked (more than 100 cells/ μ l) (Cook and DeNicola, 1988). The scoring of pleocytosis does depend on the severity of the inciting cause, as well as other factors (CSF collection site, lesion proximity to the subarachnoidal space etc). According to the predominating cell type, pleocytosis may be further classified as neutrophilic, eosinophilic, mononuclear or mixed (Freeman and Raskin, 2001).

Distinguishing erythrocytes from white blood cells requires practice, in particular when small lymphocytes are present. TNCC and CSF total protein content usually increase in parallel in most neurological disorders, however in some cases the former remain within normal limits while the latter increases (albuminocytological dissociation). Increased protein concentration with a normal TNCC (albuminocytological dissociation) suggests disruption of the BBB with subsequent leakage of serum protein in CNS or intrathecal protein production. It has been associated with a variety of primary and secondary neurological disorders such as myelitis, space-occupying lesions, degenerative vascular and compressive myelopathies (Chrisman, 1992; Vernau et al., 2008).

The microscopic examination of cytological preparations is mandatory in all CSF samples, even if the TNCC is within normal limits because differential cell count and / or morphological abnormalities may still occur (Di Terlizzi and Platt, 2009).

Differential cell count

CSF cytological slide preparation is optimally done using cytocentrifuge equipment, capable of applying low speed centrifugation in order to con-

Table 2. Methodology for the manual cerebrospinal fluid (CSF) sedimentation chamber assembly (Figure 2)

Material needed	Procedure
Filter paper	Cut a piece of filter paper to fit the glass slide dimensions
Glass microscope slide	Punch a hole in the filter paper piece
Paper binder clips	Place filter paper over glass slide
1-ml syringe with removed plunger and cut in half Keep the bottom end where plunger enters	Place the cut end of the syringe on the glass slide (over the punched hole of the paper) and hold it in place with the paper binder clips
	Fill the syringe barrel with 0.2-0.5 ml of CSF
	Allow the fluid to settle for 30 min
	Discard the syringe and filter paper, air dry the glass slide
	Stain the glass slide (Giemsa, Diff-Quick®) and examine or send to a clinical pathologist

Modified from Wamsley, 2013

concentrate cells on a small area of the slide while preserving their integrity. Alternatively, a sedimentation chamber prepared from a syringe barrel and mounted on a glass slide (Figure 2) may be used for in-house cytological preparations (Chrisman, 1992). CSF is loaded in the chamber and allowed to settle for 30 minutes to facilitate cell sedimentation onto the slide (Table 2). In the case of delayed analysis due to sample shipment to a diagnostic laboratory, cell degeneration may be prevented by refrigeration and adding either homologous serum or hetastarch to a sample aliquot. This aliquot must be labeled properly as the addition of serum will increase total protein content, whereas hetastarch will dilute the sample (Bienzle et al., 2000; Fry et al., 2006). Regardless of the methodology used, slides are then air dried and stained with a Romanowsky stain (Wright Giemsa, Diff Quick). Special staining techniques may be applied if specific pathogens are suspected (Cook and DeNicola, 1988).

Normal CSF cells are typically small lymphocytes (dog) or monocytes (cat), however eryth-

rocytes may be also present due to iatrogenic sample contamination (Cook and DeNicola, 1988). The latter may be indicated at microscopic examination of CSF sediment smears by the presence of platelets and the absence of phagocytosed erythrocytes (Wamsley, 2013).

Neutrophilic pleocytosis, usually accompanied by increased protein content, is associated with inflammatory diseases (infectious, immune-mediated) and is an indication for microbiological evaluation (culture and sensitivity testing) of CSF (Cook and DeNicola, 1988; Chrisman, 1992). Infectious meningoencephalitis may also be accompanied by systemic signs (depression, anorexia, pyrexia), along with leukocyte toxic morphologic changes which are more characteristic in bacterial infections. Pronounced neutrophilic pleocytosis is a common feature in canine steroid responsive meningitis-arteritis (Wamsley, 2013). Other causes of neutrophilic pleocytosis include CNS neoplasia, transient post-myelography meningeal (contrast media) irritation, cerebrocortical ischemia and necrosis fol-

Table 3. Common cerebrospinal fluid abnormalities in selected neurological diseases

Neurological disease	Protein content	Pleocytosis	Type of pleocytosis
Distemper	Normal to mildly increased	Absent to moderate	Lympho-/Monocytic
Feline infectious peritonitis	Markedly increased	Marked	Mixed (neutrophils, lympho-/monocytes)
Other viral encephalomyelitides	Moderately to markedly increased	Moderate to marked	Lympho-/monocytic
Bacterial encephalomyelitis	Moderately to markedly increased	Moderate to marked	Neutrophilic
Protozoal encephalomyelitis	Moderately to markedly increased	Moderate	Mixed (neutrophils, lympho-/monocytes, sporadic eosinophils)
Granulomatous meningoencephalitis	Moderately to markedly increased	Moderate to marked	Mixed (neutrophils, lympho-/monocytes, sporadic eosinophils)
Steroid responsive meningitis	Moderately to markedly increased	Marked	Mixed (neutrophils, lympho-/monocytes)
Necrotizing encephalitis of small breed dogs	Mildly to moderately increased	Moderate to marked	Lympho-/monocytic
Degenerative encephalopathies and myelopathies	Normal to increased	Absent	None
Central nervous system neoplasia	Normal to increased	Absent to marked	Mixed (neutrophils, lympho-/monocytes, neoplastic cells)

lowing severe cluster seizures or status epilepticus (Dickinson et al., 2006).

Eosinophilic pleocytosis is always associated with CNS pathology because normal CSF is devoid of eosinophils. Eosinophilic meningitis, meningoencephalitis/-myelitis are the neurological disorders most commonly accompanied by CSF eosinophilic pleocytosis (Smith-Maxie et al., 1989; Windsor et al., 2009). Similar cytomorphological changes have been observed in protozoal (toxoplasmosis, neosporosis), fungal (cryptococcosis) and

parasitic (aberrant parasitic migration) encephalomyelitis (Chrisman, 1992; Windsor et al., 2009).

Mononuclear cell pleocytosis is characterized by the abundant presence of small lymphocytes or monocytoïd (macrophage) cells. Lymphocytic pleocytosis is considered to be the hallmark of viral encephalitides (distemper, rabies), but may be present in non-infectious inflammatory CNS conditions such as granulomatous meningoencephalitis, necrotizing meningoencephalitis, or even cerebrospinal lymphoma (Christopher et al., 1988; Higgins et al., 2008).

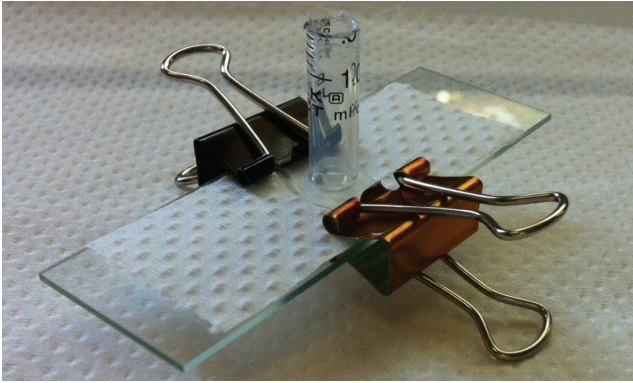


Figure 2. Sedimentation chamber for in-house CSF cytological evaluation (see also Table 2).

Mixed pleocytosis, manifested as a cell population consisting of lymphocytes, monocytes/ macrophages, neutrophils, plasma cells or eosinophils, may be recorded in several types of encephalopathies. It is typically observed in granulomatous meningoencephalitis (Di Terlizzi and Platt, 2009). Mixed pleocytosis may also represent an evolution of the cytological features of CSF over time, especially in the chronic forms of CNS disorders such as bacterial meningoencephalitis (Chrisman, 1992; Windsor et al., 2009).

Other microscopic findings in CSF examination include the presence of microorganisms (bacteria, fungi), viral inclusions in white blood cells or neoplastic cells exfoliating from CNS tumors (Wamsley,

2013). Less commonly, various types of sample contaminants, usually originating from the path of the spinal needle, may also be detected. These may be keratinized, meningeal or ependymal cells, hematopoietic bone marrow cells or even free myelin fragments, which may indicate demyelination (Di Terlizzi and Platt, 2009).

CONCLUDING REMARKS

Despite the evolution of advanced diagnostic modalities for the investigation of CNS disorders, CSF analysis still remains a vital and essential part in their diagnostic approach. Although an etiologic diagnosis is rarely established solely by CSF examination, the interpretation of its physical and chemical analysis findings and cytology patterns, along with diagnostic imaging assessment facilitates the establishment of differential diagnoses for the majority of clinical cases.

CONFLICT OF INTEREST STATEMENT

The author of this paper does not have a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper. ■

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