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A review on cerebrospinal fluid: Its cellular and biochemical composition in Veterinary species

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Abstract
The main purpose of cerebrospinal fluid investigation is often to assist in the diagnosis procedure by reducing the possibility that particular disease processes are present. The value of CSF inspection becomes evident when its outcomes are juxtaposed with the patient's history, clinical symptoms, imaging data, and supplementary lab tests, a standard procedure for tests with limited specificity. Cerebrospinal fluid analysis has been a crucial diagnostic tool in clinical neurology and subsequently veterinary neurology since the early 20th century. The CSF analysis gives professionals trustworthy information about the neurological condition and the occurrence of disease. This review's purpose is to furnish empirical validation and endorsement for the present perception of the clinical applicability of CSF analysis within veterinary neurology. Given the paucity of information on veterinary practice's biochemical and physiological lab tests and the reference values for the biological components in the CSF, this work could serve as a valuable guide for both investigators and veterinary professionals.

Keywords: Atlanto-occipital, brain, cerebrospinal, cytology, fluid, lumbosacral

Introduction
The brain needs strong defense against molecular and physical harm because it is the most complex organ. The blood-brain barrier prevents potentially dangerous foreign chemicals from entering the brain while the skull protects against mechanical trauma. A further layer of defense is provided by the cerebrospinal fluid (CSF), which is present in the ventricles and subarachnoid space and is controlled by further blood-CSF barriers at the choroid plexus & arachnoid mater. The CSF promotes a chemically & mechanically stable environment. Thus, maintaining equilibrium in the production, circulation, and assimilation of the CSF is essential for the brain's normal operation. If the CSF system is disrupted, a number of disorders could develop. The most obvious ones are 'mechanical' CSF abnormalities, like various types of hydrocephalus & idiopathic intracranial pressure. The SAS serves as an immunological surveillance site, and it is commonly accepted that the CSF serves as a "waste-sink" for the brain's toxic metabolites. This suggests that maintaining a healthy CSF is essential for delaying the start of neurodegenerative as well as neuroinflammatory diseases. The choroid plexus with in ventricular system produces cerebrospinal fluid (CSF), an ultra-filtrate of plasma that travels to the spinal cord's central canal. The central nervous system's CSF performs a variety of functions, including providing structural support, controlling pressure, transporting metabolites, nutrients, and neurotransmitters, as well as preserving the ionic equilibrium (Di Terlizzi and Platt, 2009) [8]. CSF examination is a broad indicator of neurological functioning and frequently reveals illness signs. CSF analysis has low specificity but reasonable sensitivity, much like a complete blood count. CSF changes are quite uncommon when viewed alongside the wide range of neurological diseases that can arise. The functionality and composition of the CSF may be affected, to variable degrees, by changes to the central nervous system. The neurological inquiry now includes CSF as a necessary component because of this. According to De Lahunta (1977) [7] and Vandevelde and Spano (1977) [29], knowledge of the CSF can help veterinarians treat brain illnesses such inflammatory, degenerative, or neoplastic

conditions. The collection and examination of cerebrospinal fluid is one of the most important procedures in the investigation and diagnosis of several conditions involving the spinal cord & central nervous system. The patho-physiology of the underpinning neurological illnesses is better understood because variations in CSF protein mirror pathological alterations in the brain (Gawinecka *et al*., 2010) [13]. Even though a definitive diagnosis of a CNS disease based purely on CSF analysis is uncommon, it can be helpful in differentiating toxic or metabolic lesions versus bacterial meningitis and traumatic versus infectious spinal lesions (Scott, 1992) [27]. According to George (1996) [14], CSF analysis has been suggested as a viable method for diagnosing auxiliary spinal fractures. CSF analysis may prove helpful for a precise diagnosis of CNS illnesses regardless of the cause. Early detection and management of CNS disorder are crucial. The lack of information on biochemistry and physiological lab tests, as well as the biochemical reference values of the biological components of CSF, may make this study useful for both researchers and veterinary professionals. Human medicine has been using cerebrospinal fluid (CSF) analysis for diagnostic reasons since the 19th century. Heinrich Quincke carried out the maiden lumbar puncture, a procedure for collecting CSF, in 1891. Although the precise date is not extensively reported in the literature, the approach was quickly accepted in veterinary medicine. The importance of CSF analysis for veterinary species was widely understood by the middle of the 20th century, and a number of methods for collecting it from animals were created. Techniques for CSF collection in various animals were developed and refined during 1950 to 1970. For example, studies on CSF collection sites in dogs were reported (Hoerlein, 1952) [16]. Advancements in laboratory technology facilitated more comprehensive CSF analysis. Besides the cell count, protein and glucose concentration, cytological examination started to be conducted. More research was conducted on the changes in CSF parameters in various diseases. With the advent of molecular biology techniques, detection of specific pathogens in CSF using PCR, and the search for specific disease biomarkers became possible. The era from 2000 onwards saw extensive research into CSF biomarkers for neurological conditions in dogs (Bathen-Noethen *et al*., 2008) [3], cats (Foley *et al*., 2003) [11], and horses. While significant progress has been made, challenges persist, including the risks and difficulties associated with CSF collection, small sample volumes, and the need for rapid and careful handling of samples. There is ongoing research into minimally invasive techniques for CSF collection and new biomarkers for early disease detection.

Functions of CSF

The four main roles of cerebrospinal fluid are: (1) supporting the physical integrity of neural components, (2) acting as an excretory "sink," (3) transporting materials inside the brain, and (4) regulating the chemical environment of the CNS. Cerebrospinal fluid acts as a buoyant "water jacket" for the body. A 1500-gram brain weighs only 50 gram when immersed in CSF. Additionally, the CSF serves as protection because changes in cerebral contents, notably blood, produce a reciprocal change in the CSF's volume. Because of this, the CSF protects the brain from differences in arterial & central venous pressure caused by adjustments in stance, breathing, and effort. Acute or chronic pathogenic fluctuations in cerebral contents can be somewhat accommodated by changes in CSF volume (Milhorat, 1987; Rosenberg, 1990; Fishman, 1992) [23, 25, 10]. Since CSF irrigates the whole brain, particularly regions known to support endocrine functions, it has been hypothesized that CSF may serve as a pathway for the intracerebral transfer of chemicals with physiological effects. Both chemicals that leave the brain and those that are created there easily diffuse into the CSF via the brain interstitial fluid. The removal process may then involve bulk CSF uptake or, in some circumstances, transfer through the choroid plexus and into capillaries. According to several studies (Milhorat, 1987; Rosenberg, 1990; Fishman, 1992; Davson and Segal, 1996) [23, 25, 10], opiates and other neuroactive chemicals may also be transported inside the brain via the CSF.

Collection of CSF

Sharp razors, surgical gloves, a 4.92 inch long 14 gauge with a stylet, a 3 inch long 16 gauge spinal needle, cotton swabs, scalpel handles with surgical blades, rectified spirit, sterilized test jars, and other supplies are required to collect CSF. Each of these things needs to be sterile. Additionally, aseptic collecting techniques must be used.

The CSF is retrieved from following two locations-

1. In equine, feline and canine CSF is harvested via atlanto-occipital puncture or the cisterna magna.
2. In bovine, ovine and caprine CSF is harvested via Lumbosacral or sub lumbar punctures.

Atlanto-occipital puncture

In dogs, cats, and horses under general anesthesia as well as in ruminants under sedation with xylazine hydrochloride at 0.05 mg/kg, IV, and regional analgesia with 2% lignocaine hydrochloride, atlanto-occipital punctures may be used to obtain CSF (Ettinger and Feldman, 2005; Schwarz and Piercy, 2006) [9, 26].

1. Cast a rope around the animal to restrain it.
2. Sedation of the animal using xylazine hydrochloride and local anaesthetic like 2% lignocaine hydrochloride
3. Bend and stretch the neck so that it forms a 90-degree angle with the neck's longitudinal axis. Firmly hold the head in this position.
4. Clip, wash, and sanitise the region of choice.
5. Slowly insert a 3-4" long, 16 G spinal needle with a stylet at the cranial edge of the atlas wings. The needle's path should be parallel to the head's long axis. There is no resistance experienced as the needle enters the subarachnoidal area.
6. To collect 1 to 2 ml of CSF, insert the needle inside the atlanto-occipital junction, remove the stylet to let the CSF drain.

Sub-lumbar puncture

Under local anaesthesia (2% lignocaine hydrochloride), the collection is carried out while the patient is standing.

1. Preoperative and aseptic measures are done, and the indentation between the cephalic end of the median crest of the sacrum and the dorsal process of the last lumbar vertebra is felt.
2. Here, a needle is passed. Introduce the needle vertically, then slightly obliquely by applying increasing pressure in both the forward and backward directions. As the needle enters the subarachnoid space, the resistance it faces reduces.
3. To prevent spinal cord injury, the animal must be secured securely. Remove the stylet, insert a syringe, and suction the fluid to collect CSF.

The rate of CSF production in various animal species

S. No.	Species	CSF Rate (µL/Minute)
1.	Human being	350-370
2.	Monkey	28.9-41
3.	Calf	290
4.	Goat	164
5.	Sheep	118
6.	Dog	47-66
7.	Cat	20-22
8.	Rabbit	10
9.	Guinea Pig	3.5
10.	Rat	2.1-5.4
11.	Mouse	0.325

Normal components of CSF

Erythrocytes generally do not exist in CSF. Tiny lymphocytes and monocytes are present in varied amounts in normal CSF. Albumin is a major protein in CSF. The predominant Ig in healthy CSF is Immunoglobulin G, which typically comes from serum. Between 60%-80% of blood glucose level, the CSF glucose level is considered normal. While salt and chloride are higher in CSF than plasma, proteins, potassium, glucose, sulphate, phosphorus, and cholesterol are in reduced amount in CSF than plasma. Changes in these values often suggest pathological conditions (Willard *et al*., 2011) [31].

Analysis of CSF

1) CSF Physical Examination

Color: The usual coloration of CSF is clear, colorless watery fluid that is free of flocculant elements. A crimson color, on the other hand, indicates that blood vessels were punctured during collection, and a dull red or brownish color shows an intracranial hemorrhaging or cranial fracture. A xanthochromic tint, meanwhile, indicates the appearance of bile pigments (jaundice) or a previous CNS hemorrhage. While an infection causing pus produces a greyish or greenish coloration.

Turbidity

Normal cerebrospinal fluid (CSF) is clear and transparent. By contrast, a hazy, groundglass-like turbid appearance denotes the presence of cells and white clots (pleocytosis), a cloudy or purulent appearance denotes encephalitis or bacterial meningitis, and a red turbid appearance denotes blood vessel puncture during collection.

Coagulation

There is no coagulation in healthy CSF. However, in situations of suppurative meningitis, an abnormal number of proteins, particularly fibrinogen, causes coagulation in CSF. Large amounts of blood in the CSF are a sign of an internal hemorrhage or incorrect CSF collection.

2) CSF Chemical Examination

Protein

One of the most sensitive indicators of a central nervous system disease is the CSF protein concentration. A combined measurement of the protein concentration and the fluctuating WBC count may be used to diagnose a bacterial infection of the central nervous system (Scott, 1992) [27]. Albumin makes up the majority of normal CSF, and there are very few proteins in it. It has been noted that mice (8-70 mg/dl; George, 1996) [14], dogs (11-55 mg/dl; Hoerlin, 1978) [17], and canines (23.4-66.3 mg/dl; Welles *et al*., 1992) all have protein levels in their CSF. It is believed that a more permeable blood-CSF barrier is to blame for neonatal foals' higher CSF protein concentration, which reflects higher IgG and albumin levels (Andrews *et al*., 1994) [1]. Ponies are claimed to have higher CSF protein contents than horses (Mayhew *et al*., 1977) [22]. Increased local immunoglobulin production or a deterioration of the blood-brain barrier could both lead to increased protein concentrations.

Glucose

The Folin-Wu method is used to estimate CSF glucose quantitatively. The blood glucose concentration, the rate of glucose transportation into the CSF, and the central nervous system's metabolic rate all influence the glucose concentration in CSF (Bailey and Vernau, 1997) [2]. As a result, the serum glucose should also be measured at the same time as the CSF glucose. In healthy animals, the concentration of glucose in the CSF is roughly 80% that of the serum (George, 1996; Bailey and Vernau, 1997) [14, 2]. CSF glucose levels have been observed in sheep (48-109 mg/dl), cattle (20-40 mg/dl), goats (24-40 mg/dl), and dogs (61-116 mg/dl; Hoerlin, 1978) [17], according to George (1996) [14]. Although CSF glucose levels are slightly higher in foals, they rapidly decline with age (Furr and Vender, 1994) [12]. According to Ettinger and Feldman (2005) [9], any condition that causes hyperglycemia (Diabetes mellitus), encephalitis, spinal cord compression, brain tumours, or brain abscesses is associated with an elevated glucose concentration in the CSF (hyperglycorrhacia). Animals with a reduced CSF glucose level (hypoglycorrhacia) have pronounced neutrophil pleocytosis, bacterial meningitis, and systemic hypoglycemia. A possible mechanism is glucose consumption by neutrophils and bacteria (Bailey and Vernau, 1997; George, 1996) [2, 14]. Low CSF glucose levels are present in canines with nervous distemper (Ettinger and Feldman, 2005) [9].

Chloride

Usually, there are differing concentrations of this chemical in blood and CSF. The typical range of CSF concentrations in domestic animals is 650–850 mg/dl. While CSF chloride levels are frequently higher than those in serum, lower values have been documented in circumstances such pyogenic meningitis, persistent vomiting, severe pneumonia, and hypochloremia.

Sodium

The amount of sodium in CSF is similar to that in the blood serum. According to Jamison and Lumsden (1988) [18] when the sodium level in the CSF is greater than 160 mEq/L, salt poisoning is thought to have occurred.

Cholesterol

CNS haemorrhages, malignancies, meningitis, and brain abscesses all result in higher cholesterol levels. Normal cholesterol levels are typically relatively low and range from 0.36 to 0.55 mg/dl in horses and 0.51 mg/dl in goats.

Activity of enzymes

Increased values of CSF ALT (alanine aminotransferase): 20.1 (9-46 unit) & AST (aspartate aminotransferase): 13.7 (2-32 unit) have been observed in dogs suffering from canine distemper with invasion of the CNS, purulent meningitis, & cerebral infarction. Furthermore, lactic dehydrogenase enzyme levels in the CSF are raised in cases of bacterial meningitis, metastatic malignancy, lymphoid tumor, subarachnoid hemorrhage, and cerebral infarction. Some neurological illnesses are also associated with an increase in CPK (creatinine phosphokinase) levels.

Calcium: In contrast to serum, CSF often has lower calcium levels. An increase in calcium that is protein-bound in the CSF is a sign that the blood-brain barrier is malfunctioning.

Chemical examination of CSF

Tests	Observations	Inference
Foam Test Take cerebrospinal fluid in test tube and shake the test tube for 5 mins	Slight foam that dissappears after few minutes More foam that remains	Normal protein levels Protein levels increased
Sulfosalicylic Acid Test 3 ml of 3% sulfosalicylic acid + 1 ml of CSF Mix and allow to stand	Increase in the turbidity	Presence of proteins
Nonne –Apelt Test 1ml saturated ammonia solution + 1 ml of CSF	White to greyish ring at the junction of two fluids	Presence of increased amount of globulin in CSF which is seen in *Encephatlitis, Meningitis*, Haemorrhage, Neoplasia, Hydrocephalus, Tissue destruction, Uraemia, Toxoplasmosis, Pneumonia.
Pandy's Test 1ml saturated phenol/ Pandy's reagent, 1-2 drops of CSF	White cloudy or turbid	

3) Cytological Analysis

Small lymphocytes are the most common cell type among mononuclear cells, which make up almost all of the cells in normal CSF (Bailey and Vernau, 1997) [2]. Since cells quickly degrade, the CSF's total cell counts must be determined within about 20 minutes of collection. Similar to how blood's WBCs are calculated, the number of cells is estimated. The number of cells in one cubic millimetre of CSF is calculated by multiplying the total number of cells by 0.6. Pleocytosis, or an increase in WBCs, is a symptom of inflammatory diseases of the brain, spinal cord, or meninges, encephalitis from abscesses in the brain or spinal cord, chronic inflammatory diseases, toxic diseases, or degenerative diseases.

Cattle, Sheep and Pig	0-15 cells/ cu mm
Dog	Upto 25 cells/cu mm
Horse	Upto 23 cells/cu mm

Differential Count

Prepare a CSF smear, dry it, then stain it with leishman's stain before looking at it under a microscope. While lymphocytosis is seen in conditions including uremia, toxaemia, persistent viral infections, and fungal infections, neutrophilia is a sign of bacterial or pyogenic infection, brain abscesses, bacterial meningitis, encephalitis, and hemorrhaging.

4) Bacteriological Analysis

When the protein and cell counts in the CSF are high, it is done. Through the use of culture techniques, the organisms are extracted from CSF.

Diagnostic Significance of CSF

A recent study by Bennett *et al*. 2022 assessed the CSF analysis and short-term survival outcomes in South American camelids. The study found that a CSF TNCC (Total Nucleated Cell Count) of ≥3 cells/μL is associated with decreased odds of short-term survival in these animals. In dogs, bacterial meningoencephalitis should be considered as a differential diagnosis even when a nondegenerative neutrophilic pleocytosis is found on CSF analysis (Song *et al*. 2015) [28]. Another study suggested that concentrations of Vascular Endothelial Growth Factor (VEGF) in CSF are higher in dogs with CNS neoplasia compared to those with meningoencephalomyelitis and other neurologic disorders (Mariani *et al*. 2021) [21]. In bovine species, a retrospective review proposed a cutoff around 200 RBC/μL as clinically meaningful in bovine CSF (Puerto-Parada *et al*. 2022) [24]. Zakia *et al*. 2022 aimed a study to characterize the findings in CSF analysis of horses, cattle, and sheep diagnosed with rabies. The study found that CSF from animals diagnosed with rabies was either normal or characterized by mild mononuclear pleocytosis and hyperproteinorrachia.

Prognostic Significance of CSF

Equine Parvovirus-CSF and EqCoPV were discovered to have a moderate-to-high prevalence rate in serum & fecal samples of horses, according to research done by Yoon *et al*. in 2021. The equine parvovirus infection was significantly correlated with age, the country of foaling, plus clinical colic symptoms. A dog with a neurologic condition's CSF was analyzed cytologically in order to find a rare instance of Toxoplasma gondii. The study highlighted the critical significance of CSF cytology for canine toxoplasmosis diagnosis (Borges-Silva *et al*. 2021) [5]. A CSF-based boron delivery system may boost the uptake of boron for boron neutron capture therapy in veterinary medicine, according to a preliminary study on the therapeutic approach of CSF (Kusaka *et al*. 2022) [20].

Conclusion

In conclusion, the study of cerebrospinal fluid in veterinary species is a dynamic field that continues to provide valuable insights into the pathophysiology of various neurological diseases. Further research is needed to fully understand the potential of CSF analysis in the diagnosis and treatment of these conditions. While significant strides have been made in understanding the role of CSF in various conditions, more research is needed to establish standardized protocols for CSF analysis across different animal species. Despite the progress, the biochemical analysis of CSF poses several challenges including the invasiveness of the collection procedure, potential for sample contamination, and the small volume of sample. Further advancements in minimally invasive collection techniques and the identification of new biomarkers for early disease detection are anticipated (Bathen-Noethen *et al*., 2008) [3].

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