Clinical Relevance of Cerebrospinal Fluid in Dogs (Review)

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Abstract: From the early 20th century, the cerebrospinal fluid (CSF) analysis was an invaluable diagnostic process in clinical neurology and later in veterinary neurology. For the clinicians, the CSF analysis provides reliable information about the neurological health and the presence of a disease.

The purpose of this review is to bring scientific evidence and support for the current state regarding the clinical relevance of cerebrospinal fluid analysis in veterinary neurology. The utility of this review is to highlight the canine breed specific diseases in veterinary neurology and the role of CSF analysis for the diagnosis of CSF inflammatory disorders.

The analysis of cerebrospinal fluid represents an important diagnostic tool, which has to be assessed in every neurological patient in order to obtain information about the central nervous system. Moreover, we strongly encourage to step forward with this diagnostic procedure and corroborate with the diagnostic imaging results.

Keywords: Cerebrospinal fluid, inflammation, cytology, dog

Introduction

Cerebrospinal Fluid (CSF) is an ultra-filtrate of plasma that is produced by the choroid plexus within the ventricular system to the central canal of the spinal cord. CSF has multiple roles in the central nervous system, such as physical support, pressure modulation, metabolites, nutrients, neurotransmitters transport and maintains also the ionic balance (Di Terlizzi and Platt, 2009).

Changes in the central nervous system can cause changes in the functionality and composition of the CSF to a greater or lesser degree. This is why CSF became an integral part of the neurological investigation. For veterinary practitioners information about the CSF can lead to neurological disorders, such as inflammatory, degenerative or neoplastic (De Lahunta, 1977; Vandevelde and Spano, 1977).

To obtain CSF from a patient, there are specific collection sites, such as cerebellomedullary cistern and from the lumbar subarachnoid space. Details of the CSF collection techniques were not the objective of this review and are found elsewhere (Jamison and Lumsden, 1988).

After the collection, the cerebrospinal fluid analysis should be done within 30 minutes for an
accurate cell count and cytology (Chrisman, 1992). The CSF white blood cell (WBC) count is one major part of the analysis. Normal values are considered 5 cells/μL.

Elevated CSF WBC count is called pleocytosis and usually, it is associated with inflammation of the central nervous system (CNS). CSF cytology is necessary at every CSF evaluation, even if the WBC is low (Christopher et al., 1988). Another parameter routinely evaluated on CSF is the total protein. Normal protein levels may be 10 to 25 mg/dL in the CSF, compared to normal serum level 5 to 7.5 g/dL (Jamison and Lumsden, 1988). Elevation of CSF protein level may appear in diseases that alter the BBB, local necrosis, interruption of the CSF flow or intrathecal globulin production (Sorjonen, 1990).

**Inflammatory disorders affecting the canine CNS**

Inflammatory diseases of the CNS in dogs with forebrain neurological signs are important diagnostic considerations. A variety of inflammatory conditions of the CNS can cause CSF changes. Inflammatory conditions can be divided into infectious etiology (such as bacterial, canine distemper virus, rabies, cryptococcosis, toxoplasmosis, and neosporosis infection) and non-infectious. Meningoencephalomyelitis termed also meningoencephalomyelitis of unknown origin, has several subtypes: steroid responsive meningitis - arteritis, eosinophilic meningoencephalitis, granulomatous meningoencephalo-myelitis (GME) and necrotizing encephalitis (with two subtypes: Necrotizing meningoencephalomyelitis (NME) and necrotizing leucoencephalitis) (Cornelis et al., 2019). All have a common pathological characteristic described, influx of leukocytes into the brain, spinal cord or meninges. In the inflammatory process more than one structure can be involved, for instance inflammation of the brain and meninges together (William, 1998).

A usual misconception among veterinarians is that dogs with inflammatory CNS disease are usually with systemic manifestations also but commonly have no extraneural signs. Moreover, the neurological deficits are not disease-specific, because the inflammatory process can affect any portion of the CNS and can develop a variety of neurological signs (Tipold, 1995). A retrospective study on diagnosis of inflammatory and infectious diseases of the CNS in dogs shows that generalized or focal seizures are common findings and are seen in 13% of dogs with inflammatory disease of the CNS (Tipold, 1995). Other clinical signs manifested in inflammatory disorders localized in the CNS are central vestibular dysfunction, hypermetria or disorders of consciousness (Nelson and Couto, 2014).

A retrospective study of Radaelli and Platt (2002) about bacterial meningoencephalomyelitis in dogs demonstrated that it is an uncommon disease, but should be considered when an animal is presented with CNS signs, acute neck pain, and pyrexia. Furthermore, the neurological signs, neck pain, and pyrexia with abnormal complete blood count and serum chemistry profiles were shown to be useful to indicate an infection localized in CNS. In the same study, CSF was analyzed in 14 dogs and the CSF was abnormal in 93% of samples. All of them had abnormal CSF protein level (range: 164–777.7 mg/dL; mean: 337.0 mg/dL; reference range: 15.0–35.0 mg/dL) and 11 of 13 dogs had increased WBC cell count (range: 18–10,850 cell/μL), with a prevalence of neutrophils in 9 of the 13 dogs, monocytes in 2 of the 13 dogs, lymphocytes and eosinophils in 1 of 13 dogs. The CSF was also cultured in 8 of 14 dogs. The results of the culture of CSF in 8 dogs were positive in only 1 (13%) sample (Corynebacterium spp) (Radaelli and Platt, 2002).

Canine distemper virus has various neuropathological presentations; under natural condition, acute to chronic demyelinating encephalomyelitis is the most widespread clinical forms. Neurological manifestations usually begin after 1 to 3 weeks after recovery from the initial systemic illness and may involve disorientation, seizures and circling. Moreover, “chewing gum” seizures produced by polioencephalomalacia of temporal lobes are frequently described. Additional “distemper chorea” is very common in dogs with distemper encephalomyelitis (Greene and Appel, 2006).

Related to cryptococcosis, in a large case series from 195 patients (dogs and cats) thirty percent of the dogs had CNS and/or disseminated signs. This study shows that cats are five times more prone to develop cryptococcosis than dogs (O’Brien et al., 2004).

Protozoa is not a common cause of neurological diseases in canine (Thomas, 1998), however, Toxo-
plasma gondii and Neospora caninum (Paixão and Santos, 2004) are occasionally reported. Based on a study, many animals are serologically positive for toxoplasmosis, although few develop clinical manifestations of the disease (Dubey and Lappin, 2012). However, studies showed that the most common clinical signs of CNS in toxoplasmosis were ataxia, seizure, tremor, cranial nerve disorders, progressive paresis and paralysis (Averill and De Lahunta, 1971; Nesbit et al., 1981; Suter et al., 1984; Braund, 1988; Davidson, 2000).

In a recent report in which Neospora caninum and Erlichia canis co-infection was described (Aroch et al., 2018), CSF obtained from cisterna magna showed a marked pleocytosis, the total nucleated cell count was 650 cell/µL and increase protein concentration was observed (791.3 mg/dL). CSF cytology showed a mixed pleocytosis with 44%, eosinophils, 34% monocytes, 14% neutrophils, 6% lymphocytes and 2% reactive macrophages (Aroch et al., 2018). CSF cytology may reveal bacteria or fungal elements, further CSF culture can solution the definitive diagnosis (Chrisman, 1992). Meningoencephalomyelitis of unknown origin (MUO) enclose the idiopathic CNS diseases (Talarico and Schatzberg, 2010). This group of diseases has a worldwide distribution and was reported for 5% to 25% of all CNS disorders in canine patients (Cuddon and Smith-Maxie, 1984). An anti-astrocyte autoantibody was recently identified in the cerebrospinal fluid of dogs with GME or NME, indicating a possible relationship between these two diseases and the autoantibody (Matsuki et al., 2004). Clinical signs secondary to MUO may be acute or chronic and can result in focal or multifocal lesions. In recent studies, Pugs, Maltese and Chihuahuas were considered to have a possible genetic predisposition for developing MUO (Schauffen et al., 2014; Barber et al., 2012). GME may have a mild to moderate CSF lymphocytic pleocytosis (Bailey and Higgins, 1986b). Other study described the cytological aspects of pleocytosis associated with GME, in which the predominant cells are mononuclear, including small lymphocytes (60% to 90%), monocytes (10% to 20%) and large macrophages (Braund, 2005). Neutrophils usually are 1% to 20% of the cell population; but occasionally they can be the predominant cell type, accounting from up to 50%-60% of the cell type (Braund, 2005; Munana and Luttgen, 1988; Bailey and Higgins, 1986a). According to Braund (2005) in dogs with GME, the total nucleated cell count usually ranges from 50 to 900 cell/µL, varying from 0 to 11,840 cell/µL. Thomas and Eger (1989) showed that about 10% of dogs with GME had normal cell count values.

In another study (Lamb et al., 2005) the authors described the signs that may be associated with meningoencephalitis on magnetic resonance imaging (MRI). Twenty-five dogs with inflammatory CSF were included, 76% of them showing MRI abnormalities. Although as shown above, several diagnostic techniques were employed for the diagnosis of MUO a definitive diagnosis can only be made by histopathological examination (Uchida et al., 2016).

In order to reach a diagnosis, the infectious diseases of the CNS should be commonly ruled out by serum/CSF titers and polymerase chain reaction testing, although studies demonstrated that infectious etiologies are uncommon causes of inflammatory disease in the USA and Europe (Schatzberg et al., 2005; Barber et al., 2012). MRI and CSF analysis are also important diagnostic tools and could be considered for the definitive diagnosis (Smith et al., 2009).

Degenerative and neoplastic disorders on canine CSF

In CNS neoplastic disorders CSF analysis is frequently nonspecific, but occasionally, if neoplastic cells are exfoliated as may occur in lymphoma, CSF analysis could confirm the diagnosis (Meinkoth and Crystal, 1999; Freeman and Raskin, 2001; Baker and Lumsden, 2000). More frequently, CSF analysis may help to distinguish the inflammatory or neoplastic nature of a mass seen on MRI (Bohn et al., 2006). In canine primary intracranial neoplasia, CSF inflammatory changes can be consistent with albumino-cytological dissociation (Bagley et al., 1999). Elevated nucleated cell counts are caused not only by primary CNS inflammation, but also in secondary inflammatory responses to trauma, neoplasia, infarction, haemorrhage related with intervertebral disc disease (IVDD) and fibro-cartilaginous embolism (total nucleated cell count 6-1200 cells/µL) (Meinkoth and Crystal, 1999; Bagley and Bohn, 2003; Lamb et al., 2005). It has been recommended that CSF analysis is avoidable
in those cases in which MRI findings is strongly suggesting of IVDD (Bohn et al., 2006), although CSF pleocytosis is positively associated with the severity of the spinal cord injury in IVDD. Moreover, the percentage of macrophages can be used as a prognosticating value for dogs with IVDD and loss of deep pain sensation (Srugo et al., 2011).

Conclusion

Central nervous system inflammation is an important disorder to be considered when a dog is presented with a history of abnormal behaviour, vestibular signs or seizures. Cerebrospinal fluid analysis is an ancillary diagnostic test that can give important information about the types of CNS inflammation and provide a differential diagnosis. Additional diagnostic tests as advanced clinical imaging and molecular biology can further corroborate the information obtained by CSF analysis and provide more accurate clinical diagnosis. Despite its clinical usefulness, the information obtained by cerebrospinal fluid analysis should be interpreted as a preliminary diagnostic. Furthermore, new biomarkers which can improve the clinical diagnosis of neurological diseases need to be introduced and tested also in veterinary medicine.

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