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DIAGNOSIS AND TREATMENT OUTCOME OF A DOG WITH MENINGOENCEPHALITIS OF UNKNOWN ORIGIN USING A COMBINATION OF PREDNISOLONE AND CYTOSINE ARABINOSIDE: A CASE STUDY

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Abstract

One of the most common causes of brain dysfunction in small dogs is meningoencephalitis of unknown origin. Prognosis and treatment outcome for this disease are often challenging, so diagnosis and therapeutic protocols must be strictly followed in order to increase the patient survival rate. This article presents the clinical features and the therapy results of a 4 years-old Yorkshire terrier dog in which neurological examination and MRI scan findings were subsequent for an inflammatory lesion of the forebrain. A protocol including cytosine arabinoside and prednisolone at immunosuppressive doses was started and neurological reassessment was performed before each administration and one month after the completion of the protocol. The findings consisted of a slightly improvement of mental status, posture, proprioception and gait. Additionally, the owner claimed that the patient has a better quality of life. To the best of the authors knowledge, this is the first reported case in which cytosine arabinoside in combination with prednisolone was used to treat meningoencephalitis of unknown origin in a dog in our country.

Key words: *cytosine arabinoside, meningoencephalitis of unknown origin, forebrain disease, MRI diagnostic*.

INTRODUCTION

Meningoencephalitis of unknown origin (MUO) is an inflammatory disease of the brain that is unrelated to infectious agents and in general it has a good response to immunosuppressive treatment (Dewey, 2016). The group of non-infectious or autoimmune type of meningoencephalitis includes several diseases, such as: granulomatous meningo-encephalitis, necrotizing meningoencephalitis, necrotizing leukoencephalitis and eosinophilic meningoencephalitis (de Lahunta & Glass, 2009). Although many attempts have been made to corelate brain lesions to a specific etiological agent, so far, the most plausible hypothesis remains the involvement of an immune-mediated mechanism in triggering the disease (Schatzberg et al., 2005). Considering this, the therapy of choice for this condition is represented by immunosuppressants, especially steroids. However, recent studies have shown that the addition of cytosine arabinoside to the classic treatment plan has prolonged patients' lives and has improved clinical signs (Menaut et al., 2008; Nuhsbaum et al., 2002; Lowrie et al., 2013; Zarfoss et al., 2006).

Cytosine arabinoside is a drug with anti-inflammatory and antineoplastic properties able to cross the blood - brain barrier (Scott-Moncrieff et al., 1991). Compared with corticosteroids, this medicine does not cause polyuria, polydipsia and liver dysfunction (MacEwen & Young, 1989).

The aim of this paper is to present the clinical features and the therapy results of a 4 years-old Yorkshire terrier dog in which neurological examination and MRI scan findings were subsequent for an inflammatory lesion of the forebrain.

MATERIALS AND METHODS

The dog included in the case study was referred at the Clinic of the Faculty of Veterinary Medicine of Bucharest for a specialised consultation. The evaluation was performed according to the protocol already implemented in our clinic for neurological patients which has the following steps: animal signalment, history,

physical and neurological examination, neurolocalisation of the disease, differential diagnosis using the acronym VITAMIND (vascular, inflammatory / infectious, traumatic, anomalous, metabolic, idiopathic, neoplastic, degenerative), recommendations of paraclinical investigations, diagnostic and treatment (Neagu et al., 2018; Turbatu et al., 2019).
Therapy included immunosuppressive doses of prednisolone (1 mg/kg twice a day tapered over 6 months) and cytarabine arabinoside (50 mg/m² twice per day for 48 hours, repeated every three weeks and administered subcutaneously) (Menaut et al., 2008).
A reassessment was performed before each use of the protocol and one month after the end of the therapy in order to record all changes and the possible side effects.

Animal signalment and history

A 4-year-old dog, male, spayed, Yorkshire terrier was referred for a neurological consultation with a two weeks history of walking into objects and falling on the right side. Two days prior to consultation, the patient also started circling (in small circles) on the right side. The appetite for food and water was normal and the owner did not notice any changes in urination or defecation. Until the moment of examination, there was no other treatment in progress for this case. The vaccination and deworming schemes were updated according to the standard protocols and included also the rabies vaccine- considering the fact that the dog was presented with a nervous symptomatology and rabies cases have been reported in our country, this was an important information to consider (Vuță et al., 2017). Previously, the dog had been examined by an ophthalmologist, as the owner considered that the apparent lack of vision determined the patient to walk into objects, who concluded that the symptomatology was not caused by ocular lesions and recommended a neurological examination.
After the physical examination, we proceeded to neurological examination in order to identify and establish the localisation of the lesion within the nervous system. Mental status, posture, cranial nerves, proprioception, gait, spinal reflexes and sensory testing were assessed. Findings were recorded in the neurological examination sheet, which has been used to monitor the subsequent evolution of the case.

RESULTS AND DISCUSSIONS

Physical and neurological examination findings

The physical examination revealed a normal body temperature (38.7 ºC), a cardiac frequency of 118 beats per minute synchronous with femoral pulse, a respiratory rate of 23 respiration per minute, pink mucous membranes and a capillary refill time of 1.5 seconds. The palpable lymph nodes were normal in shape and consistency and the patient did not express pain when the abdomen was deeply palpated.
First step of the neurological examination was based on observation, so we started by evaluating mentation, posture and gait. Findings were a depressed mental status, head turn to the right side and lumbar hyperlordosis to the same side, kyphosis. Gait was characterized by small circles on the right side, also. Proprioception tests revealed deficits characterized by a delayed reaction in the left thoracic and pelvic limbs on proprioceptive positioning, hemiwalking, tactile placing and extensor postural thrust. Cranial nerves assessment shown anisocoria (right pupil smaller than the left pupil), an absent cotton ball response on both eyes, a menace response delayed for the left eye and absent for the right eye and positional ventrolateral strabismus (Figure 1).

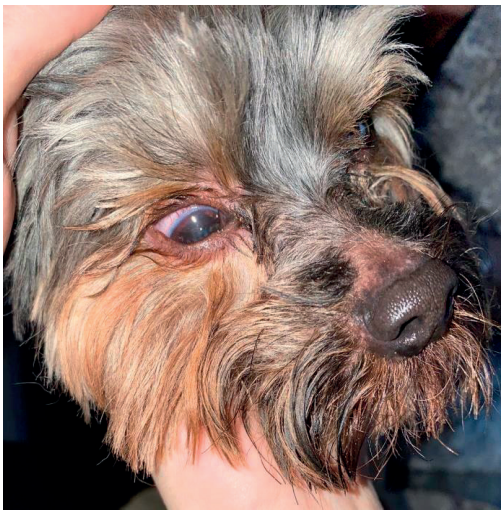


Figure 1. Cranial nerve deficits: positional ventrolateral strabismus

Palpebral, corneal reflexes and sensitivity of the face were normal. Following gait and postural reactions testing, we evaluated spinal reflexes, which were normal in all four limbs, but with a delayed flexion on both pelvic limbs. Panniculus and perianal reflexes were also normal.
Based on main neurological examination findings, the lesion was localised in forebrain and right central vestibular system, being characterised as a diffuse or multifocal lesion.

Paraclinical investigations and diagnosis

After we localised the lesion, the next step was to establish the list of differential diagnoses using the acronym VITAMIND.
Considering the subacute and progressive evolution of the disease and the neurological deficits, the main pathologies taken into account were the ones with vascular, inflammatory or neoplastic origin. An anomaly (like ventricular asymmetry or hydrocephaly) could not be ruled out given signalment of the case and specific clinical signs like bilateral ventrolateral strabismus, depression or lack of vision (Przyborowska et al., 2013).
In order to obtain an etiological diagnosis, we recommended a set of biochemistry and haematology analyses, a cardiologic examination and an MRI scan. No abnormalities were detected on blood analysis and the cardiologist ruled out any modification of the heart that could have produced the symptomatology.
An MRI examination and a cerebrospinal fluid collection test were conducted 1 month after the presentation.
The magnetic resonance examination was performed on the neurocranium with a VET MR GRADE device from ESAOTE with a power of 0.3 Tesla. Protocols used to obtain images consisting of T1 Spin Eco (SE) and T2 Fast Spin Eco (FSE) sequences in three planes (sagittal, transverse, and dorsal) and post contrast images were obtained in T1 sequences, after intravenous contrast administration. The animal underwent inhalation anaesthesia to obtain high quality images and free of motion artefacts.
Interpretation of the MRI results demonstrated a lesion with T2 / FLAIR hyperintense signal, T1 hypo-signal and slight post-administration T1 contrast enhancement, with localization at the right thalamus and the temporal lobe, without mass effect (Figures 2, 3, 4A, 4B and 5).

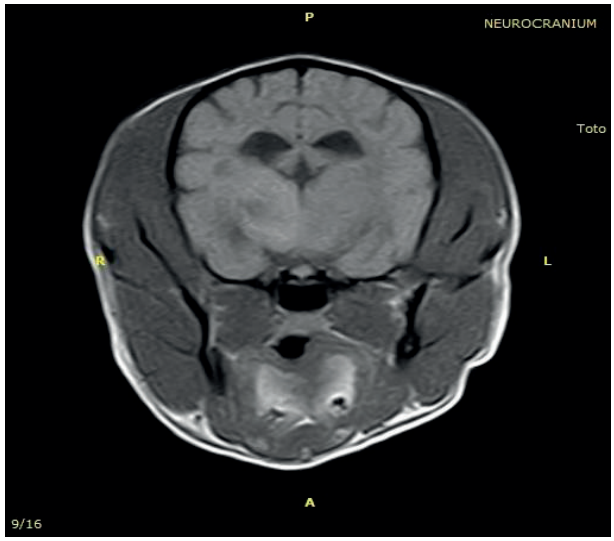


Figure 2. T2 / transversal: Transverse section at the level of the thalamus and the ventricular system, area with hyperintense signal, diffused at the level of the cerebral nervous substance, with localization at the level of the right temporal lobe and the right thalamus, without mass effect

The findings on MRI scan supported a diagnosis of multifocal inflammation. In this case differential diagnosis was made between meningoencephalitis of unknown origin (especially necrotizing encephalitis) and a neoplastic process, although there was no mass effect that compresses the ventricular system or other structures.

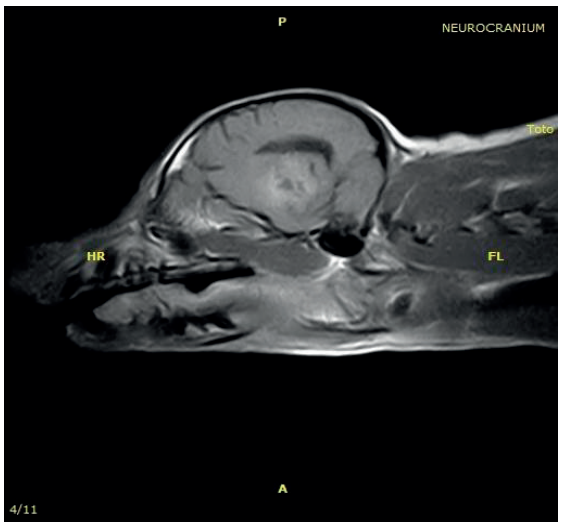
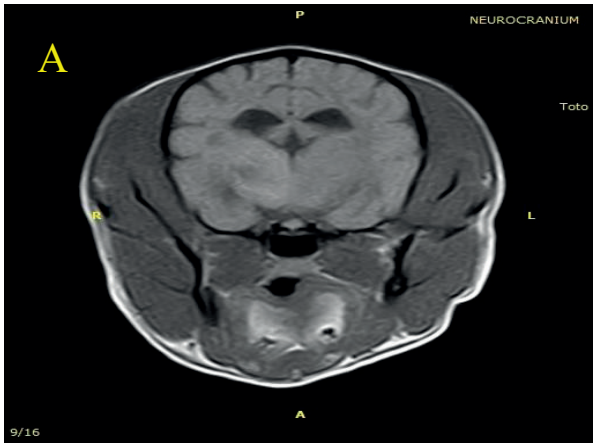


Figure 3. Sagittal section in the right temporal lobe, areas with hypointense signal, with slightly perilesional hypersignal, diffused in the cerebral nervous substance, without mass effect



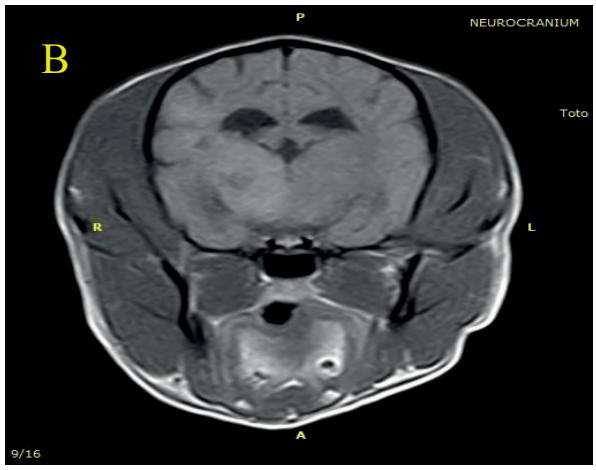


Figure 4A and 4B. **A:** Transverse section at the level of the thalamus and the ventricular system, areas with hypointense signal, diffused at the level of the cerebral nerve substance, with localization at the level of the right temporal lobe and the right thalamus, without mass effect.
B (contrast enhancement): Transverse section at the level of the thalamus and ventricular system, slight hyperintense signal outlet at the level of the lesion

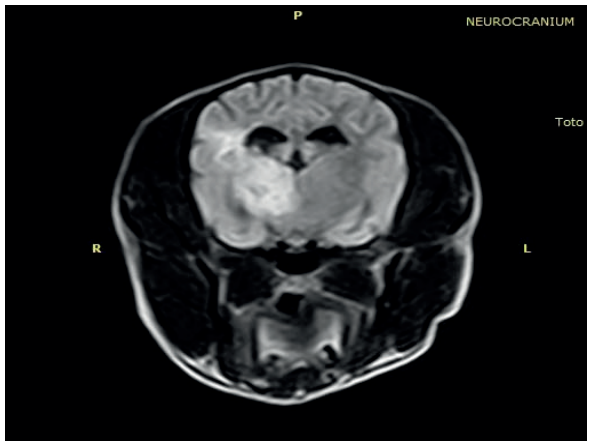


Figure 5. Transverse section at the level of the thalamus and the ventricular system, area with hyperintense signal, diffused at the level of the cerebral nerve substance, with localization at the level of the right temporal lobe and the right thalamus, without mass effect

Cerebrospinal fluid examination shown mild pleocytosis (mononuclear cells) and elevated protein levels: protein level in mg per dl- 36 (normal < 30), total nucleated cell count in µl: 9 (normal < 6).
Necrotizing encephalitis of unknown etiology has been reported in several breeds of dog and Yorkshire terrier is one of that breeds. Considering that clinical signs for this pathology include visual deficits, circling or depression, which means deficits compatible with a diffuse lesion of forebrain and central vestibular system, diagnostic suspicion in the case presented in this article has a strong scientific basis (Kuwamura et al., 2002).

Treatment and follow-up

Before we started the protocol of treatment with cytosine arabinoside (Cytarabine 100 mg/1ml, solution for injection or infusion – Accord Healthcare®) and immunosuppressive doses of prednisolone, the patient was under treatment with prednisolone (1 mg/kg BID), ceftriaxone- beta lactam antibiotic (25 mg/kg BID) and a product that supports liver function for 4 weeks, as we initially suspected an infectious encephalitis. During this time, the clinical condition and neurological deficits worsened with partial extrusion of the tongue as a consequence of multiple cranial nerves deficits and depressed mental status, left hemiparesis, loss of balance, more often circling and falling on the side.
Considering that this case did not responded to the classic immunosuppressive therapy, a protocol of cytosine arabinoside was used and the patient was re-examined before each administration and one month after treatment. To the best of the authors knowledge, this is the first reported case in which cytosine arabinoside in combination with prednisolone was used to treat meningoencephalitis of unknown origin in a dog in our country.
The protocol of cytosine arabinoside and prednisolone was started on 6 May 2019 and it was followed in accordance with guidelines from previous studies (Menaut et al., 2008; Nuhsbaum, 2002; Zarfoss, et al., 2006). In addition, we completed the treatment with a product that supports function of the liver (administered to diminish the adverse side effects of the prednisolone).

We administered 9 cycles of 4 subcutaneous injections of cytosine arabinoside (Figure 6) given 12 hours apart for 2 days and we lowered the dose of prednisolone every 6 weeks.
A reexamination was performed before every administration of the protocol and one month after the end of treatment. The doses used and clinical evolution can be seen in Table 1.
In the first six weeks of treatment, the neurological deficits were stationery and owner did not observe any changes in the behavior or the quality of life of the dog, excepting polyuria and polydipsia which have been associated with the administration of prednisolone.
After the 4th administration, neurological examination showed a normal position of the head, improved proprioception, a better ability to walk and a decreased frequency of circling on the right side.

Table 1. Treatment schedule for the cytosine arabinoside and prednisolone protocol and evolution of clinical condition

Date of administration	Cytosine arabinoside	Prednisolone	Clinical evolution
6.05.2019	50 mg/m² BID for 48 hours	1 mg/kg BID	Worsen
27.06.2019	50 mg/m² BID for 48 hours	1 mg/kg BID	stationary
18.07.2019	50 mg/m² BID for 48 hours	0.5 mg/kg BID	stationary
8.08.2019	50 mg/m² BID for 48 hours	0.5 mg/kg BID	Improved
29.08.2019	50 mg/m² BID for 48 hours	0.25 mg/kg BID	Improved
19.09.2019	50 mg/m² BID for 48 hours	0.25 mg/kg BID	Improved
10.10.2019	50 mg/m² BID for 48 hours	0.25 mg/kg every other day	Improved
31.10.2019	50 mg/m² BID for 48 hours	0.25 mg/kg every other day	Improved
21.11.2019	50 mg/m² BID for 48 hours	0.25 mg/kg every third day	Improved
BID= twice a day			

The favorable evolution could be observed also in the following reassessments, including an improvement of the cranial nerve deficits: normal pupils' size, a present cotton ball response on both eyes and a better menace response. Owner noticed that the animal was more active and able to navigate skillfully around obstacles. Also, it began to resume activities that were common before the onset of clinical signs.
In this condition, the cytosine arabinoside was removed and the clinical recommendation was to continue with prednisolone at a very low dose (0.25 mg/kg every third day) and supplements that support the activity of the brain. In addition, dietary recommendations included optimized nutrition for the nervous system have been made.
Approximately 4 months after discontinuing the treatment, the dog was very actively and with a normal behavior.

CONCLUSIONS

Meningoencephalitis of unknown origin is a common disease of small breeds.
In order to obtain a correct diagnosis for this disease, findings of physical and neurological examination, as well as the imaging aspects and the results of the examination of the cerebrospinal fluid must be correlated.
The protocol of treatment including cytarabine arabinoside and prednisolone was used successfully to treat a case of 4-years-old Yorkshire Terrier, whose clinical, imagistic and cerebrospinal fluid results were subsequent for a diagnostic of necrotizing encephalitis.
Since the evolution of the patient was favorable, the histological confirmation of the diagnostic could not be accomplished.

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