Cushing reflex associated with a presumed global brainstem ischemia in a dog: diagnostic procedures and outcome

A. COLSON[1]*, D. FANUEL-BARRET[1], R. JOSSIER[1], M. FUSELLIER-TESSON[1], P. COSTIOU[1], J.Y. DESCHAMPS[1]

[1]*Veterinary Teaching Hospital, Nantes-Atlantic National College of Veterinary Medicine, Food Science and Engineering – Oniris. Atlanpôle-La Chantrerie, route de Gachet, B.P. 40706, 44307 Nantes cedex 3, FRANCE.*

**Corresponding author: arnaudcolson@yahoo.fr*

SUMMARY

A dog was admitted for peracute onset of coma and Cushing reflex. This report describes diagnostic procedures, successful management, and outcome of a suspected brainstem ischemia with transient sequel in a dog.

Keywords: Dog, brainstem, stroke, Cushing reflex, intensive care.

RÉSUMÉ

Réflexe de Cushing associé à une probable ischémie du tronc cérébral chez un chien : prise en charge diagnostique et suivi

Un chien a été hospitalisé pour un coma associé à un réflexe de Cushing aigus. Ce cas illustre la prise en charge diagnostique et thérapeutique et le suivi d'une suspicion d'ischémie du tronc cérébral avec des séquelles transitoires chez un chien.

Mots clés : Chien, tronc cérébral, accident cérébro-vasculaire, réflexe de Cushing, soins intensifs.

Introduction

Ischemic encephalopathies are characterized by an acute, focal, and non progressive onset of neurological signs resulting from a pathological decrease of the supplying intracranial blood vessels [7, 11, 21]. Cerebrovascular diseases (strokes) are the third leading cause of death in humans but are often misdiagnosed in veterinary medicine [7]. Definitive diagnosis is difficult to establish and requires advanced techniques of medical imaging. Unfortunately, the diagnosis is most often hypothetic. Neurologic signs depend on the affected part of the brain.

Strokes are divided into ischemic events (about 77% of strokes in human medicine) and haemorrhagic events (the remaining 23%) [7]. Several causes are recognized or have been proposed, as severe hypotension, cardiopulmonary arrest, thrombosis, embolism, vasospasm, chronic renal failure, etc [11, 21]. However, acute onset of neurological signs can also be observed in intracranial neoplastic processes due to rupture of cerebral blood vessels supplying the tumour.

The Cushing response is clinically defined as a severe bradycardia associated with a slight arterial hypertension. This life-threatening condition is a sign of global brainstem damage [1, 19].

The present report describes a strongly suspected global brainstem ischemia with an outcome over three months. Several investigations were conducted to explore the extent and find a possible explanation of the damage.

Case history

A five-year-old neutered female Brittany spaniel was admitted with a history of sudden onset of insomnia, non-stop walking, and circling several hours earlier. On admission (day 1), the dog was just amaurotic and its physical examination was normal: heart rate was 100 beats per minute (bpm) and mean systemic arterial pressure was 90 mmHg. Complete blood cell count and blood chemistry profile (total serum protein, glucose, alanine aminotransferase, alkaline phosphatase, blood urea nitrogen levels, and ionogram) were within the referral values. The modified Glasgow score was 16.

On day 2, the dog experienced bilateral menace deficit with normal pupillary light reflex, deafness, abasia, and head pressing. Intracranial hypertension was suspected and mannitol therapy was started at a rate of 1 g/kg intravenously (IV) over 30 minutes every 8 hours. On day 3, the physical examination revealed hypothermia (about 36.5°C) and, several hours later, bradycardia up to about 40 bpm with systemic arterial hypertension up to about 150 mmHg were observed. Then, the dog expressed pendular nystagmus and its level of consciousness decreased progressively up to coma; the modified Glasgow score was 11. These neurological features suggested an acute and symmetric lesion of the brainstem. As a consequence, the dog was placed on a mattress and its jugular veins were kept from external compression. It was intubated and manually ventilated when necessary.

On day 4, the dog was semi-comatose and a 1 T-magnetic resonance imaging (MRI) of the brain under general anaesthesia

was performed using T1-weighted (T1W), post contrast (0.1 mmol/kg IV gadoteric acid; Dotarem; Guerbet) T1-weighted (Gd-T1W), T2-weighted (T2W), T2*-weighted (T2*W), and fluid-attenuated inversion recovery (FLAIR) images. T1W and T2W images showed a slight hyposignal and a strong hypersignal involving the brainstem respectively. The lesion was not highlighted on Gd-T1W images. The T2W hypersignal was also observed on FLAIR and T2*W images. Moreover, nothing abnormal in the lumen of the basilar artery and the arterial circle of the brain was seen. There was no sulci enlargement on the different sequences. To conclude, MRI was consistent with diffuse brainstem oedema, from the diencephalon to the ventral metencephalon. Hence, a diagnosis of global brainstem ischemia was made.

On day 6, the dog was depressive but walking. It was able to drink and eat alone. The modified Glasgow score was 13. Three days later, echocardiography was performed and showed no abnormality concerning the contractility and the anatomy of the heart, in order to exclude a cardiogenic origin of the presumed vascular encephalopathy. The dog was still in bradycardia but the electrocardiogram was normal.

On day 10, short- and middle-latency brainstem auditory-evoked potentials (BAEPs) under sedation, 0.2 mg/kg IV butorphanol tartrate (Dolorex; Intervet), were decided. BAEP recording showed decreased amplitudes of waves II to V, consistent with brainstem involvement (figure 1). Waves VI and VII were normal and therefore demonstrated the integrity of the thalamocortical pathways. On day 12, Doppler ultrasonography with a multi-hertz (5.0-12.0 MHz) sector scanning probe through the suboccipital acoustic window was performed to measure the cerebral blood flow velocity in the basilar artery (figure 2). No sedation was necessary. In spite of slight bradycardia (55 bpm), mean velocity in this artery was about 60 cm/sec and its lumen was free from thrombus. The day after, a second MRI was decided using T1W and T2W images to explore the evolution. The lesion involving the brainstem was still present but only at the level of the pons (figure 3). A second BAEP was assessed and was comparable with the first one.

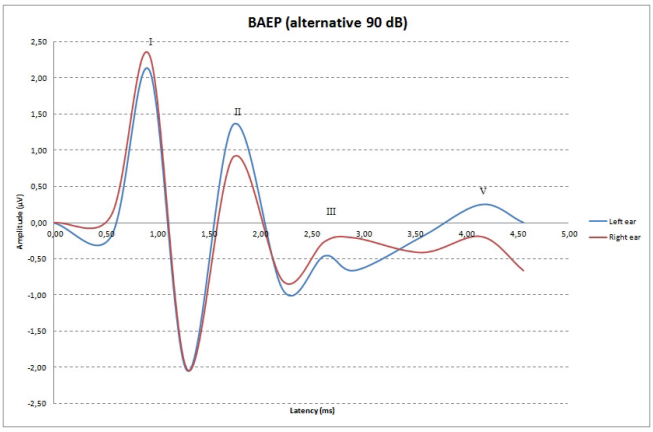

FIGURE 1: Brainstem Auditory Evoked Potential (BAEP) under light sedation with representation of waves I, II, III, and V. The decreased amplitudes of waves II to V are consistent with a brainstem involvement.

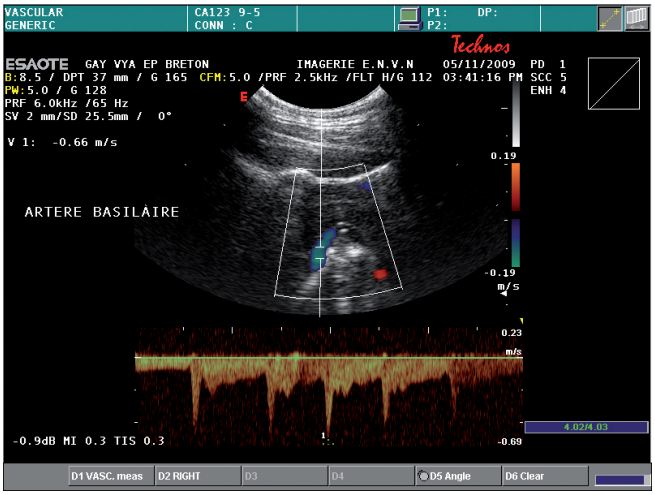

FIGURE 2: Transoccipital Doppler ultrasonography. Sagittal view of the basilar artery showing nothing abnormal in its lumen.

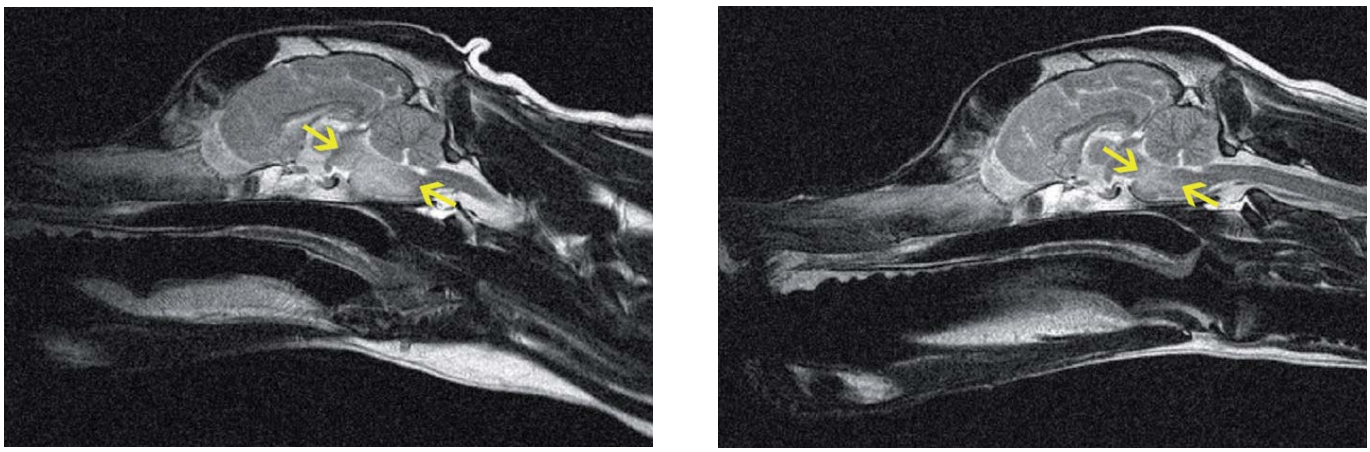

FIGURE 3: Sagittal T2W. **A.** Diffuse hyperintense lesion (arrows) involving the brainstem on Day 4; **B.** Resorption of the lesion involving only the pons (arrows) on Day 13.

During the second week of hospitalization, the dog enhanced polydipsia and polyuria. Urinalysis was performed and showed severe hyposthenuria (urine specific gravity equal to 1.002) compatible with a diabetes insipidus, probably central in origin. Consequently, the dog was given one drop of the 0.1 mg/ml intranasal solution of desmopressin acetate (Minirin; Ferring) in one eye three times a day. Several serum diencephalic hormone concentrations were measured and thyroid stimulating hormone (TSH), growth hormone (GH), and adrenocorticotrophic hormone (ACTH) concentrations were within the referral values in dogs.

The menace response was normal for each eye within 14 days after the admission. The dog seemed to be more attentive to its environment and was discharged 2 weeks after admission. Desmopressin therapy was continued up to the control visit. For the next month, the owners were phoned weekly. The dog was reviewed four weeks after the discharge. Physical and neurological examinations were normal. Urine specific gravity was 1.032. The owners described partial but progressing behavioural recovering.

Discussion

According to the diagnostic procedures, the course of the disease, and the location of the lesion, a global brainstem ischemia was strongly suspected. The brainstem contains, among others, the reticular formation (called "ascending reticular activating system") and all the nuclei of the cranial nerves III to XII. In the caudal part of the brainstem lay the solitary tract and its nucleus, the parasympathetic nucleus of the vagus nerve, the ambiguous nucleus, and the retroambiguous nucleus, that control both the respiratory and the cardiovascular systems [3]. Bradycardia concomitant with slight hypertension is called "the Cushing response", or Cushing reflex (CR) in human neurology [1, 19] but had rarely been described in veterinary medicine. Although physiology and pathophysiology of the CR are not well understood, it has been associated with situations of brainstem ischemia [19]. Unfortunately, CR is often an indicator of imminent death [12]. It is thought that hypoxia of a particular group of sympathetic neurons lying in the brainstem (rostral ventro-lateral medulla) triggers its activation and lead to vasoconstriction [19]. In human medicine, CR has been reported to occur following intracranial hypertension [19], but not in veterinary neurology [12].

Decreased level of consciousness together with abasia and Cushing response helped to locate the lesion diffusely in the brainstem. Amaurosis can be explained by lesions of the afferent pathways of the diencephalon. Interestingly, all cranial nerve tests were normal and there was no proprioceptive deficit until the dog fell into coma. In a cohort of 40 suspected brain infarctions in dogs, 8 were located in the thalamus/midbrain and neurologic dysfunctions included ipsilateral head tilt and hemiparesis [9]. Another report of brainstem infarction described a unilateral involvement of the trigeminal motor nucleus and pyramidal tract [13].

Magnetic resonance imaging showed a lesion in the entire brainstem, hyperintense on T2W, FLAIR, and T2*W images without any mass effect, suggesting a global brainstem oedema [2, 18]. Considering the onset of the disease, the rapid recovery, and the medical imaging conclusions, vasospasms of the basilar artery might have occurred and were responsible for vasogenic oedema and hypoxia of the brainstem. As the forebrain and the cerebellum were both normal on MRI, the vasospasms probably occurred between the arterial circle of the brain (or "circle of Willis") and the caudal cerebellar arteries. The forebrain was indeed still being irrigated by the arterial circle of the brain via the internal carotid arteries [3, 7, 21]. Other advanced techniques of medical imaging exist but are not available routinely in veterinary medicine: magnetic resonance angiography (MRA) and positron-emission tomography (PET-scan). In MRA, data collection occurs immediately after intravenous administration of a paramagnetic contrast agent, which permits to enhance the encephalon vasculature and to measure the diameters of the main arteries [15]. In this case, MRA was not available but no abnormality in the lumen of brainstem vasculature was seen in any conventional MRI sequences. PET-scan is based on the detection and computed analysis of the widespread of a radioactive marker administered intravenously. Administration of 2-18fluoro-2-deoxyglucose, a metabolic marker, is actually helpful in detecting hypoxic territories in the neuroparenchyma [4]. The combination of MRA and PET-scan should have helped us in determining the origin of the suspected vascular encephalopathy reported here. In order to assess functionally and morphologically the basilar artery, transoccipital Doppler ultrasonography was performed without anaesthesia. Cerebral blood flow velocity had already been studied in the case of ischemic brain damage after cardiopulmonary arrest in dogs [6]. Unfortunately, in this study, there were no statistical differences between ischemic brains and normal brains.

BAEPs are a suitable electrodiagnostic test to assess the integrity of auditory pathways [16]. Short-latency BAEP recording is composed of five waves (I to V) and corresponds to the structures situated caudally to the caudal colliculi. Middle-latency BAEP recording is composed of waves VI and VII and corresponds to the thalamocortical pathways [20]. In a previous study of 14 cases of brain diseases in dogs [17], BAEP recordings showed normal wave I together with loss of amplitudes of waves II to V. In our case, latency and amplitude of wave I showed integrity of the inner ear structures whereas low amplitudes of waves II to V demonstrated a loss of auditory integration in the rostral part of the brainstem (cochlear nuclei, nuclei of the trapezoid bodies and lateral lemnisci). According to the owners, the dog seemed to have recovered from deafness and, as a consequence, no other BAEP was performed. Each caudal cerebellar artery delegates a labyrinth artery that supplies the inner ear. To corroborate our hypothesis, vasospasms might have occurred rostrally to the caudal cerebellar arteries.

During its hospitalization, the dog expressed diabetes insipidus. A case of panhypopituitarism following brain trauma was recently described in a dog [5] and that is the reason why several serum diencephalic hormone concentrations were measured in order to evaluate the functional integrity of the hypothalamic-pituitary axis. The dog was administered desmopressin and the urinary specific gravity returned to normal. On the other hand, as the pathophysiology of head trauma and vascular encephalopathies are similar, the neurological status was monitored with the Glasgow coma scale that showed a constant improvement [14].

As a conclusion, the onset of vascular encephalopathies is peracute and neurological signs are often spectacular and disappointing. No specific treatment exists but the outcome is often good if no underlying cause is discovered [8]. Patience from the clinician and the owner, and supporting procedures are required. Euthanasia should not be systematically performed even if the patient is comatose or the Cushing reflex is present. Typically, the patient gets better within 72 hours. However, neurological sequel could persist for weeks or months [10, 21]. The Cushing response is a useful pathophysiological reflex for anatomic diagnosis and sometimes for the prognosis, considering the course of the disease.

Acknowledgement

The authors would like to thank Dr. A. GARAND, Dr. O. MARIE-MAGDELEINE and I. NICHOLSON for their useful help.

References

1. - AGRAWAL A., TIMOTHY J., CINCU R., AGARWAL T., WAGHMARE L.B.: Bradycardia in neurosurgery. *Clin. Neurol. Neurosurg*., 2008, **110**, 321-327.

2. - BENIGNI L., LAMB C.R.: Comparison of fluid-attenuated recovery and T2-weighted magnetic resonance images in dogs and cats with suspected brain disease. *Vet. Radiol. Ultrasound*, 2005, **46**, 287-292.

3. - DE LAHUNTA A., GLASS E.N.: Veterinary neuroanatomy and clinical neurology., Saunders Elsevier, Saint-Louis, 2009, 544 pages.

4. - EOM K.D., LIM C.Y., GU S.H., KANG B.T., KIM Y.B., JANG D.P., WOO E.J., KIM D.Y., CHO Z.H., PARK H.M.: Positron emission tomography features of canine necrotizing meningoencephalitis. *Vet. Radiol. Ultrasound*, 2008, **49**, 595-599.

5. - FOLEY C., BRACKER K., DRELLICH S.: Hypothalamic-pituitary axis deficiency following traumatic brain injury in a dog. *J. Vet. Emerg. Crit. Care*, 2009, **19**, 269-274.

6. - FUKUSHIMA U., SASAKI S., OKANO S., OYAMADA T., YOSHIKAWA T., HAGIO M., TAKASE K.: Non-invasive diagnosis of ischemic brain damage after cardiopulmonary resuscitation in dogs by using transcranial Doppler ultrasonography. *Vet. Radiol. Ultrasound*, 2000, **41**, 172-177.

7. - GAROSI L.S., Mc CONNELL J.F.: Ischaemic stroke in dogs and humans: a comparative review. *J. Small Anim. Pract*., 2005, **46**, 521-529.

8. - GAROSI L.S., Mc CONNELL J.F., PLATT S.R., BARONE G., BARON J.C., DE LAHUNTA A., SCHATZBERG S.J.: Results of diagnostic investigations and long-term outcome of 33 dogs with brain infarction (2000 - 2004). *J. Vet. Intern. Med*., 2005, **19**, 725-731.

9. - GAROSI L.S., Mc CONNELL J.F., PLATT S.R., BARONE G., BARON J.C., DE LAHUNTA A., SCHATZBERG S.J.: Clinical and topographic magnetic resonance characteristics of suspected brain infarction in 40 dogs. *J. Vet. Intern. Med.*, 2006, **20**, 311-321.

10. - HILLOCK S.M., DEWEY C.W., STEFANACCI J.D., FONDACARO J.V.: Vascular encephalopathies in dogs: diagnosis, treatment, and prognosis. *Compend. Contin. Educ. Pract. Vet*., 2006, **28**, 208-217.

11. - HILLOCK S.M., DEWEY C.W., STEFANACCI J.D., FONDACARO J.V.: Vascular encephalopathies in dogs: incidence, risk factors, pathophysiology, and clinical signs. *Compend. Contin. Educ. Pract. Vet.*, 2006, **28**, 196-207.

12. - PACKER R.A., SIMMONS J.P., DAVIS N.M., CONSTABLE P.D.: Evaluation of an acute focal epidural mass model to characterize the intracranial pressure-volume relationship in healthy Beagles. *Am. J. Vet. Res.*, 2011, **72**, 103-108.

13. - PALMER L.: Pontine infarction in a dog with unilateral involvement of the trigeminal motor nucleus and pyramidal tract. *J. Small Anim. Pract*., 2007, **48**, 49-52.

14. - PLATT S.R., RADAELLI S.T., Mc DONNELL J.J.: The prognostic value of the modified Glasgow coma scale in head trauma in dogs. *J. Vet. Intern. Med*., 2001, **15**, 581-584.

11. - SAGER M., ASSHEUER J., TRÜMMLER H., MOORMANN K.: Contrast-enhanced magnetic resonance angiography (CE-MRA) of intra- and extra-cranial vessels in dogs. *Vet. J*., 2009, **179**, 92-100.

12. - SHIU J.N., MUNRO K.J., COX C.L.: Normative auditory brainstem response data for hearing threshold and neuro-otological diagnosis in the dog. *J. Small Anim. Pract*., 1997, **38**, 103-107.

13. - STEISS J.E., COX N.R., HATHCOOK J.T.: Brain stem auditory-evoked response abnormalities in 14 dogs with confirmed central nervous system lesions. *J. Vet. Intern. Med.*, 1994, **8**, 293-298.

14. - TIMM K., FLEGEL T., ÖCHTERING G.: Sequential magnetic resonance imaging changes after suspected global brain ischaemia in a dog. *J. Small Anim. Pract*., 2008, **49**, 408-412.

15. - WAN W.H., ANG B.T., WANG E.: The Cushing response: a case for a review of its role as a physiological reflex. *J. Clin. Neurosci*., 2008, **15**, 223-228.

16. - WEBB A.A.: Brainstem auditory evoked response (BAER) testing in animals. *Can. Vet. J*., 2009, **50**, 313-318.

17. - WESSMANN A., CHANDLER K.E., GAROSI L.S.: Ischaemic and haemorrhagic stroke in the dog. *Vet. J.*, 2009, **180**, 290-303.