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A novel encephalopathy in a thiamine-deficient dog resembling human Wernicke's disease with atypical MRI pattern

Floriana Gernone and Mario Ricciardi*

"Pingry" Veterinary Hospital, via Medaglie d'Oro 5, Bari, Italy

Abstract

Thiamine is a water-soluble vitamin, which participates in several vital metabolic pathways involved in energy metabolism and neurotransmitter synthesis of mammals. In companion animals thiamine deficiency is classically associated with signs of diffuse encephalopathy and lesions on brainstem nuclei and mesencephalic colliculi evident on magnetic resonance imaging. This paper describes a novel clinical presentation in a thiamine-deficient dog showing multifocal, central and peripheral nervous and cardiovascular system alterations. Brain MRI showed bilateral caudate nuclei damage, with necrotic-malacic evolution, similar to the atypical MRI pattern found in Wernicke's encephalopathy in humans. Detection of bilateral symmetrical lesions of the caudate nuclei in dogs should prompt consideration of a thiamine deficiency among the differential diagnoses.

Keywords: Caudate nuclei, Dog, MRI, Thiamine deficiency, Wernicke's encephalopathy.

Introduction

Thiamine, or vitamin B1, is a water-soluble vitamin of the vitamin B complex that plays a vital role in the normal function of the mammalian body (Manzetti *et al.*, 2014). Thiamine must be provided in the diet because of the inability to produce it endogenously (Manzetti *et al.*, 2014). After ingestion, thiamine is adsorbed in the small intestine and mostly transported within the red blood cells (RBCs); the remaining part is bound to plasma proteins or is free in the plasma (Manzetti *et al.*, 2014). In the organism thiamine is present in cationic (T⁺) and phosphorylated forms (Manzetti *et al.*, 2014). The main role of T⁺ is as an antioxidant (Huang *et al.*, 2010) while the pyrophosphate thiamine among the phosphorylated forms has been recognized as biochemically active (Manzetti *et al.*, 2014). Vitamin B1 acts as a coenzyme in the catabolism of carbohydrates and amino acids and has per se an antioxidant role. Notably, it also plays an essential role in a series of metabolic processes related to energy production and conversion of glucose to ATP, as a catalyst in the Krebs cycle (Manzetti *et al.*, 2014). Lastly, it also takes part in the synthesis of neurotransmitters and plays a major role in the central and peripheral nervous and immune system (Chisolm-Straker and Cherkas, 2013; Manzetti *et al.*, 2014). Therefore, thiamine deficiency (TD) causes increased tissue and serum levels of lactic acid and reduced concentrations of several cellular substrates leading to metabolic and developmental diseases that often result in neurological dysfunction primarily affecting the brain and cerebellum (Manzetti *et al.*, 2014).

In humans, TD affects the peripheral nervous system (dry beriberi), central nervous system (Wernicke-Korsakoff syndrome) and cardiovascular system (wet beriberi) (Abdou and Hazell, 2015), and may occur in acute lethal forms (shoshin beriberi, Wernicke's encephalopathy) (Moskovitz *et al.*, 2017).

In animals TD has been associated with a series of clinical conditions related to disorders of nerve and brain development, energy metabolism, digestion, cell proliferation, and cell cycle activity (Manzetti *et al.*, 2014).

In small animal practice, TD has been identified rarely in dogs (Platt and Garosi, 2012).

At first, clinical signs are vague and non-specific and, if not treated, dogs may rapidly show sign of encephalopathy characterized by altered mental status, central vestibular signs, mydriasis and blindness, cervical ventroflexion (only in cats), seizures, coma and even death (Platt and Garosi, 2012).

Classically reported MRI findings associated with vitamin B1 deficiency are characterized by bilateral symmetrical signal changes in the brainstem nuclei and caudal colliculi of the midbrain (Garosi *et al.*, 2003) that microscopically correspond to areas of cerebral oedema, endothelial proliferation, neuronal necrosis, and myelin degeneration (Markovich *et al.*, 2013).

In this paper the authors describe the clinical signs, MRI findings, treatment, clinical and imaging follow up in a dog with a novel encephalopathy associated with TD which differ from the clinical and imaging presentation of classical thiamine-related disorders reported to date in small animal veterinary literature.

*Corresponding Author: Mario Ricciardi. "Pingry" Veterinary Hospital, via Medaglie d'Oro 5, Bari, Italy.

Email: ricciardi.mario@alice.it

Case Details

A 3-year-old intact male Golden Retriever was presented at Pingry Veterinary Hospital because of acute onset of altered mentation characterized by unmotivated vocalization, compulsive gait and involuntary generalized movement observed by the owner the day before the clinical evaluation. On physical examination the dog showed hypothermia (37°C), tachycardia (145 bpm) and hypotension (90 mmHg). The neurological exam emphasized the altered mental status with compulsive gait and head pressing, hypometria, bilateral ophthalmoplegia, reduced bilateral menace response and decreased flexor reflexes in all four limbs. Multifocal, central and peripheral nervous system involvement was suspected. Complete blood count (CBC), serum chemistry, serum protein electrophoresis and urinary analysis were unremarkable.

MRI of the brain was performed under general anaesthesia using a 0.25 Tesla permanent magnet (ESAOTE VET-MR GRANDE, Esaote, Genoa, Italy). The MRI sequence protocol included sagittal and transverse Fast Spin Echo T2-weighted images, transverse and dorsal FLAIR, transverse native and contrast-enhanced Spin Echo T1-weighted images and a dorsal Spin Echo T1-weighted sequence acquired after intravenous administration of paramagnetic contrast medium (MagneGita-gadopentatedimeglumine 500 mmol/mL-insight agents; 0.15 mmol/kg BW). MRI showed bilateral and symmetric T2 and FLAIR hyperintensity and a mild increase in size of the caudate nuclei. The lesions were isointense on T1-weighted images with strong and homogeneous contrast enhancement (Fig. 1). Mass effect or loss of anatomical architecture was not present. Based on the imaging findings toxic-metabolic or degenerative disorders involving the grey matter of caudate nuclei were considered the main differential diagnoses. Infiltrative neoplasm, inflammatory process and vascular lesion were believed to be less likely. Following the owner's request, a CSF exam was not performed. TD was suspected among toxic-metabolic disorders, and thus we checked for thiamine blood level and immediately supplemented the dog with 100 mg/day of vitamin B1 subcutaneously. Thiamine, thiamine pyrophosphate (TPP) and thiamine monophosphate (TMP) blood level were checked by mass spectrometry. The reference ranges for thiamine, TPP and TMP have previously been standardized by a certified veterinary laboratory (San Marco Veterinary Laboratory, Padova, Italy) for each canine breed. The results for thiamine level showed a severe thiamine deficiency (7.5 ng/ml, reference interval [RI] 14.1–40.9 ng/ml). TPP was normal (15.3 ng/ml, [RI] 8.4–72.3 ng/ml) and the TMP level was low (0.6 ng/ml, [RI] 2.9–50.6 ng/ml).

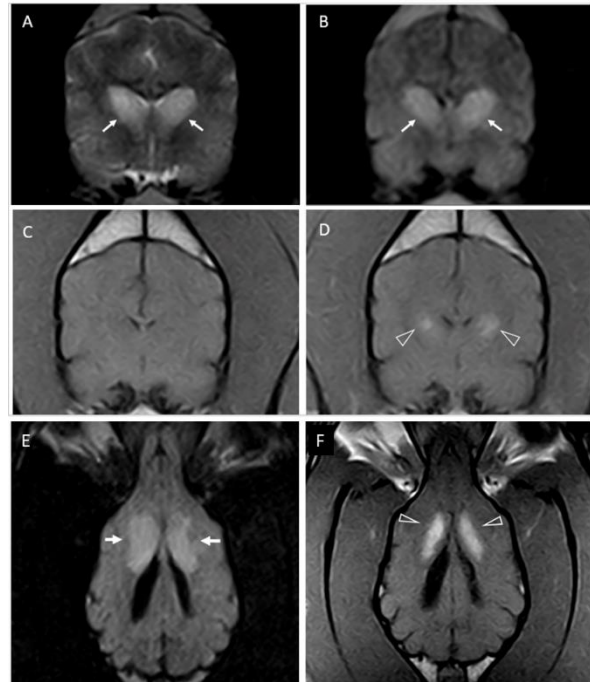


Fig. 1. First magnetic resonance images of the brain. Transverse T2-weighted (A), FLAIR (B), T1-weighted (C), and T1-weighted after IV gadolinium administration (D) images at level of caudate nuclei. There is bilateral and symmetrical T2 and FLAIR hyperintensity and a mild increase in size of both caudate nuclei (arrows). The lesions appear isointense to the normal grey matter on T1-weighted images with clear contrast enhancement (arrowheads). There is no mass effect or loss of anatomical architecture. Oblique-dorsal FLAIR (E) and T1-weighted after IV gadolinium administration (F) images according to the orientation of the caudate nuclei, showing their full extent. Affected areas show extensive hyperintensity on FLAIR images associated with a mild increase in size suggesting swelling (E-arrows), and diffuse contrast-enhancement suggesting blood-brain-barrier breakdown (F-arrowheads).

After one week, the dog showed mild clinical improvement and after three weeks the dog was almost clinically normal. On neurological exam performed after one month the dog showed mild compulsive gait. After two months the dog showed continued improvement.

A MRI of the brain was repeated using the same sequence protocol. At the second MRI examination the caudate nuclei showed T2-hyperintensity with strong homogeneous T1 and FLAIR hypointensity and did not enhance after contrast medium administration. There was no mass effect or loss of anatomical architecture (Fig. 2).

These findings were suggestive of acquired bilateral focal encephaloclastic porencephaly at level of the caudate nuclei secondary to the suspected necrotic-malacic evolution of the original lesions.

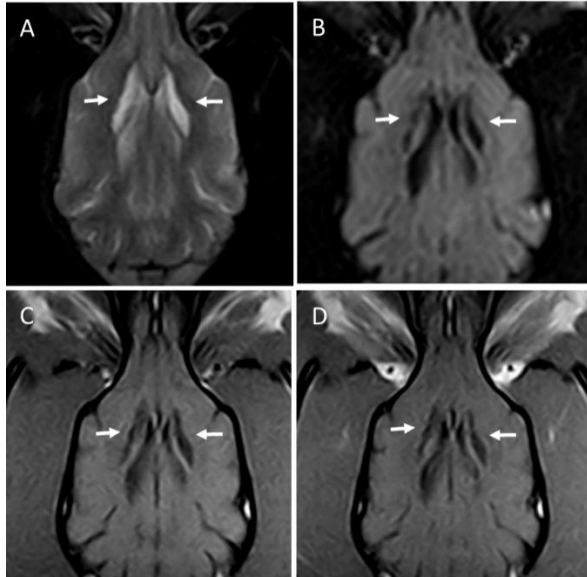


Fig. 2. Control magnetic resonance images of the brain acquired 2 months after the first scan. Dorsal T2-weighted (A), FLAIR (B), T1-weighted (C), and T1-weighted after IV gadolinium administration (D) images at the level of the caudate nuclei. The caudate nuclei showed an MRI fluid pattern with T2-hyperintensity, strong homogeneous T1 and FLAIR hypointensity without contrast enhancement. There was no mass effect or loss of anatomical architecture. These findings were suggestive of necrotic-malacic evolution of the originary lesions.

After 10 months of continuous thiamine supplementation, the vitamin levels were checked again and the results were as follow: thiamine 8.9 ng/ml (RI 14.1–40.9 ng/ml), TPP 35.2 ng/ml (RI 8.4–72.3 ng/ml), TMP 1.3 ng/ml, (RI 2.9–50.6 ng/ml). The dog has now completely recovered.

Discussion

In dogs and cats the risk factors for developing TD include an inadequate intake of thiamine due to an incomplete or unbalanced commercial diet, the presence of thiaminase in food, and inadequate food storage by the owner as the vitamin could be susceptible to heat, humidity and exposure to the air (Markovich *et al.*, 2013). Medications (e.g., diuretics) may potentiate the urinary excretion of vitamin B1 (Sica, 2007). The diagnosis of TD is initiated by recognition of clinical signs and evaluation of the medical state and dietary history.

However, since our patient was fed with a complete and well-balanced commercial food and was not on treatment with diuretics we were unable to identify an obvious cause for TD, as detected by mass spectrometry measurement in blood. In our patient, the blood level of thiamine and its phosphorylated forms confirmed the thiamine deficiency associated with clinical and imaging findings. In the body, thiamine is present in four main forms: cationic (T^+),

monophosphate, diphosphate and triphosphate forms (Manzetti *et al.*, 2014). The T^+ form is phosphorylated extracellularly to the neutral form thiamine monophosphate (TMP). TMP is an otherwise inactive form of thiamine located outside the cell that serves as a substrate for the generation of active thiamine forms. The diphosphorylated form, TPP, participates in several metabolic functions (e.g. energy metabolism) and is the most abundant form of thiamine in the body (>80%) (Manzetti *et al.*, 2014).

In animals the phosphorylated form of thiamine is the most biologically active form within the body (Markovich *et al.*, 2013) but TPP is only available intracellularly (Manzetti *et al.*, 2014), and transfer across the membrane takes place after conversion back to the TMP and T^+ forms (Manzetti *et al.*, 2014). The biological behaviour of TPP, and the impossibility to know the specific physiologic TPP range of this dog may explain why the blood level of TPP in our dog was normal despite the extremely low levels of thiamine and TMP. Furthermore, after thiamine supplementation a wide increase in TPP level was observed. In the authors' opinion, this finding would suggest a previous TPP-deficiency state since the unnecessary vitamin excess would be excreted through urine, being thiamine a hydro-soluble substance. Hence, the final TPP value after supplementation would testify the amount of TPP needed in order to restore the physiologic requirement. No specific syndromes associated with TD have been described in dogs and clinical signs are variable and nonspecific (Platt and Garosi, 2012). Neurological signs are most commonly reported and include depression, dilated unresponsive pupils, positional vertical nystagmus, mild ataxia, seizures, hyperesthesia, abnormal behaviour, upper motor neuron tetraparesis, and opisthotonus (Garosi *et al.*, 2003). A fatal brain disease associated with a genetic mutation for the gene encoding for a thiamine transporter predominantly within the central nervous system has been described in an Alaskan Husky (Vernau *et al.*, 2015).

In our patient the overall clinical presentation differed from that previously described for TD in dogs (Platt and Garosi, 2012) and it was characterized by multifocal, central and peripheral nervous and cardiovascular system alterations. The main arterial hypotension and tachycardia suggested cardiovascular system alteration that in humans is related to posterior hypothalamic area involvement during TD (Ackerman, 1974). The presence of hypothermia also seems to be related to hypothalamic involvement (Ackerman, 1974). The nervous system involvement in our dog was characterized by altered mental status, ophthalmoplegia and ataxia, which in humans are typical signs associated with Wernicke's syndrome, an uncommon, but well-documented, acute and severe neurological

consequence of TD (Harper *et al.*, 1986) that has never been described in veterinary medicine. In Wernicke's encephalopathy the triad of altered mental status, ophthalmoplegia and nystagmus and ataxia is present in only 16% of cases (Harper and Butterworth, 1997) and in 19% of patients there are no symptoms (Harper *et al.*, 1986; Harper and Butterworth, 1997). In patients affected by Wernicke's encephalopathy TD is classically associated with alcoholism, although several other pathological conditions are predisposing factors (Kumar, 2011).

In our dog hypometria and decreased withdrawal reflexes in all four limbs were supportive of peripheral nervous system dysfunction. In humans peripheral nervous system involvement with a sensory-motor peripheral neuropathy may lead to dry-beriberi syndrome in 11% of cases of Wernicke's syndrome (Abdou and Hazell, 2015; Huertas-González *et al.*, 2015). Interestingly, symptoms of dry-beriberi have been described as atypical manifestations during classical wet beriberi syndrome characterized by hypotension, tachycardia and hypothermia (Sechi and Serra, 2007). Furthermore, a combination of dry and wet beriberi has been reported in a thiamine-deficient alcoholic man with axonal sensorimotor polyneuropathy and cardiac symptoms (Cox *et al.*, 2006). Hence, in the current case we did not exclude the possibility of a concomitant dry-beriberi-like syndrome as the cause of the observed peripheral nervous system dysfunction.

Wernicke's encephalopathy, wet beriberi, and polyneuropathy have also been reported all together in a man as a consequence of chronic thiamine malabsorption (Huertas-González *et al.*, 2015). This rare but possible occurrence would make it reasonable to assume that in our dog cardiac, peripheral and central neurological signs might reflect the presence of all three clinical syndromes of TD in the same patient.

Choreic dyskinesia has also been described among atypical forms of Wernicke's syndrome (Sechi and Serra, 2007). In the current case, MRI findings showed no evidence of cerebral cortex lesions but only extrapyramidal system involvement. Hence, we assumed that the clinical signs described by the owner as involuntary movements could have been related to dyskinesia more than seizures, even if convulsive event could not be ruled out. However, we did not rule out the possible inability of the low field MRI to find evidence of involvement of other cerebral areas because of its intrinsic low spatial and contrast resolution in comparison to high field systems or histopathological evaluation. In humans with Wernicke's syndrome, the detection of signal intensity alterations in typical (periaqueductal grey matter, periventricular regions of the third ventricle, mammillary bodies, tectal plate of the midbrain and thalami) (Park *et al.*, 2001) and

atypical (cerebellum, dentate nuclei, cranial nerve nuclei, red nuclei, caudate nuclei, the splenium, and cerebral cortex) brain areas on MRI (Zuccoli and Pipitone, 2009), is an essential feature in order to reach the right imaging diagnosis associated with clinical presentation (Manzo *et al.*, 2014). Atypical MRI findings always arise in association with the typical pattern of brain lesions in the same patients (Zuccoli and Pipitone, 2009).

In humans and dogs affected by TD, MRI findings suggest that both vasogenic and cytotoxic oedema are involved in the pathogenic mechanism of the lesions found in the affected brain areas (Harper and Butterworth, 1997). These pathological alterations are typically seen as bilateral and symmetrical hyperintensities on T2-weighted and FLAIR sequences, both in humans (Manzo *et al.*, 2014) and dogs (Palus *et al.*, 2010; Chisolm-Straker and Cherkas, 2013). Bilateral and symmetrical involvement of specific anatomical areas of the CNS, with anatomical preservation, is typical of metabolic-toxic and degenerative diseases (Gavin and Bagley, 2009; Ricciardi *et al.*, 2014). Among metabolic disorders, TD has been widely reported as one of the major causes of selective, bilateral gray matter damage detectable during MRI examination in humans (Manzo *et al.*, 2014) and small animals (Garosi *et al.*, 2003; Palus *et al.*, 2010).

In dogs, the brain areas typically involved during TD include the red nuclei, caudal colliculi, vestibular nuclei of the brainstem, cerebellar nodulus (Garosi *et al.*, 2003), mesencephalic periventricular grey matter, claustrum, lateral geniculate nuclei, occipital and parietal cortex (Vernau *et al.*, 2013).

Although bilateral and symmetrical MRI signal changes in the caudate nuclei have been described in dogs as a generic hallmark of metabolic and degenerative disease (Mandara *et al.*, 2011) it is noteworthy that this peculiar MRI pattern has never been reported as a consequence of TD.

Similarly to our MRI findings, lesions of the caudate nuclei have been reported in humans as an atypical manifestation of TD (Zuccoli and Pipitone, 2009). In particular, in children with Wernicke's encephalopathy and in patients with genetic alterations in thiamine transport, the caudate nuclei are usually involved (Sechi *et al.*, 2016). The selective involvement of different brain areas during TD seems to be due to their different rate of thiamine-related glucose and oxidative metabolism (Zhong *et al.*, 2005). Hence, we hypothesized that the caudate nuclei in our dog were the most sensitive brain areas suffering from the acute vitamin imbalance and secondary impaired energy metabolism.

Furthermore, in our patient the imaging pattern of caudate nuclei lesions and its evolution from the first to

the second MRI examination, correlated well with the pathophysiology of TD-induced tissue damage. In the acute phase of the disease the most susceptible brain areas during such energetic unbalance are unable to maintain cellular osmotic gradients, which results in swelling of intra- and extracellular spaces (Zuccoli and Pipitone, 2009) and cytotoxic oedema (Manzo *et al.*, 2014). This was reflected in the T2 and FLAIR hyperintensities and the apparent increased volume (swelling) of the caudate nuclei in our dog (Fig. 1).

Breakdown of the blood-brain barrier is a typical consequence of local biochemical events in the damaged areas (Zuccoli and Pipitone, 2009), meaning that the strong contrast-enhancement shown by the caudate nuclei in our dog may be related to the increased permeability of blood vessels to contrast material.

On the follow-up MRI the signal pattern of the caudate nuclei was strongly suggestive of malacic evolution of the lesions. In humans, although the signal abnormalities found in the acute phase of the disease are prone to regression following thiamine supplementation, gliotic-malacic changes of the initial lesions have also been reported in clinical cases with follow-up imaging (Buccoliero *et al.*, 2013). Malacic foci have also been reported in brain histopathological examination in thiamine-deficient foxes (Okada *et al.*, 1987) and dogs (Read *et al.*, 1977).

We hypothesized that at the time of the first MRI the cellular damage was already irreversible and, even following thiamine supplementation, the degradation and resorption of necrotic tissue would lead, in the end, to the formation of malacic areas within the caudate nuclei. The reason why the complete neurologic recovery was observed following thiamine supplementation despite bilateral and presumptive irreversible malacic changes in the caudate nuclei is currently not fully explainable.

In conclusion, in this dog the clinical presentation, the MRI findings with bilateral and symmetrical lesions in the caudate nuclei, the low thiamine blood level, the rapid clinical improvement after thiamine supplementation and the imaging evolution of the lesions 2 months later were, overall, highly suggestive of typical Wernicke's encephalopathy with atypical magnetic resonance imaging. The concomitant presence of wet and dry beriberi could not be ruled out. Based on these findings we consider it reasonable to include thiamine deficiency among the differential diagnoses of bilateral symmetrical lesions of the caudate nuclei detected on brain MRI in dogs.

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Conflict of interest

The authors declare that there is no conflict of interest.

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