NOTE *Surgery*

Measurement of Brain Trace Elements in a Dog with a Portosystemic Shunt: Relation between Hyperintensity on T1-Weighted Magnetic Resonance Images in Lentiform Nuclei and Brain Trace Elements

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(Received 11 April 2008/Accepted 2 August 2008)

ABSTRACT. Prior to euthanasia, brain magnetic resonance imaging (MRI) was performed for a five-year-old male Yorkshire Terrier following portosystemic shunt (PSS) surgical attenuation. Hyperintensity was observed on T1W images of the lentiform nuclei. Trace elements in this area were measured by inductively coupled plasma atomic emission spectrometry. The manganese concentration in the lentiform nuclei was four times higher than that in the control group. Therefore, the manganese accumulation would be the substance that causes the hyperintensity on T1W images of the lentiform nuclei in PSS dogs.

KEY WORDS: canine, manganese, MRI, portosystemic shunt.

J. Vet. Med. Sci. 70(12): 1391–1393, 2008

A portosystemic shunt (PSS) is an anomalous vessel in which the bypass vessel exists between the portal vein and systemic circulation. When a PSS is present, the nutrients necessary for normal growth are not provided to the liver because some portal blood, which is expected to flow to the liver, bypasses it and enters the systemic circulation. Since metabolism or detoxication is not normally performed in the liver, hepatic encephalopathy occurs. Although encephalopathy is induced in dogs that have a PSS, diagnostic imaging of the brain has never been performed. Therefore, we performed brain magnetic resonance (MR) imaging in dogs that had a PSS and reported characteristic findings of enlarged sulci and hyperintensity on T1 weighed (T1W) images in the region of lentiform nuclei [9]. It has been suggested that the causative agent for this hyperintensity is manganese in humans [7, 8], but there are no reports concerning this in dogs. In the present study, we performed brain MR imaging on a PSS dog in a coma, confirmed hyperintensity on T1W images in the region of lentiform nuclei, measured brain trace elements at autopsy and identified the causative agent as manganese.

A 5-year-old castrated, male Yorkshire Terrier (body weight: 4.2 kg) was taken to the teaching hospital of Nippon Veterinary and Life Science University for close investigation of hyperammonemia and a high serum bile acid level.

The dog had experienced intermittent vomiting and convulsions for the previous three months. The results of routine blood biochemistry and hematologic examination revealed high values for alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), ammonia and serum bile acids (SBA) and low values for serum albumin (Alb), blood urea nitrogen (BUN) and blood glucose (Glu: Table 1). Abdominal radiography and ultrasonography showed microhepatica. Based on these results, PSS was suspected, and an exploratory laparotomy was performed. Mesenteric portal venography revealed a shunt vessel bypassing to the caudal vena cava. The shunt vessel was occluded by cellophane banding.

The dog quickly recovered from anesthesia. However, it suddenly showed depression and seizures, and fell into a coma 5 days after the operation. A blood examination showed no abnormal values except for hyperammonemia (368 μg/dL). The seizures were thought to be an attack following PSS ligation or the result of hepatic coma, and brain MR imaging (VISART® Toshiba Medical System, Tokyo, Japan) was performed.

MR imaging showed cerebral edema (hyperintensity on T2 weighted images, T2W; TR 4000 msec, TE 100 msec) in the cerebral cortex, swelling of the sulci (Fig. 1), hypointensity on T1W (TR 410 msec, TE 15 msec) images of the cerebral cortex and hyperintensity on T1W images of the lentiform nuclei (Fig. 1). Treatments to decrease intracranial pressure from the cerebral edema and intravenous drip infusion and enema for hyperammonemia were performed, but the symptoms did not remarkably improve. Therefore, the dog was euthanized at the owner's request.

To identify the causative agent of the hyperintensity on

Table 1. Biochemistry results

Blood parameter	Value	Range
ALT(U/L)	233	10–100
AST (U/L)	141	0–50
ALP (U/L)	225	23–212
Ammonia (μg/d*l*)	256	0–40
SBA (μmol/*l*)	342	0–25
Alb (mg/d*l*)	1.9	2.7–3.8
BUN (mg/d*l*)	4.6	7.0–27.0
Glu (mg/d*l*)	65	77–120

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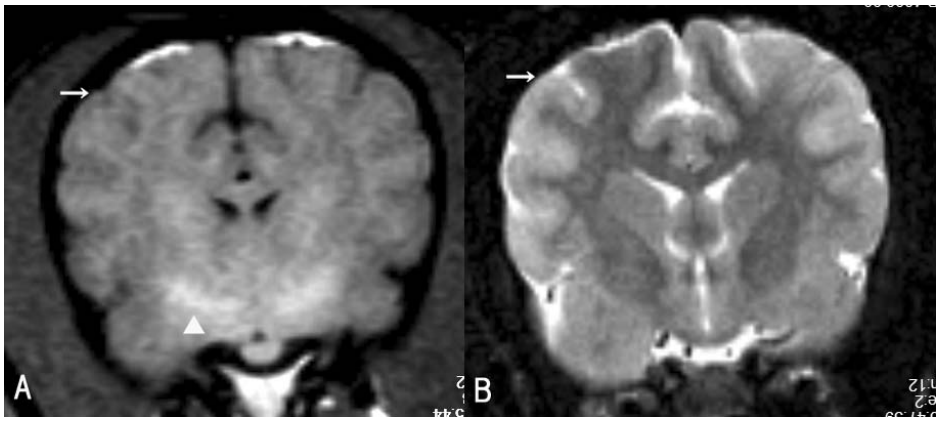

Fig. 1. A T1W image is shown on the left (A). A T2W image is shown on the right (B). The edema of the cerebral cortex is confirmed by swelling of the gyrus and hypointensity on the T1W image and hyperintensity on the T2W image (arrow). Hyperintensity was observed on the T1W image in the lentiform nuclei in the present case (triangle marks).

Table 2. Brain concentration of each trace element (μg/g wet weight)

	Cu	Fe	Zn	Mn
Cerebral cortex	7.38	20.07	6.86	0.63
	(2.11–4.37)	(4.14–11.83)	(4.99–6.44)	(0.30–0.99)
Lentiform nucleus	8.31	27.62	6.18	1.68
	(3.83–4.05)	(10.51–11.09)	(4.97–5.14)	(0.34–0.37)
Cerebellum	8.59	11.09	4.78	0.52
	(4.38–5.41)	(7.17–11.90)	(4.25–6.07)	(0.35–0.40)

( ) : Control range Cu: copper Fe: iron Zn: zinc Mn: manganese.

T1W images of the lentiform nuclei, the brain was nonmetallically excised at autopsy, and brain trace elements (i.e., iron, copper, zinc and manganese) were analyzed by inductively coupled plasma atomic emission spectrometry (ICP-AES: FTP08, Spectro A. I., Germany). The levels of copper, iron, zinc and manganese in the cerebral cortex, lentiform nuclei and cerebellum were measured and compared with those in the control group. As a control, the brains of three dogs that were used for another study were utilized for the trace elements measurements. The three dogs had no hepatic or nervous diseases and received a brain MRI to show no abnormalities at autopsy.

In the present case, the levels of copper, iron, zinc and manganese in the cerebral cortex, lentiform nuclei and cerebellum were measured by ICP-AES (Table 2). The results suggested that manganese, iron and copper accumulated in the lentiform nuclei. In particular, the level of manganese in this dog was over 4 times that in the control group. Approximately 2 times more copper and iron were accumulated in the cerebral cortex compared with the controls, but there was no remarkable difference in the cerebellum.

We previously reported that brain MR imaging showed hyperintensity on T1W images in the region of lentiform nuclei in dogs with a PSS [9]. In human patients with portosystemic encephalopathy, manganese accumulates in the region of lentiform nuclei, especially the pallidum, and hyperintensity on T1W images is observed [8]. Copper [11] and iron [4] are known to be trace elements that influence MR signal intensity, and zinc [10] is known to be related to hepatic encephalopathy. Therefore, in this study, the brain trace elements (i.e., iron, copper, zinc and manganese) that were possible causative agents for hyperintensity on T1W images in the region of lentiform nuclei were measured in a dog with a PSS.

Table 3. Comparison of MRI signal intensity among copper, iron and manganese

	T1W	T2W	References
Cu	Iso	Hyper	8, 11
Fe	No date	Hypo	4
Mn	Hyper	Iso	7, 8

Hyper: hyperintensity. Hypo: hypointensity. Iso: isointensity.

Copper, iron and manganese are substances that influence MR signal intensity [4, 7, 11]. In the present case, copper, iron and manganese accumulated in the lentiform nuclei as shown by hyperintensity on T1W images and isointensity on T2W images. These trace elements can be differentiated by MR signal intensity. Accumulation of iron is shown as hypointensity on T2W images [4], accumulation of copper is shown as hyperintensity on T2W images [11], and accumulation of manganese is shown as hyperintensity on T1W images and isointensity on T2W images [7, 8] (Table 3).

Therefore, the trace element that accumulated the highest concentration in the region of lentiform nuclei and influenced MR signal intensity in the present case was thought to be manganese.

Manganese is a trace element that is essential for normal development and function of the brain in all mammals [6]. Generally, 98% of orally taken manganese is excreted via the bile, and 1–3.5% of it is available in the blood [2]. The manganese in the blood passes the blood brain barrier through several types of calcium transport and flows into the brain. Manganese is a cofactor of many enzymes including glutamine synthetase, which is an enzyme specific to the brain, and superoxide dismutase-2 and pyruvate carboxylase, which exist in all tissues [10]. However, excessive accumulation of manganese in the brain may induce neurotoxicity and parkinsonian-like neurological symptoms [2]. In the present case, the manganese consumed orally was not removed by the liver and flowed into the systemic circulation, which was thought to result in hypermanganemia and accumulation of manganese in the brain.

An increased blood concentration of manganese and preferential accumulation in the region of basal nuclei are observed in human patients with hepatic diseases [8]. Furthermore, in patients who receive long-term total parenteral nutrition infusion containing manganese and have parkinsonian-like syndrome with hyperintensity on T1W images of basal nuclei, the neurological symptoms and T1W-hyperintensity improve when manganese is removed from the infusion [5]. Since the substance showing hyperintensity on the T1W images of the lentiform nuclei in the present PSS case was manganese, accumulation of manganese might be related to hepatic encephalopathy even in dogs. This is supported by the fact that hyperintensity on T1W images disappears several months after operation [9].

Since hyperintensity on T1W images of the lentiform nuclei was observed in 10 out of 13 dogs with a congenital PSS [9], manganese accumulation was confirmed in the brain in PSS, but the relation between manganese accumulation and neurological symptoms in hepatic encephalopathy was unknown. However, since excessive manganese accumulation in the brain may induce neurological symptoms in hepatic encephalopathy, it might be necessary to decrease dietary manganese or to chelate manganese as medical management for hepatic encephalopathy.

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