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Source: Journal of Feline Medicine and Surgery Open Reports, 4(2)

Published By: SAGE Publishing

URL: <https://doi.org/10.1177/2055116918801602>

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# MRI of lobar holoprosencephaly in a cat with hypodipsic hypernatraemia

Genya Shimbo<sup>1\*</sup>, Michihito Tagawa<sup>1</sup>,  
Masashi Yanagawa<sup>2</sup> and Kazuro Miyahara<sup>1</sup>

*Journal of Feline Medicine and Surgery Open Reports*  
1–5

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DOI: 10.1177/2055116918801602

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## Abstract

**Case summary** A 2-year-old neutered female domestic shorthair cat presented with a history of hypodipsia, recurrent hypernatraemia, pelvic limb ataxia and tremor. The serum arginine vasopressin level was low for the serum osmolality. MRI of the brain revealed a failure of separation of the cerebrum, which manifested as absence of the rostral part of the corpus callosum, fornix and septum pellucidum, thus resulting in a single fused ventricle. The diagnosis was lobar holoprosencephaly with hypodipsic hypernatraemia.

**Relevance and novel information** To our knowledge, this is the first description of the MRI characteristics of lobar holoprosencephaly in a cat. This report suggests that MRI examination should be considered for precise diagnosis of hypodipsic hypernatraemia in young cats.

**Keywords:** Brain malformation; holoprosencephaly; hypernatraemia; hypodipsia; magnetic resonance imaging

**Accepted:** 23 August 2018

## Case description

A 2-year-old spayed female domestic shorthair cat was referred to the Veterinary Medical Center at the Obihiro University of Agriculture and Veterinary Medicine with a 2 month history of pelvic limb ataxia, mild muscle tremors in the pelvic limbs, hypodipsia and poor appetite. One month prior, testing had shown marked hypernatraemia and hyperchloraemia (sodium >180 mmol/l [reference interval {RI} 150–165 mmol/l]; chloride 158 mmol/l [RI 112–129 mmol/l]), as well as negative feline leukaemia virus (FeLV) and feline immunodeficiency virus tests. The cat was treated with fluid therapy and exhibited an improved appetite.

Initial examination on presentation to the authors (day 1) revealed dry and dull hair coat, mild muscle tremors in the pelvic limbs and reduced postural reactions in the pelvic limbs; notably, gait abnormality was difficult to evaluate because the cat was unwilling to walk. Laboratory investigations revealed hypernatraemia (178 mmol/l), hyperchloraemia (141 mmol/l), hypercalcaemia (11.6 mg/dl; RI 7.8–11.3 mg/dl) and hyperphosphataemia (8 mg/dl; RI 3.1–7.5 mg/dl) (Table 1). Complete blood count was within the normal RI. The cat's serum osmolality, calculated with the

formula  $(2[\text{Na}^+] + \text{glucose} + \text{blood urea nitrogen})$ ,<sup>1</sup> was high (372 mOsmol/kg; RI <330 mOsmol/kg). The cat did not exhibit polyuria, and urinalysis revealed hypersthenuria (specific gravity 1.058). Thicknesses of both the left and right adrenal glands, measured using ultrasound, were within normal limits (left: 3.3 mm; right: 3.8 mm). The differentials for hypernatraemia included pure water loss (eg, heatstroke, diabetes insipidus, inadequate access to water and primary hypodipsia), hypotonic fluid loss (eg, gastrointestinal fluid loss, kidney dysfunction, diuresis and burns), or excess sodium gain

<sup>1</sup>Veterinary Medical Center, Obihiro University of Agriculture and Veterinary Medicine, Obihiro, Hokkaido, Japan

<sup>2</sup>Department of Veterinary Medicine, Division of Clinical Veterinary Medicine, Obihiro University of Agriculture and Veterinary Medicine, Obihiro, Hokkaido, Japan

\*Current address: Veterinary Teaching Hospital, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

### Corresponding author:

Michihito Tagawa DVM, PhD, Veterinary Medical Center at Obihiro University of Agriculture and Veterinary Medicine, Obihiro, Hokkaido, Japan

Email: mtagawa@obihiro.ac.jp



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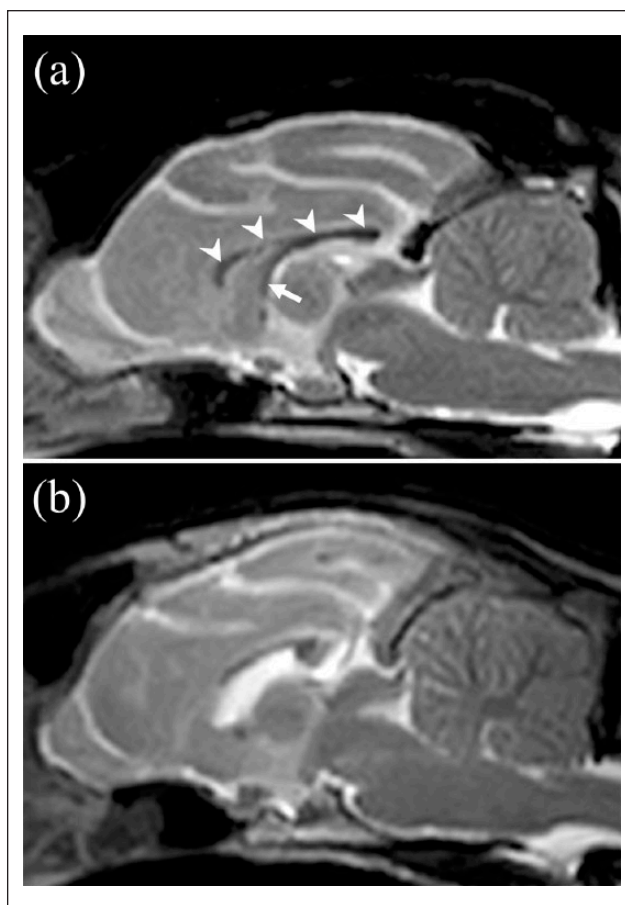
**Table 1** Blood chemistry findings

Parameter	Measured value		RI
	Day 1	Day 51	
Total protein (g/dl)	8.2	7.7	5.9–8.5
Albumin (g/dl)	3.0	–	2.2–4.0
Alanine aminotransferase (U/l)	64	–	12–130
Aspartate transaminase (U/l)	9	–	0–48
Alkaline phosphatase (U/l)	30	–	14–111
Gamma glutamyltransferase (U/l)	0	–	0–1
Total cholesterol (mg/dl)	148	–	65–225
Glucose (mg/dl)	130	–	74–159
Blood urea nitrogen (mg/dl)	24	–	16–36
Creatinine (mg/dl)	1.5	–	0.8–2.4
Sodium (mmol/l)	178	170	150–165
Potassium (mmol/l)	4.1	3.4	3.5–5.8
Chloride (mmol/l)	141	136	112–129
Phosphate (mg/dl)	8	5.2	3.1–7.5
Calcium (mg/dl)	11.6	11	7.8–11.3
Arginine vasopressin (pg/ml)	–	1.1	NE*

RI = reference interval; NE = not established

(eg, excessive sodium intake, hyperaldosteronism and hyperadrenocorticism). For the cat described in this report, primary hypodipsia was suspected as the most likely cause of hypernatraemia. The owner then refused further investigation for several weeks, and feeding with a water-enriched canned food diet was instructed.

Follow-up examination was performed on day 51. The plasma sodium concentration was 170 mmol/l; therefore, the patient's serum osmolality was apparently high (>340 mOsmol/kg). The serum arginine vasopressin (AVP) level was considered low (1.1 pg/ml) for the serum osmolality, based on the results of a previous study.<sup>2</sup> Because primary hypodipsia was suspected for the present case, brain MRI was performed for further investigation, with a 0.4 Tesla open magnet (APERTO Lucent; Hitachi Medical Systems). The imaging protocol included T2-weighted images in transverse, sagittal and dorsal planes; T1-weighted images before and immediately after manual intravenous administration of gadoteridol (0.1 mmol/kg; ProHance, Eisai) in transverse, sagittal and dorsal planes; T2-weighted fluid attenuated inversion recovery images; and T2\*-weighted images in transverse planes. The cranial portion of the corpus callosum (CC), including the rostrum and genu, was absent, whereas the body and splenium were present (Figure 1). The fornix and septum pellucidum were also absent, resulting in a single fused forebrain ventricle (Figure 2). The olfactory bulbs were hypoplastic. On transverse images, the lateral ventricles revealed upturned and pointed corners (Figure 3). The cingulate gyri were well

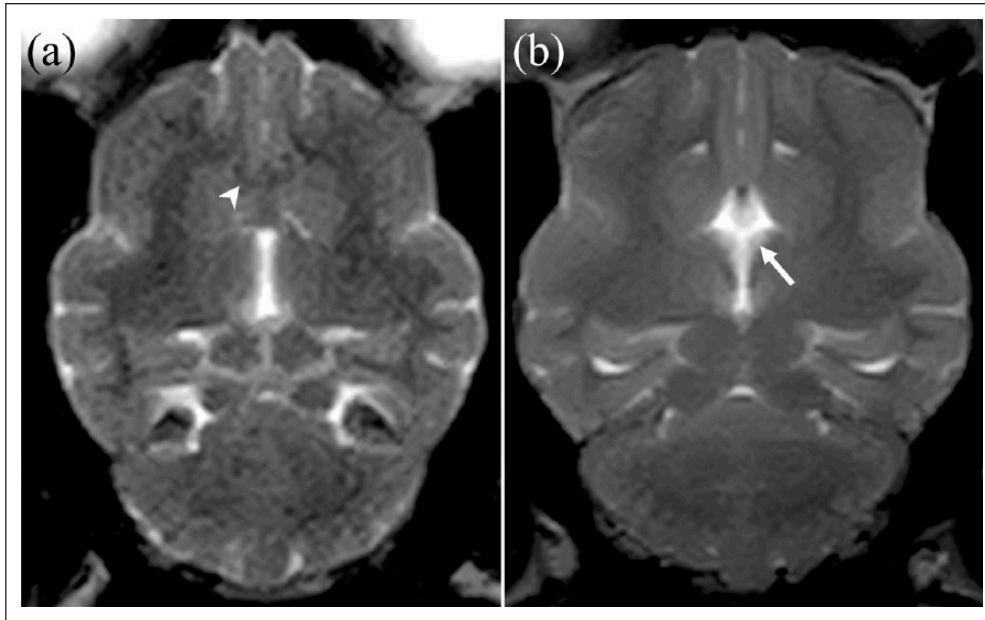


**Figure 1** Midsagittal T2-weighted MRI image of a normal cat (a) and corresponding image from the present case (b). Arrowheads indicate the corpus callosum and the arrow indicates the fornix. Note the absence of the fornix and rostral portion of the corpus callosum, as well as the presence of hypoplastic olfactory bulbs, in the present case

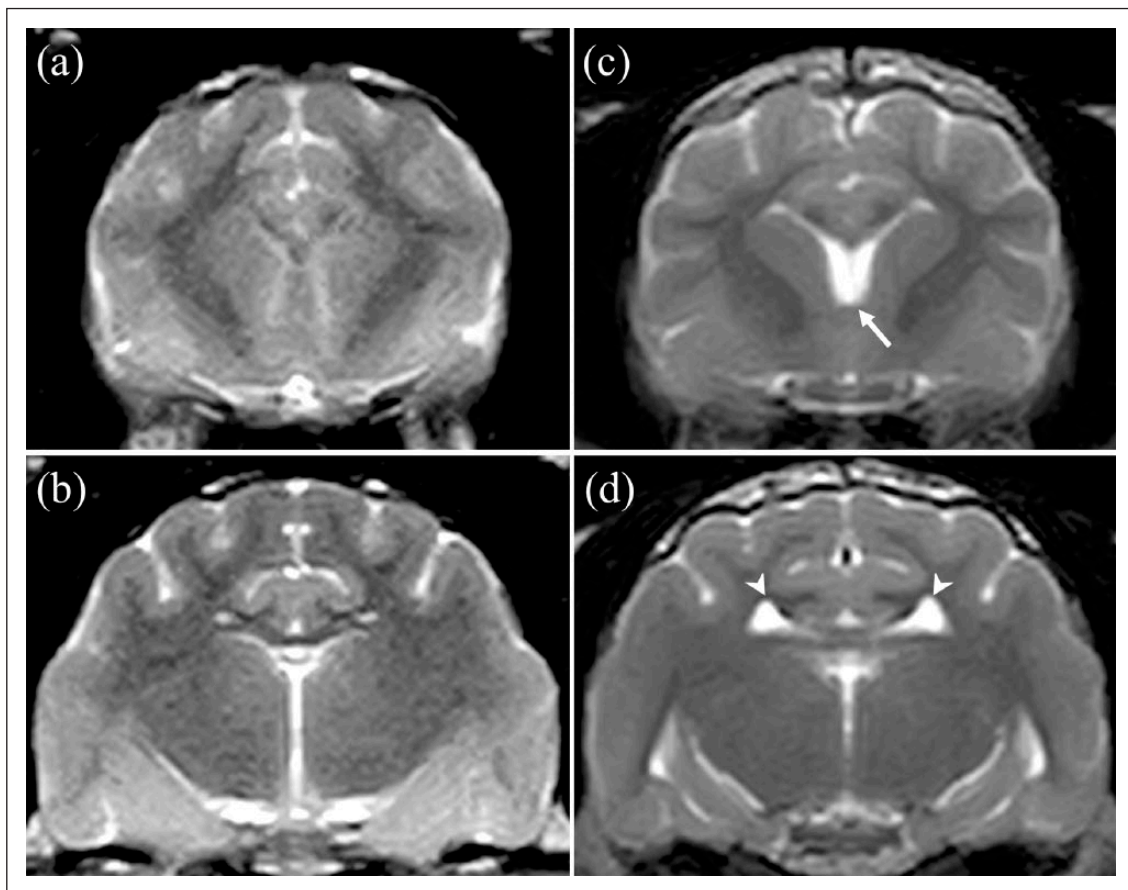
separated, while the most rostroventral portion of the frontal neocortex was not separated. On the basis of the imaging findings, symptoms and clinical signs, the diagnosis was lobar holoprosencephaly (HPE) with hypodipsic hypernatraemia. The owner was instructed to continue feeding water-enriched canned food, and the cat remained clinically healthy and showed normal activity, with the exception of a mild gait abnormality, at the time of writing of this report, 3 months after diagnosis.

## Discussion

HPE is a congenital brain malformation that results from failure of the prosencephalon to sufficiently divide into two cerebral hemispheres; it is the most common malformation of the prosencephalon in humans.<sup>3,4</sup> The incomplete separation of the cerebral hemispheres results in incomplete cleavage or non-separation of midline structures. HPE is classified into four types (alobar, semi-lobar,



**Figure 2** Dorsal T2-weighted image at the level of the corpus callosum of a normal cat (a) and corresponding image from the present case (b). The arrowhead indicates the corpus callosum. The lateral ventricles are not separated in the present case (arrow)



**Figure 3** Transverse T2-weighted images at levels immediately (a) rostral or (b) caudal to the interthalamic adhesion of a normal cat and (c,d) corresponding images from the present case. The lateral ventricles were abnormally fused (arrow), and demonstrated upturned and pointed corners (arrowheads)

lobar and middle interhemispheric variants), depending on the degree of severity.<sup>3,4</sup> In the most severe form – alobar HPE – there is a near-complete lack of separation of the cerebral hemispheres. Although the distinction between semi-lobar and lobar HPE is poorly defined, the anatomical characteristics of lobar HPE in humans include relatively well-developed and separated cerebral hemispheres with only rostroventral portions non-separated, absence of the CC in the affected region (typically rostrum and genu), rudimentary formation of the frontal horns, a fully formed third ventricle and hypoplastic olfactory bulbs.<sup>4</sup> The imaging findings of the cat in the present report were consistent with the characteristics of lobar HPE in humans.

To our knowledge, this is the first report of feline HPE presenting as an isolated disorder. Reports of HPE in cats have been limited to three cases with severe concurrent malformation or disease: a kitten with malformation caused by teratogenesis,<sup>5</sup> a pair of conjoined kittens,<sup>6</sup> and a cat with concurrent pure red cell aplasia and FeLV infection.<sup>7</sup> In dogs, the clinical and MRI characteristics of lobar HPE have been described, although the term HPE is not typically used (eg, CC abnormalities).<sup>8–12</sup> Reported imaging findings such as absence of the rostral CC, septum pellucidum and fornix, as well as non-separated ventral frontal lobes, are similar to those of the cat in the present report. However, contrary to the present case, non-separation of cingulate gyri has been identified in almost all cases of HPE in dogs.<sup>8</sup> Several genetic mutations that are causative for HPE have been found in humans.<sup>3,13</sup> In dogs, Miniature Schnauzers and Staffordshire Bull Terriers appear to be predisposed to lobar HPE;<sup>8–12</sup> however, the genetic causes of lobar HPE in dogs and cats remain unknown.

Hypodipsic hypernatraemia has been sporadically reported in cats: in two cases of intracranial neoplasia,<sup>14,15</sup> a case of hydrocephalus,<sup>16</sup> a case of head trauma<sup>17</sup> and two cases of undetermined origin.<sup>18,19</sup> In our case, there were no neoplastic or traumatic causes; thus, lobar HPE was suspected as the cause of hypodipsic hypernatraemia. Hypodipsic hypernatraemia is a rare complication of semi-lobar HPE in humans.<sup>20,21</sup> It consists of a defective thirst mechanism, either alone or in combination with impaired AVP release, which causes chronic hypernatraemia with hypodipsia and no signs of dehydration. Affected patients experience no thirst sensations, regardless of plasma osmolality; importantly, they are never motivated to drink spontaneously. In one report, hypodipsic hypernatraemia was the most common clinical sign in dogs with HPE; however, serum AVP levels were not evaluated.<sup>8</sup> Although no published RI is available for serum AVP in cats, a previous study demonstrated a mean AVP value of 84.6 pg/ml in water-restricted cats.<sup>2</sup> In addition, an AVP concentration of 1.1 pg/ml in one cat was considered low and aided in the

diagnosis of central diabetes insipidus.<sup>22</sup> Based on the results of these reports, the serum AVP level of the cat in this report was low (1.1 pg/ml), given the high serum osmolality. This can be explained by impaired function of hypothalamic osmoreceptors, which control thirst and vasopressin secretion, as observed in human patients with neurogenic hypernatraemia.<sup>20,21,23</sup>

Although it is suspected that HPE is associated with a defect in hypothalamic osmoreceptors, little is known about the relationship between abnormal development of the CC and dysfunctional osmoregulation. There have been two reported cases of hypodipsic hypernatraemia in cats with very similar clinical characteristics to the cat in our case. One was a 7-month-old domestic shorthair cat with hydrocephalus.<sup>16</sup> In that report, the diagnosis of hydrocephalus was made based on a computed tomographic study; however, it may be difficult to clearly differentiate lobar HPE from hydrocephalus without an MRI study. The other cat was a 4.5-year-old domestic shorthair cat with primary hypodipsia of unknown origin.<sup>19</sup> The cat in that report underwent no imaging study, but the author suspected malformation of the CC or prosencephalon. In humans and dogs, hypodipsic hypernatraemia associated with HPE has an excellent prognosis with appropriate management;<sup>11,12,20</sup> therefore, early definitive diagnosis with MRI should be recommended for cats with hypodipsic hypernatraemia.

## Conclusions

This is the first report of the MRI characteristics of lobar HPE in a cat with hypodipsic hypernatraemia. Lobar HPE should be considered as a differential diagnosis for young cats with hypodipsic hypernatraemia. The MRI characteristics described in this case were relatively similar, although not identical, to those of lobar HPE in humans and dogs.

**Acknowledgements** The authors would like to thank Hisao Inukai for supportive care of the patient at the referral animal hospital.

**Conflict of interest** The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding** The authors received no financial support for the research, authorship, and/or publication of this article.

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