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CASE REPORT

Treatment of central diabetes insipidus with anemia in a dog

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A 10-year-old, spayed female miniature schnauzer was referred to the Veterinary Medical Teaching Hospital of Chungnam National University due to evaluation of sudden polyuria (PU) and, polydipsia (PD) (540 mL/kg/day) with severe anemia and weight loss. Blood examination results were normal except for severe anemia (hematocrit, [HCT]: 11.8%). Urinalysis revealed a urine specific gravity (USG) of 1.003, whereas urine sediment was not specific. Urine osmolality was 90 mOsm (reference range: 800～2500 mOsm), and plasma osmolality was 303 mOsm. No specific lesions were found using diagnostic imaging including radiography, ultrasonography and magnetic resonance imaging (MRI). The serum cortisol level was normal in cosyntropin stimulation test. Plasma arginine vasopressin (AVP) concentration was <0.4 pg/mL (reference range: 3.49～5.45 pg/mL). Blood transfusion was initiated in addition to an oral prescription of desmopressin acetate (DDAVP, 0.1 mg/head) thrice a day for one week. The patient was rechecked for clinical signs, urine osmolality, and USG; the clinical signs of PU/PD were resolved, urine osmolality increased to 1106 mOsm, and, USG increased to 1.021. Considering the improved clinical signs, and increased urine osmolality, and USG after DDAVP treatment, the dog was diagnosed with central diabetes insipidus. USG and urine osmolality increased to >1.030 and 2200 mOsm, respectively. Anemia also gradually improved and HCT increased to >37%. DDAVP was tapered to 0.1 mg/head twice a day and all clinical signs in the patient have completely resolved.

Key Words: Central diabetes insipidus, Anemia, Polydipsia, Polyuria, Dog

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INTRODUCTION

Diabetes insipidus is a polyuric disorder that results from either insufficient arginine vasopressin (AVP) to concentrate urine, which impairs water conservation or due to impaired responsiveness of nephrons to AVP. The former is called central diabetes insipidus (CDI), whereas the latter is nephrogenic diabetes insipidus (NDI). CDI can be categorized as either complete or partial CDI, depending on the extent of AVP (Aroch et al, 2005; Feldman et al, 2014; Ettinger et al, 2017).

AVP is produced in the supraoptic and paraventricular nuclei of the hypothalamus and is stored and secreted from the posterior pituitary gland in response to a small increase in plasma osmolality or a decrease in extracellular fluid volume (Nelson and Couto, 2019). AVP acts on the kidney and cardiovascular system (Feldman et al, 2014; Ettinger et al, 2017), and its receptors include V2 receptors present in the collecting duct of the kidney and V1 receptors present in the arterioles (Feldman et al, 2014; Ettinger et al, 2017). The V2 receptor is involved in the resorption of water, whereas the V1 receptor modulates on vasoconstriction. The vasopressin analog desmopressin acetate (DDAVP) has a strong affinity for V2 receptors and affects water resorption (Feldman et al, 2014; Ettinger et al, 2017; Nelson and Couto, 2019).

Idiopathic CDI accounts for majority of CDI cases (Feldman et al, 2014). CDI, which can be congenital or secondary due to any condition that damages the neurohypophyseal system (e.g, infection, neoplasm, trauma, vascular disease, autoimmune hypothalamitis, and

cysts), destruction of the antidiuretic hormone (ADH) production site in the hypothalamus, loss of major axons that transport ADH to storage sites in the posterior pituitary, or disruption of release of ADH stores (Aroch et al, 2005; Foley et al, 2009; Lee and Park, 2011). A prolonged hypoxic event, such as a cardiac arrest, can lead to the development of CDI (Bellis et al, 2015). The hallmarks of CDI are severe polyuria (PU) and polydipsia (PD).

Confirming a diagnosis of CDI is based on exclusion of other causes of PU/PD, followed by differentiation among CDI, primary NDI, and psychogenic PD using a modified water deprivation test, random plasma osmolality test, or checking response to trial therapy with DDAVP (Ettinger et al, 2017). In clinical practice, responses to DDAVP are mostly commonly used or diagnosis (Ettinger et al, 2017).

In a human study, several patients with CDI concomitant with anemia due to low vasopressin levels were reported (Mayer et al, 2017). It was found that, vasopressin agonist drugs may help such patients to recover from anemia (Mayer et al, 2017). To date, there have been no reports of CDI associated with anemia in dogs.

However, in the case described herein, PU/PD and anemia were reported in a CDI-affected dog, which was improved by DDAVP treatment.

CASE

A 10-year-old spayed female miniature schnauzer, weighing 4.9 kg, was referred to the Veterinary Medicine Teaching Hospital of Chungnam National University with sudden PU/PD, and weight loss. Physical examination revealed a pale mucous membrane and a left apex grade III systolic murmur. Blood examination revealed, severe anemia (hematocrit, HCT: 11.8%, reference range: 37.1~58%); the reticulocyte and reticulocyte production index were 58,900 and 0.5, respectively. Urinalysis revealed hyposthenuria (urine specific gravity, USG: 1.003), and no specific findings for urine sediment. Urine osmolality was 90 mOsm (reference range: 800~2500 mOsm), and plasma osmolality was 303 mOsm (reference range: 290~311 mOsm).

No specific lesions were found using diagnostic imaging including radiography, ultrasonography, and magnetic resonance imaging (Fig. 1). In the cosyntropin stimulation test, pre-cortisol and post-cortisol levels were 7.2 μg/dL (reference range: 1~6 μg/dL) and 17.6 μg/dL (reference range: 6~18 μg/dL), respectively. Therefore, hypoadrenocorticism and hyperadrenocorticism were less likely to be the causes of PU/PD. Plasma AVP concentration was <0.4 pg/mL (reference range: 3.49~5.45 pg/mL). Based on these results, CDI was strongly suspected. The dog had a water intake of 540 mL/kg/day, and the USG was confirmed to be 1.003. In addition, being a neutered female, pyometra, hypercalcemia, and hyperadrenocorticism were ruled out through history, physical examination, and blood examination. Since there was no abnormality in the sediment on the urine test and any protein and glucose were not identified, other diseases that could cause PU/PD were excluded. CDI, NDI, and psychogenic PD were considered as possibilities based on the USG. Secondary NDI was all ruled out because there were no specific findings

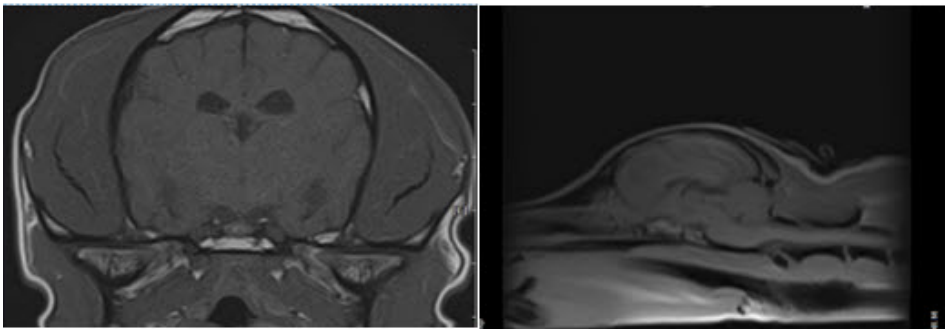

Fig. 1. No abnormalities were observed in and around the pituitary gland on MRI.

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for electrolytes and, kidney and liver function, as per previous blood examinations. Further radiography and ultrasonography of the liver, adrenal glands, and kidney showed no remarkable findings. Thus, CDI primary NDI, and psychogenic PD were considered as possible differential diagnoses. Among them, the possibility of NDI was low because the typical age of occurrence of this condition is less than 3 months. Since the dog had severe anemia, before confirming the response to trial therapy with DDAVP, packed red blood cell (pRBC) transfusions were performed twice, which initially increased HCT from 11.6% to 16.6% and then eventually to 23.2%. As a diagnostic method, DDAVP (Desmin, Dong Kook, Seoul, South Korea; 0.1 mg/head PO q8h) was administered for one week. After one week, the owner reported a significant improvement in PU/PD, and urine osmolality and USG had increased to 1106 mOsm, and 1.021, respectively. Two weeks after the start of treatment, the USG increased to 1.040, which was 1.5 times the USG level before treatment, and more than the USG threshold of 1.030; thus, the dog was diagnosed with CDI. In addition, the dog's anemia status improved during DDAVP treatment, with HCT gradually rising from 23.2% to 35.6% at two weeks after DDAVP treatment and normalizing to 45% at one month after treatment. During the one-month treatment period following CDI diagnosis, the dog's daily water intake was normalized to 50~60 mL/kg/day, and its weight increased from 4.9 kg to its original weight of 5.5kg. The urine osmolarity was 90 mOsm, which was much lower than normal, but it gradually increased to 2200 mOsm, which indicating good urine concentration. Currently, the dog is doing well without any problems with the frequency of DDAVP administration reduced to twice a day.

DISCUSSION

Several diseases are known to cause PU/PD. Among them, CDI is an uncommon disease in dogs and should be considered after ruling out secondary NDI. In particular, patients with CDI typically have a water intake of >200 mL/kg/day (Feldman et al, 2014).

In this case, the dog suddenly showed symptoms of drinking 540 mL/kg/day of water. Based on physical examination, blood tests, and imaging, all possible diseases except psychogenic PD, primary NDI, and CDI were excluded. In a random plasma osmolarity test, the possibility of psychogenic PD would be high if the result was <280 mOsm, but indicative values for CDI, primary NDI, and psychogenic PD overlap past that threshold (Feldman et al, 2014). Since the plasma osmolarity for the dog was 300 mOsm, it was not possible to discriminate among these diagnoses. A modified water deprivation test is designed to determine whether AVP is released in response to dehydration and whether the kidneys respond to this stimulus, but it can be time-consuming and is associated with risks (e.g, severe dehydration, and hypernatremia) (Feldman et al, 2014). In addition, although useful in differentiating primary NDI from CDI, a modified water deprivation test may not differentiate partial CDI from psychogenic PD with complete certainty (Ettinger et al, 2017). The normal range of vasopressin concentration in healthy dogs is 3.49~5.45 pg/mL, which suggested CDI (Scollan et al, 2013). Therefore, we decided to test the clinical response to DDAVP in this dog. After a week, the dog showed noticeable clinical improvements, and urine osmolarity and USG also increased. CDI can be diagnosed when the USG increases by 1.5 times compared to USG before treatment, or when the USG is 1.030 or higher (Aroch et al, 2005). In this case, the USG increased from 1.003 to 1.021 a week after DDAVP administration and then to 1.040 two weeks after treatment; thus, the dog was diagnosed with CDI.

Unlike in ordinary CDI patients, severe non-regenerative anemia was observed in this case. There was no evidence of bleeding or hemolysis, and no clear cause of anemia was found. Therefore, to improve the dog's condition, initially transfusions were performed twice, which was followed by DDAVP administration, during which PU/PD and, HCT improved and normalized.

In human, anemia is reported more frequently in pa-

tients with CDI compared to that in general population (Mayer et al, 2017). Vasopressin receptors are thought to play an important role in RBC production, as they are present in the hematopoietic stem cells and progenitor cells (Mayer et al, 2017). AVP may stimulate the movement of large numbers of immature reticulocytes from the bone marrow into the circulation (Mayer et al, 2017). AVP increases the number of circulating RBCs independent of erythropoietin and is thought to facilitate the rapid resolution of anemia by promoting the differentiation and proliferation of RBCs (Mayer et al, 2017).

In a human study, several CDI patients were anemic despite DDAVP treatment (Mayer et al, 2017). Although the doses of DDAVP used to treat CDI were sufficient to restore water homeostasis, it is possible that they were not sufficient to normalize RBC production in the anemic patients (Mayer et al, 2017). Finally, the authors concluded that DDAVP, a mixed AVPR1B/ AVPR2 agonist, helps patients' water imbalance, but that dosage may not completely compensate for the lack of AVP with respect to blood cell production. Therefore, a specific AVPR1B agonist may be useful to induce RBC production (Mayer et al, 2017).

In our case, HCT of the dog increased to 23.2% with two consecutive transfusions and then gradually increased with DDAVP administration. Anemia was completely resolved as HCT reached 45% after a month of DDAVP treatment. Therefore, this case suggest possibility that the DDAVP dose used was sufficient to normalize RBC production.

Therefore, in similar cases where a dog has CDI with anemia, DDAVP should be considered as therapy.

CONCLUSION

In veterinary medicine, anemia has not been reported in dog patients with CDI. To our knowledge, this is the first report of the same as well as of effective DDAVP treatment in such a patient.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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