PRIMARY HYPOADRENOCORTICISM IN A DOG

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ABSTRACT: This report describes the clinical and laboratorial findings as well as the therapeutic protocol performed in a three-year-old mongrel female intact dog, referred to the Veterinary Hospital of FAMEZ/UFMS. The animal had a previous history of recurrent gastrointestinal signs (such as lethargy, vomiting, loss of appetite, melena and abdominal pain), acute crisis episodes, bradycardia, hypotension, hypothermia and increase of capillary refill time, recognized as addisonian crisis due to primary hypoadrenocorticism. Laboratorial findings included anemia, eosinophilia, neutrophilia, lymphocytosis, sodium-potassium ratio of 14,02 mEq/L and prerenal azotemia. Based on that, it was confirmed the diagnosis of primary hypoadrenocorcitism. Thus, it was recommended supplementation therapy with mineralocorticoid (aldosterone) and glucocorticoid (cortisol) corresponding respectively, fludrocortisone acetate of 0.2 mg per kg of BW, by mouth, once daily and prednisone 0.2 mg per kg of BW, by mouth, twice daily until further recommendations. The prognostic was excellent, since the animal significantly improved body condition, andclinical signs disappeared after therapy which lead the sodium-potassium ratio to 35.11 mEq/L. Thus, the clinician must always suspect of primary hypoadrenocorticism in dogs with intermittent nonspecific signs that get better with support therapy. Presumably, hypoarenocorticism must be under diagnosed in veterinary medicine, reinforcing the need to require specific exams in patients that show this wax and wane feature of clinical signs.
KEYWORDS: Addison's disease. Dogs. Endocrinopathies. Glucocorticoid. Mineralocorticoid. Sodium-potassium ratio.

HIPOADRENOCORTICISMO PRIMÁRIO EM UM CÃO

RESUMO: O presente relato descreve os achados clínicos, laboratoriais e conduta terapêutica de um animal da espécie canina, fêmea, com três anos de idade, inteiro, sem raça definida, diagnosticado com hipoadrenocorticismo primário atendido no Hospital Veterinário da FAMEZ/UFMS. O animal apresentou histórico de recidivas de sinais gastrintestinais (letargia, vômitos, perda de apetite, melena e dor abdominal), crise adrenal aguda, bradicardia, hipotensão, hipotermia e aumento do tempo de preenchimento capilar. As alterações laboratoriais compreenderam linfocitose, anemia, eosinofilia, neutrofilia, densidade urinária < 1.030, relação sódio: potássio 14,02 mEq/L e azotemia pré-renal. Baseado nos achados clínicos-laboratoriais confirmou-se o hipoadrenocorticismo primário. Em seguida, foi instituído terapia de suplementação de mineralocorticoide (aldosterona) e glicocorticoide (cortisol), correspondendo respectivamente ao acetato de fludrocortisona na dose de 0,2 mg/kg por via oral uma vez ao dia e prednisona 0,2 mg/kg por via oral duas vezes por dia até novas recomendações. O prognóstico foi excelente para este caso, já que houve melhora significativa do animal, com o desaparecimento dos sinais clínicos e com nova relação sódio: potássio de 35,11 mEq/L. Assim, deve-se sempre suspeitar de hipoadrenocorticismo primário canino em pacientes com o curso de aparecimento e desaparecimento com sinais inespecíficos que melhorem com terapia de suporte. Presume-se que o hipoadrenocorticismo primário em cães seja subdiagnosticado na medicina veterinária, por isso a importância dos clínicos em suspeitar e solicitar exames específicos em pacientes que apresentam esse curso da doença.
PALAVRAS-CHAVE: Cães. Endocrinopatias. Glicocorticoides. Mineralocorticoides. Relação sódio: potássio. Síndrome de Addison.

HIPOADRENOCORTICISMO PRIMARIO EN UN PERRO

RESUMEN: El informe describe los hallazgos clínicos, de laboratorio y manejo terapéutico de un perro, hembra, con tres años de edad, entera, mestizo, con diagnóstico de hipoadrenocorticismo primario atendido en el Hospital Veterinario de la FAMEZ/UFMS. El animal tuvo un historial de signos gastrointestinales recurrentes (letargia, vómitos, pérdida de apetito, melena y dolor abdominal), crisis renal aguda, bradicardia, hipotensión, hipotermia y un aumento del tiempo de llenado capilar. Las alteraciones de laboratorio presentaron linfocitosis, anemia, eosinofilia, neutrofilia, densidad de la orina < 1,030, relación sodio: potasio 14,02 mEq/L y azotemia prerrenal. Con base en los hallazgos clínicos y de laboratorio, se confirmó el hipoadrenocorticismo primario. A continuación, se introdujo terapia con administración de mineralocorticoide (aldosterona) y glucocorticoide (cortisol), que correspondieron respectivamente al acetato de fludrocortisona a una dosis de 0,2mg/kg por vía oral una vez al día y prednisona 0,2 mg/kg por vía oral dos veces al día hasta nuevas recomendaciones. El pronóstico fue excelente para este caso, ya que hubo mejora significativa del animal, desapareciendo los signos clínicos y con una nueva relación sodio: potasio de 35,11 mEq/L. Por lo tanto, siempre se debe sospechar del hipoadrenocorticismo primario canino en pacientes con el curso de aparecimiento y desaparecimiento con signos inespecíficos que mejoran con terapia de soporte. Es posible que el hipoadrenocorticismo primario en perros sea diagnosticado en la medicina veterinaria, así la importancia de

los clínicos en sospechar y solicitar exámenes específicos en pacientes que presentan ese curso de la enfermedad.

PALAVRAS CLAVE: Endocrinopatias. Enfermedad de Addison. Glucocorticoide. Mineralocorticoide. Perros. Relación sodio: potasio.

Introduction

Hypoadrenocorticism (HA) or Addison's diseases, is an uncommon disease, with an estimate incidence between 0.06% and 0.28% (KELCH et al., 1998) caused by deficiency of adrenal secretion of mineralocorticoid and/or glucocorticoid (SCOTT-MONCRIEFF, 2015). Addison's disease has been referred to as "the great pretender" due to its ability to mimic other common diseases in dogs representing a diagnostic challenge (KLEIN; PETERSON, 2010a). HA can be caused by the destruction of the adrenal cortex or, less commonly, by the deficiency of the production of adrenocorticotropic hormone (ACTH) (FELDMAN; NELSON, 1996; PETERSON; KINTZER, 1996). It is believed that the immune-mediate adrenalitis is the most common etiology for the spontaneous cases of primary canine HA (SCHAER et al., 1986). Main findings in affected dogs were severe lymphoplasmacytic inflammation and atrophy of all layers of the adrenal cortex (FRANK et al., 2013). Other rare causes included granulomatosis destruction, amyloidosis, hemorrhage, metastatic neoplasm (LABELLE; DE COCK, 2005; ROCKWELL et al., 2005; REUSCH et al., 2007; FRANK et al., 2013) and the use of drugs as mitotane and trilostane which induce the adrenal glands necrosis (REUSCH et al., 2007).

In secondary HA, the cause is due to the inadequate secretion of ACTH by pituitary gland, leading to the deficiency of synthesis and secretion of adrenocortical hormones, mainly the glucocorticoids (SCOTT-MONCRIEFF, 2015).

There is sexual predilection, in which 70% of the affected dogs are female (PETERSON; KINTZER, 1996; MELIÁN et al., 1999). Young-to-middle age bitches with mean of four years of age are the most affected animals (PETERSON; KINTZER, 1996). History of gastrointestinal episodes that improve with support therapy should alert the veterinarians of the possibility of HA, especially if the signs are intermittent (SCOTT-MONCRIEFF, 2015). The stimulation test with ACTH must be considered as part of the diagnostic plan in dogs with intermittent signs of lethargy, vomiting, diarrhea and weight loss (LIFTON; KING; ZERBE, 1996).

The clinical syndrome occurs when at least 90% of the adrenocortical tissue is destroyed causing deficiency of mineralocorticoids (aldosterone) and glucocorticoids (cortisol) (KLEIN; PETERSON, 2010b; SCOTT-MONCRIEFF, 2015). The lack of aldosterone is presumable in dogs with hypocortisolemia, hyponatremia and hyperkalemia. However, there are some dogs with HA that may show normal electrolyte concentration even in face of decreasing aldosterone concentration (BAUMSTARK et al., 2014). Once most dogs with HA undergo cortisol and aldosterone deficiency, routine diagnostic is based on cortisol measurement test. Other classic laboratorial findings include normocytic normochromic anemia, lymphocytosis, hyponatremia and hyperkalemia; however, these abnormalities not always are present (SCOTT-MONCRIEFF, 2015).

Treatment of primary HA consists of supplementation with mineralocorticoids and glucocorticoids (PETER-SON; KINTZER, 1997). Prognosis for both primary and secondary HA is usually excellent, but guarded for patients with neoplasms. Age, breed and body weight do not influence survival time. The most important factor in relation to long-term recovery is the care the owner dispenses to the animal (SCOTT-MONCRIEFF, 2015).

The aim of this report was to describe the clinical and laboratorial findings as well as the therapeutic protocol performed in a three-year-old mongrel female intact dog diagnosed with primary HA.

Case report

A three-year-old mongrel female intact dog, weighing 13 kilos was referred to the Veterinary Hospital of the Faculty of Veterinary Medicine and Zootechny of the Federal University of Mato Grosso do Sul. The animal arrived at the emergency section of the Hospital with cardiopulmonar arrest. After the reanimation technique, the animal remained in stupor. The physical exam showed bradycardia (<40bpm), hypothermia (35.1ºC), increase capillary refill time (CRT) and hypotension (unable to be measured).

She was put on emergency therapy with intensive fluid therapy (sodium chloride 0.9% solution), 60ml/kg/hour in the first two hours, continuous infusion of dobutamine 10µg/kg/minute and intravenous glucocorticoid (dexamethasone) at dose of 0.2 mg/kg. Complete blood cell and biochemical evaluation (albumin, alanine aminotransferase [ALT], alkaline phosphate [ALP], BUN and creatinine) have were solicited. The only abnormality found was azotemia (BUM: 80 mg/dL; range value [21,4-59,9] and creatinine: 3,24 mg/dL; range value [0,5-1,5 mg/dL]). Two days after intensive care, the animal was sent home without clinical signs.

After 15 days, the animal returned to the hospital with history of vomiting, loss of appetite and shaking. The new exams showed the persistency of azotemia so that she was put on fluid therapy with sodium chloride 0.9% solution, and sent home two days after admission. Few days later, the animal returned with lethargy, vomiting, shaking, abdominal pain and loss of appetite. At this moment, there was a suspicion of pancreatitis because the owner referred the animal did the "prayer position" at home. Abdominal ultrasound and thoracic radiographs (lateral and ventrodorsal views) have been performed. There were no abnormalities in the abdominal ultrasound; radiographs showed a slight decreased size of the heart with VHS (Vertebral Heart Size) of 9.0. Blood exams revealed lymphocytosis (7.748mm³ [1.000-4.800mm³]). In urinary evaluation, it was observed urine specific gravity of 1.020, little protein content, 15 leucocytes per field, and bacteriuria.

Due to these alterations, clinician prescribed scopolamine (Buscopan®) at 0.4 mg by mouth once daily for seven days, dipirone at 25 mg/kg by mouth every eight hours for five days, amoxiciline at 22mg/kg by mouth twice a day during 10 days and proper nutrition.

The patient had several episodes of nonspecific signs from December 2013 to February 2014 as showed in

table 1.Laboratorial abnormalities detected were normocytic normochromic anemia, lymphocytosis (ranging from 5,590 to 8,492mm³; range value [1,000-4,800 mm³]), neutrophilia, eosinophilia and azotemia. Albumin, ALP and ALT did not show any alterations. Therefore, after the second severe crisis, we suspected of primary HA, so that serum concentrations of sodium and potassium have been analysed and turned to be 115 mEq/L and 8.2 mEq/L, respectively, with sodium-potassium ratio of 14.02 mEq/L, that lead to the con-

firmation of primary HA.

It was instituted the fludrocortisone acetate treatment at a dose of 0.02mg/kg once daily by mouth and prednisone at 0.2 mg/kg twice daily until further recommendations. After this treatment, the animal did not show any clinical signs and after 15 days, as she returned for reevaluation, the new sodium-potassium ratio was 35.11 mEq/L. Thirteen months later, the dog is still under medication with no clinical signs and a good quality of life.

Table 1: Clinical signs of a dog with primary HA showing commonly wax and wane history referred to the Veterinary Hospital of FAMEZ during 2013-2014.

Consultations at HV	Lethargy	Vomiting	Shaking	Loss of appetite	Abdominal pain	Melena
05/11/13 (D0) *	-	-	-	-	-	x
20/11/13 (D15)	-	x	x	x	-	-
28/11/13 (D23)	x	-	x	x	x	-
02/12/13 (D27)	x	x	x	x	x	-
30/01/14 (D86)	x	x	x	x	x	-
20/02/14 (D107)	x	x	x	x	-	-
27/02/14 (D114)	x	-	-	-	-	-
28/02/14 (D115) *	-	x	-	-	-	x

*Presumably an addisonian crisis. Hypothermia, bradycardia, hypotension and increased capillary refill time.

Discussion

The studied animal is a three-year old female which corroborates the findings of Peterson and Kintzer (1996). Although literature cites some breeds in which the disease has a genetic autosomal recessive feature, as Standard Poodle and Nova Scotia Duck Tolling Retriever (SCOTT-MONCRIEFF, 2010), the animal of this case was a mongrel dog.

Clinical signs can be acute or insidious in onset and commonly wax and wane, and could be triggered by a stressful event (SCOTT-MONCRIEFF, 2015). Such intermittent feature of clinical presentation lead the clinicians to a delay in determining the final diagnosis. The animal presented several recurrent episodes of gastrointestinal signs and other nonspecific signs such as shaking, lethargy and loss of appetite. Furthermore, throughout the completely monitoring period, it was observed two episodes of addisonian crisis (acute adrenal crisis) consisting of hypovolemic shock with hypotension, bradycardia (< 40bpm), hypothermia and increased capillary refill time. All these manifestations are according to Peterson and Kintzer (1996), Melián and Peterson (1996) and Lifton, King and Zerbe (1996), which related anorexia, vomiting, lethargy/depression, weakness, weight loss, diarrhea, shaking, polyuria, polydipsia, abdominal pain, hypovolemic shock, collapse, hypothermia, bradycardia, melena and dehydration as common signs in patients with HA. Less commonly, it may occur seizures due to hypoglycemia, muscle cramps and gastrointestinal bleeding (MEDINGER et al., 1993; LEVY, 1994; SYME; SCOTT-MONCRIEFF, 1998; SAITO et al., 2002), but these signs were not present in our patient.

Thereby, the history of recurrent episodes of gastrointestinal diseases (as lethargy, vomiting, diarrhea and/or dehydration) which improved with support therapy (fluid therapy and administration of corticoid) were indicative of HA, as reports of Scott-Moncrieff (2015).It is believed that

the pathogenesis of gastrointestinal signs in dogs with HA are multifactorial. Glucocorticoids deficiency results in lethargy, weakness, hypotension, hypoglycemia, anorexia, vomiting, weight loss, decreased mobilization of proteins and fat leading to muscle weakness and inability to maintain the integrity and endothelial vascular tone (ROMÃO; ANTUNES, 2012; SCOTT-MONCRIEFF, 2015).

Although the basal cortisol has not been determined in this report, it is assumed that it should be somehow decreased, due to clinical signs and good response after administration of dexamethasone, with significant improvement of general condition. According to Lennon et al. (2007), the concentration of plasm cortisol has a high negative predictive value and can be used to rule out the diagnosis of HA. In that same report, the authors say that values ≤ 1µg/dL present an excellent sensitivity (100%) and specificity (98.2%) to detect dogs with HA.

Laboratory changes found in this report include normocytic, normochromicanemia, eosinophilia, lymphocytosis, prerenal azotemia, urine density gravity 1.020, hyperkalemia and hyponatremia, with sodium-potassium ratio of 14.02 mEq/L. These findings corroborate the ones reported by Scott-Moncrieff (2010) and Melián and Peterson (1996).The urine specific gravity may be low (<1.030), but not so low when compared to those found in dogs with primary kidney disease (SCOTT-MONCRIEFF, 2010). Besides, the presence of leukocytes and protein could justify the increased urine specific gravity of the animal in this report.

Despite it has not been measured the concentration of chlorine, electrolyte changes such as hyponatremia and hyperkalemia found here are in accordance with Peterson et al. (1996). The low sodium:potassium ratio observed in this case was determinant for the suspicion of HA, once the usual ratio ranges from 27:1 to 40:1 (SCOTT-MONCRIEFF, 2015),and values lower than 24:1 (ADLER et al., 2007)or 20:1 (SETH et al., 2011) correspond to 100% specificity for

the diagnosis of HA. However, other studies have identified that the proportion of dogs with sodium:potassium ratio lower than 24:1 that suffered from HA varied from 17% to 24% of the animals, suggesting that other diseases may also cause changes in sodium:potassium ratio (ROTH; TYLER, 1999; NIELSEN et al., 2008).

In a retrospective study of 225 dogs with HA, 96% of them had hyperkalemia and 81% hyponatremia (PETERSON et al., 1996).

Unfortunately, the owner had not authorized the stimulation test with ACTH in this case, because of its high cost. However, clinical signs, laboratory changes and therapeutic response confirmed the disease, as affirmed by Lathan and Tyler (2005), who said that diagnosis is based on history findings, clinical signs, laboratory changes and evaluation of adrenocortical reserve.

In addition, another study noted that the lymphocyte count was 100% sensitive and more specific for the detection of HA than the sodium:potassium ratio (SETH et al., 2011), as found in this case report, in which there was lymphocytosis during the course of the disease.

During the addisonian crisis, emergency management was carried out as recommended by Scott-Moncrieff (2015), based on fluid therapy with sodium chloride 0.9% solution IV between 40 to 80 ml/kg/hour for the first two hours, dexamethasone (0.1 to 0.2 mg/kg IV), as well as hematological and biochemical profile. Unfortunately, it was not performed the measurement of basal cortisol, urinalysis and dosages of sodium and potassium.

There has been significant improvement of the clinical signs with treatment and after diagnosis of HA the animal was sent home with both supplementation drugs (fludrocortisone acetate and prednisone) for life.

The main factor that led us to a delayed diagnosis was the fact that the HA can mimic other diseases, as liver failure (hypoglycemia, hypoalbuminemia, hypocholesterolemia and increased ALT and ALP), renal failure (anemia, azotemia, hyperkalemia, hyperphosphatemia and decreased of urine specific gravity), insulinoma (hypoglycemia, increased ALT and ALP), protein-losing enteropathy (hypoalbuminemia, hypocolesterolemia and non-regenerative anemia). Thus, unless the veterinarian keep high index of suspicion for the diagnosis of HA, the diagnosis is often lost (SCOTT-MONCRIEFF, 2015). As the addisonian crisis represents a serious life-threatening complication which can lead to death, it is mandatory an immediate veterinarian's intervention (ROMÃO; ANTUNES, 2012).

Conclusions

Dogs with clinical and laboratory findings suggestive of primary HA should be carefully investigated, in order not be masked by other diseases, since many signs are nonspecific, recurrent and reverted with support therapies. The clinicians must therefore include HA in the list of differential diagnosis of all animals, especially those who showepisodes of weakness, gastrointestinal signs, azotemia, bradycardia, hypotension, and laboratorial changes such as low Na: K ratio, lymphocytosis and low urine specific gravity.

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