

## Combined atypical primary hypoadrenocorticism and primary hypothyroidism in a dog

### *Gecombineerde primaire atypische hypoadrenocorticisme en primaire hypothyroïdie bij een hond*

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## A BSTRACT

A dog with combined atypical primary hypoadrenocorticism and primary hypothyroidism is described. The dog presented with waxing and waning, vague complaints since more than a year and had been treated with several drugs without complete resolution of signs. Based on the abnormalities on physical examination, blood examination and abdominal ultrasonography, atypical primary hypoadrenocorticism and primary hypothyroidism were diagnosed. Glucocorticoid supplementation was started and gradually tapered to maintenance rate because of polydipsia. Ten days later, levothyroxine supplementation was started at a very low dose and was gradually increased based on serum total thyroxine concentrations. The dog rapidly improved and recovered completely. Follow-up over a one-year period did not reveal new abnormalities. The presence of combined primary hypoadrenocorticism and primary hypothyroidism has been infrequently described in dogs and may resemble the Schmidt's syndrome in humans.

## SAMENVATTING

In deze casus wordt een hond met gecombineerde atypische primaire hypoadrenocorticisme en primaire hypothyroïdie beschreven. De hond vertoonde reeds meer dan een jaar intermitterende, vage klachten. Ondanks meerdere medicamenteuze behandelingen vertoonde de hond geen volledige beterschap. Gebaseerd op de resultaten van het algemeen lichamelijk onderzoek, het bloedonderzoek en de abdominale echografie werd de hond gediagnosticeerd met primaire atypische hypoadrenocorticisme en primaire hypothyroïdie. Een supplementatie met glucocorticoiden werd meteen opgestart en geleidelijk afgebouwd tot een onderhoudsdosis wegens polydipsie. Levothyroxinesupplementatie werd tien dagen nadien opgestart aan een zeer lage dosis en geleidelijk opgebouwd aan de hand van de totale thyroxine-serumconcentratie. De hond verbeterde snel en herstelde compleet. Controleconsultaties gedurende meer dan een jaar toonden geen nieuwe abnormaliteiten aan. De combinatie van primaire hypoadrenocorticisme en primaire hypothyroïdie wordt niet vaak beschreven bij honden en vertoont gelijkenissen met het humane schmidtsyndroom.

## INTRODUCTION

Addison's disease, also called primary hypoadrenocorticism (HA), is a well-known, yet uncommon endocrinopathy, in which the adrenal glands are incapable of producing sufficient concentrations of steroids (glucocorticoids and/or mineralocorticoids) (Scott-Moncrieff, 2010; Baumstark et al., 2014). Female, young to middle aged dogs have a predisposition for this disease (Sadek and Schaer, 1996; Thompson et al., 2007). The steroid deficiency can

be due to destruction of the adrenal cortex (primary HA), mostly caused by an immune mediated process, or due to pituitary dysfunction (secondary HA) (Kintzer and Peterson, 1997; Scott-Moncrieff, 2010). In a minority of cases with primary HA, only the zona fasciculata and zona reticularis and not the zona glomerulosa of the adrenal cortex are affected (Sadek and Schaer, 1996). Thereby, only the glucocorticoid production is impaired and no electrolyte abnormalities are noted. This is referred to as atypical primary HA (Sadek and Schaer, 1996; Lifton et al. 1996.). Sodium

and potassium concentrations may also be normal in dogs with secondary HA due to adrenocorticotrophic hormone (ACTH) deficiency as this deficiency does not impair mineralocorticoid production (Thompson et al., 2007). Atypical primary HA often causes vague complaints with a waxing and waning history, such as anorexia, vomiting, lethargy, depression, weakness, weight loss, diarrhea and shaking or shivering (Melendez et al., 1996; Kintzer and Peterson, 1997; Thompson et al., 2007; Scott-Moncrieff, 2010). On physical examination, non-specific abnormalities can be noticed or the physical examination can even be unremarkable (Thompson et al., 2007; Scott-Moncrieff, 2015). Hematology and serum biochemistry results show only subtle clinicopathological changes, such as absence of a stress leukogram, mild non-regenerative normocytic, normochromic anemia and hypoglycemia (Scott-Moncrieff, 2010).

Dogs with clinical signs as described above, which do not react properly to symptomatic treatment, and do not show a stress leukogram, may be suspected of atypical HA and further testing is recommended. The gold standard to confirm the diagnosis of HA is an ACTH-stimulation test. Serum cortisol should be measured prior to and 60 to 90 minutes after ACTH administration (Scott-Moncrieff, 2010; Scott-Moncrieff, 2015a). To differentiate between primary and secondary HA, it is necessary to evaluate the pituitary function by evaluating ACTH-stimulated aldosterone concentrations or basal canine ACTH concentrations (Scott-Moncrieff, 2015a).

In primary HA, the destruction of the adrenal gland is mostly caused by an immune-mediated process which, in rare cases, can occur concurrently with other immune-mediated endocrine disorders, such as hypothyroidism (HT), diabetes mellitus and hypoparathyroidism (Melendez et al., 1996; Scott-Moncrieff, 2015a; Scott-Moncrieff, 2015b). In one study, 5 % of the 225 dogs with HA had concomitant endocrinopathies (Peterson, 1996). The presence of multiple endocrine disorders in dogs resembles polyglandular deficiency syndrome in humans (Neufeld et al., 1980).

In the present case, a dog is presented that was diagnosed with a combination of atypical primary HA and primary HT compatible with a type II polyglandular syndrome, or the Schmidt's syndrome in humans. Both atypical HA and Schmidt's syndrome are rare and poorly characterized endocrinopathies in the dog. The purpose of this case report is to make this disease entity more familiar to practicing veterinarians.

## CASE REPORT

A six-year-old, female, neutered, mixed-breed dog of 26 kg was presented at the Faculty of Veterinary Medicine of Ghent University. The complaints had started more than a year before admission. Summarized, the dog had a waxing and waning history of

exercise intolerance, depression, drowsiness, partial anorexia, nausea, vomiting, ptyalism, diarrhea, polydipsia, sneezing, nasal discharge, purulent ocular discharge, conjunctivitis, otitis externa due to malassezia infection, hair loss and reduced skin and coat quality. Several physical and blood examinations had been performed by different veterinarians. Additionally, urinalysis, serological tests, abdominal ultrasonography and echocardiography had been performed. According to the referring veterinarians, the physical examination did not reveal significant abnormalities, except for mild generalized lymphadenopathy two months prior to admission. Serum biochemistry profiles revealed moderate azotemia, mild polyclonal hypergammaglobulinemia, very mild hyperkalemia, mild hypoglycemia, increased lactate dehydrogenase (LDH) and moderately increased creatine kinase (CK) (Table 1). On complete blood count (CBC), a mild microcytic, hypochromic anemia and lymphocytosis were noticed (Table 1). Additional blood tests revealed increased total thyroxine (TT4), increased *Borrelia* IgG and a negative *Leishmania* screening (direct agglutination test). Because of mild hypoglycemia, the insulin concentration was also evaluated to rule out insulinoma and this was below reference interval (6.3 mU/L (9.0-25.0)). The higher described abnormalities on serum biochemistry and CBC were not all consistently present. Complete urinalysis of free catch urine revealed isosthenuria (USG 1.014), rare calcium oxalate crystals and a negative culture. On abdominal ultrasonography, two months before admission, the kidneys were mildly decreased in size (5.4-5.9 cm), but showed no other abnormalities. The adrenal glands had a normal shape, but were also small (3.9-5.2 mm). There was a small amount of sediment in the urinary bladder and the medial iliac lymph nodes were prominent, but had a normal echogenicity. The peripheral lymph nodes were also ultrasonographically evaluated at that time and appeared mildly heterogeneous and more oval shaped. Cytology of the peripheral lymph nodes was suggestive for reactive lymphadenopathy. For all previously summarized vague complaints, several symptomatic treatments were attempted (metoclopramide, nandrolonlaurinaat, vitamin B complex, ranitidine, metronidazole, cyclosporine, enrofloxacin, meloxicam, doxycycline, probiotics, Surolan® (miconazolenitrate, polymyxine-B-sulfate, prednisoloneacetate), Aurizon® (marbofloxacin, clotrimazole, dexamethasone), maropitant, omeprazole). Most of these therapies had no effect or only yielded temporary, partial amelioration. Because of the positive *Borrelia* serology, doxycycline was given for a period of four weeks. However, as none of the treatments resulted in complete recovery and because of ongoing exercise intolerance, weakness and stiff gait, the dog was referred for a suspicion of a diffuse peripheral neuromuscular problem.

On physical examination at the Department of Medicine and Clinical Biology of Small Animals, Faculty of Veterinary Medicine of Ghent University,

**Table 1. Complete blood count, serum biochemistry profile, electrolyte concentrations, hormonology from the referring veterinarians expressed in ‘# weeks before admission’.**

Variable	Units	45 weeks	8 weeks	7 weeks	6 weeks	4 weeks	Reference interval
<b>CBC</b>							
HCT	%	41.4	/	35.8	/	36.2	43.0-59.0
Hemoglobine	mmol/L	8.66	/	7.60	/	/	8.72-12.46
MCV	fl	63.2	/	60.4	/	/	63.0-77.0
MCH	pg	21.2	/	20.6	/	/	21.0-25.0
WBC	/μL	10610	/	12190	/	/	6000-16000
Segmented neutrophils	/μL	4371	/	4888	/	/	3000-11500
Band neutrophils		0	/	0	/	/	0-300
Lymphocytes	/μL	5379	/	6522	/	/	1000-4800
Monocytes	/μL	329	/	280	/	/	<1350
Basophils	/μL	11	/	24	/	/	0-100
Eosinophils	/μL	520	/	488	/	/	<1250
Thrombocytes	K/μL	274000	/	312000	/	/	164000-510000
Reticulocyte	%	0.8	/	0.3	/	/	
<b>Biochemistry</b>							
Urea	mmol/L	13.49	7.83	5.16	8.82	8.16	0.99-9.49
Creatinine	μmol/L	98.1	256.4		160.9	136.1	<60
Total protein	g/L	56	58	61	69	69	53-80
Albumin	g/L	/	22.0	24.1	29	32	22-44
Gamma globulines	g/L	/	11.3	11.7	12.3	10.4	3.6-9.1
Glucose	mmol/L	3.39	3.55	3.61	/	/	3.05-4.99
ALT	U/L	65	/	122	/	/	<70
AST	U/L	69	/	69	/	/	<50
ALP	U/L	33	/	41	/	/	<111
GGT	U/L	5	/	7	/	/	<9
LDH	U/L	/	/	676	/	584	<605
Bile acids	U/L	/	/	8	/	/	<19
CK	U/L	/	/	1359	/	319	<331
<b>Electrolytes</b>							
Sodium	mmol/L	/	/	145	/	/	143-154
Potassium	mmol/L	/	/	5.9	/	/	4.2-5.6
Calcium	mmol/L	/	/	2.54	/	2.64	2.02-2.85
Phosphorus	mmol/L	/	/	1.08	/	1.87	0.96-1.88
<b>Hormonology</b>							
TT4	nmol/L	60.63	/	/	/	/	6.45-43.86

HCT: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, WBC: white blood cells, ALT: alanine transferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT: Gamma globulintransferase, LDH: lactate dehydrogenase, CK: creatinine kinase, TT4: total thyroxine. Increased values are colored in red, decreased values are colored in green.

the dog appeared slow, dull and depressive (Figure 1). Inspection of the dog revealed a stiff gait on the fore limbs and lethargy. A video of a walk with the owner also showed exercise intolerance and weakness. The heart rate (80 beats per minute), the respiration rate (20 per minute) and the temperature were all normal. Cardiovascularly, the dog had intermittently weak femoral pulses, a sinus arrhythmia, poorly filled jugular veins and prolonged capillary refill time. The presence of mild prominent peripheral lymph nodes, serous ocular discharge and seromucoid nasal discharge, was also noticed. The abdominal palpation and rectal toucher were normal. The skin had an ery-

thematous aspect and there was mild to severe alopecia on the neck, the ventral abdomen, the genital region and it was expanding distally and medially to the legs (Figures 1 and 2). On neurological examination, no abnormalities were present besides the abnormal gait and lethargy. There were no indications for neck, back, bone, muscle and/or joint pain. Considering the prolonged and multiple vague complaints and minimal abnormalities on neurological examination, metabolic problems needed to be considered first.

The last bloodwork dated from one month before admission, and therefore, a complete blood examination was repeated (Table 2). The CBC showed mild non-



**Figure 1.** The dog at the day of presentation. Dull and depressive expression. Alopecia in the neck region, in the inguinal region and at the hind legs. General poor skin- and coat quality.

regenerative microcytic anemia and mild thrombocytopenia. The serum biochemistry revealed mild azotemia and mildly increased creatine kinase. The serum electrolytes were within the reference interval. Because of the weak femoral pulses, the poorly filled jugular veins and prolonged capillary refill time, an echocardiography and electrocardiography (ECG) were performed. On echocardiography, there was a mild regurgitation at the level of the mitral- and tricuspid valve. The ECG performed during echocardiography showed a sinus arrhythmia with occasional supraventricular premature complexes and a heart frequency of 80 bpm. The fractional shortening was borderline low (27% (30-35%)). Thoracic radiographs showed a mild diffuse broncho-interstitial pattern, probably related with the slightly increased body condition of this dog. Because of the ongoing gastrointestinal complaints, the abdominal ultrasonography was repeated, revealing bilateral small adrenal glands but no further abnormalities. Special attention was paid to signs of vascular thrombosis, considering the weakness, the stiff gait and the weak femoral pulses, but these were not present. Urine was collected by ultrasound-guided cystocentesis and complete urinalysis only revealed urine specific gravity of 1.018.

Because of the subnormal fractional shortening, the bilateral alopecia and depressive behavior, HT was an

important differential diagnosis but could not explain all clinical signs nor clinicopathological abnormalities. Secondly, based on the sustained vague and non-specific complaints, the bilateral small adrenal glands, the absence of a stress leukogram, the recurrent azotemia and non-regenerative microcytic anemia, HA was also considered to be an important possibility. Therefore, canine total thyroxine (TT4) and thyroid-stimulating hormone (TSH) concentrations were measured and an ACTH-stimulation test was performed (Table 2). Before executing the ACTH-stimulation test, all referring veterinarians were contacted to confirm that no corticosteroids had been given to the dog in the last two months since these could influence the results of the ACTH-stimulation test. The decreased TT4 and increased TSH concentrations were consistent with a diagnosis of primary HT. Additionally, the ACTH-stimulation test revealed HA. A diagnosis of atypical HA was made considering that the serum concentrations of sodium and potassium were within normal limits. To differentiate between atypical primary or secondary HA, serum aldosterone concentrations were measured before and after ACTH-stimulation. Both were very low, consistent with primary HA (Table 2).

Initial treatment consisted of prednisolone and levothyroxine. The prednisolone (Prednisolone, Kela Laboratories, Sint Niklaas, Belgium) was started at 0.14 mg/kg, twice a day (BID) and was gradually tapered based on the clinical improvement of the dog and the known side-effects of prednisolone (Table 3). The initial dose of levothyroxine (Forthyron, Eurovet Animal Health BV, Bladel, the Netherlands) was 0.002 mg/kg BID and this was increased every two weeks up to 0.008 mg/kg BID (Table 3). The levothyroxine supplementation was started ten days after the prednisolone supplementation and at a very low dose because otherwise an Addison crisis may be induced (Scott-Moncrieff, 2015b). Two weeks after diagnosis, the dog's clinical condition had improved markedly



**Figure 2.** The affected genital region at the day of presentation. General poor skin- and coat quality and severe alopecia in the genital region.

**Table 2. Complete blood count, serum biochemistry profile, electrolyte concentrations, hormonology. Day 0 is the day of admission at the Faculty of Veterinary Medicine.**

Variable	Units	Day 0	2 weeks	1 month	2 months	3 months	6 months	9 months	Reference interval
<b>CBC</b>									
HCT	%	30.2	26.7	31 *	38.1	/	/	50.1	37.3-61.7
Hemoglobine	g/dl	11.2	10.1	/	13.6	/	/	17.8	13.1-20.5
MCV	fL	56.6	57.9	/	62.4	/	/	64.9	61.6-73.5
MCH	pg	21	21.9	/	22.3	/	/	23.1	21.2-25.9
Reticulocyte	K/ $\mu$ L	18.2	29.5	/	63.5	/	/	42.5	10-110
WBC	10 <sup>9</sup> g/L	9.3	11.6	/	10.28	/	/	8.09	5.05-16.76
Neutrophils	10 <sup>9</sup> g/L	3.6	7.66	/	7.51	/	/	6.35	2.95-11.64
Lymphocytes	10 <sup>9</sup> g/L	4.76	3.08	/	2.18	/	/	1.25	1.05-5.1
Monocytes	10 <sup>9</sup> g/L	0.32	0.65	/	0.42	/	/	0.35	0.16-1.12
Basophils	10 <sup>9</sup> g/L	0	0	/	0.01	/	/	0.01	0-0.1
Eosinophils	10 <sup>9</sup> g/L	0.62	0.07	/	0.16	/	/	0.13	0.06-1.23
TBC	K/ $\mu$ L	135	372	/	329	/	/	212	148-484
<b>Biochemistry</b>									
Urea	mmol/L	13.7	/	/	/	/	/	7.1	2.5-9.6
Creatinine	$\mu$ mol/L	227	/	/	/	/	/	152	44-159
Total protein	g/L	64	/	/	/	/	/	67	52-82
Albumin	g/L	26	/	/	/	/	/	37	23-40
Globulines	g/L	38	/	/	/	/	/	30	25-45
Glucose	mmol/L	3.89	/	/	/	/	/	6.00	3.05-4.99
ALT	U/L	61	/	/	/	/	/	93	10-100
ALP	U/L	19	/	/	/	/	/	78	23-212
CK	U/L	454	/	/	/	/	/	/	10-200
<b>Electrolytes</b>									
Sodium	mmol/L	152	156	157	155	158	158	158	144-160
Potassium	mmol/L	5.4	5.5	4.6	4.8	4.2	4.2	4.1	3.5-5.8
Chloride	mmol/L	120	116	117	118	119	120	118	109-122
Calcium	mmol/L		2.51	/	/	/	/	2.50	1.98-3
Phosphorus	mmol/L		1.61	/	/	/	/	1.03	0.81-2.2
<b>Hormonology</b>									
TT4	nmol/L	<6.45	16.77	/	52.89	/	/	43.86	6.45-43.86
TSH	ng/ml	6.43	/	/	/	/	/	/	
ACTH stim. Test	nmol/L								
Cortisol pre		<3	/	/	/	/	/	/	
Cortisol post		<3	/	/	/	/	/	/	
Aldosterone	pmol/L	<27.74							

HCT: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, WBC: white blood cells, TBC: thrombocytes ALT: alanine transferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, CK: creatinine kinase, TT4: total thyroxine, TSH: thyroid stimulating hormone, ACTH: adrenocorticotropic hormone. \* means: microhematocrit or packed cell volume. Increased values are colored in red, decreased values are colored in green.

(e.g. less depressed, able to make long walks, good appetite, no more nausea, etc.). Nevertheless, there were new complaints of polyuria and polydipsia (pu/pd). The coat and skin quality was still poor and even worsened at the beginning of therapy. There were complaints of excessive hair loss and cold intolerance (shivering) (Figure 3). Laboratory tests showed a normalized TT4 value and stable electrolyte values, but a moderate microcytic anemia persisted (Table 2). Because of pu/pd, the prednisolone dose was tapered to 0.1 mg/kg BID and two weeks later to once a day (SID) (Table 3). Follow-up appointments were scheduled after one, two, three, six and nine months. The

general condition of the dog kept improving and was considered normal after two months. During follow-up, no new abnormalities were noticed on physical examination. Three weeks after diagnosis, all cardiovascular parameters (heart rate, capillary refill time, pulse quality) normalized. However, on follow-up, ECG a lone atrial fibrillation (LAF) with a ventricular response rate of 104 beats per minute was noticed. No underlying structural cardiac disease could be identified. The first improvement of coat quality and quantity was seen after two months. After nine months, the haircoat completely recovered (Figure 4). Blood examinations were frequently repeated during a



**Figure 3.** The dog one and a half month after initiation of therapy. Worsening of skin- and coat quality and the alopecia is more severe and more generalized. At that time, the dog suffered from excessive hair loss and cold intolerance.



**Figure 4.** The dog nine months after initiation of therapy. The skin- and coat quality is completely normalized.

nine-month follow-up period showing normalization of all initial abnormalities. Serum electrolytes always remained within normal limits (Table 2). After nine months, a complete blood work was repeated, which revealed no abnormalities (Table 2). After one year, a control ECG did not show any more abnormalities either.

## DISCUSSION

HA is a well-described endocrinopathy. Nevertheless, the atypical primary form is not that well known by practicing veterinarians and is more challenging to diagnose. In cases with a chronic history of waxing and waning complaints, without major abnormalities on blood examination, especially with an absent stress leukogram, which do not improve permanently on symptomatic treatment, the suspicion of HA should arise (Scott-Moncrieff, 2015a). In the present case,

the dog had already been suffering from these vague complaints for more than a year. Several symptomatic treatments were given but gave only mild, temporary improvement. HA is mostly seen in young to middle-aged, female dogs; so the dog in this case fits with the typical signalment. Moreover, many of the abnormalities, which were seen on physical and blood examinations and on medical imaging (e.g. dull and depressive expression, weakness, intermittently weak femoral pulses, mild generalized lymphadenopathy, mild microcytic non-regenerative anemia, mild azotemia, bilateral small adrenal glands) were all findings that may be indicative for HA. An ACTH-stimulation test was performed after contacting all referring veterinarians to ensure no corticosteroids were given two months prior to admission. As this was not the case, the test was reliable and confirmative for HA. A less expensive test to rule out HA is the basal cortisol concentration (bcc) (Lennon et al., 2007). This test has a high negative predictive value (100%) and so, dogs with bcc's higher than  $2\mu\text{g/dL}$  are highly unlikely to have HA (Lennon et al., 2007). It is important to realize that values below  $2\mu\text{g/dL}$  are not sufficient to diagnose HA, and an ACTH-stimulation test is always required to confirm the diagnosis (Lennon et al., 2007). In the dog described, the bcc was not measured but an ACTH-stimulation test was immediately performed. After confirmation of HA, the next step was to differentiate between primary and secondary HA by evaluating endogenous ACTH or ACTH-stimulated aldosterone concentrations. In theory, the measurement of basal ACTH concentration is more accurate than measuring aldosterone concentrations to differentiate between primary and secondary HA (Scott-Moncrieff, 2015a). Unfortunately, plasma ACTH measurement is not practical, because specific and strict guidelines must be followed for sample collection and handling. Endogenous ACTH is very labile, it has a short half-life, is not thermostable and should not come into contact with glass (Behrend et al., 2013). In contrast, aldosterone is more stable, specific handling precautions are not needed and assays are more widely available (Sieber-Ruckstuhl, 2006). Therefore, it was decided to measure ACTH-stimulated aldosterone concentrations in the present case. Aldosterone secretion should be impaired in case of primary HA and should be normal with secondary HA. Dogs with atypical primary HA are suspected of having normal aldosterone concentrations due to the sparing of the zona glomerulosa (Baumstark et al., 2014). In this case, the decreased aldosterone concentrations before and after ACTH administration led to the diagnosis of atypical primary HA. These low aldosterone concentrations are contradictory to the normal sodium and potassium concentrations measured in this dog (Table 2). It has been assumed that normal aldosterone concentrations are mandatory to maintain normal electrolyte values as seen with primary atypical HA (Baumstark et al., 2014; Scott-Moncrieff, 2015a).

**Table 3. Schematic representation of the posology of the initiated treatment after diagnosis.**

Time	Drug	Time	Drug
	Prednisolone (mg/kg)		Levothyroxine(mg/kg)
D1	0.14 BID	D1	0.002 BID
D14	0.1 BID	D14	0.004 BID
D30	0.1 SID	D30	0.006 BID
		D 44	0.008 BID
D 60	0.1 SID	D 60	0.008 BID

D1: first day of treatment; SID: once daily; BID: twice daily

It is difficult to underpin this assumption because in most reported cases, aldosterone concentrations were not evaluated (Scott-Moncrieff, 2015a). However, in a recent study describing aldosterone concentrations in dogs with HA, four dogs with atypical primary HA had low baseline- and ACTH- stimulated aldosterone concentrations (Baumstark et al., 2007). These findings and the laboratory results of the present case, imply that there have to be other mechanisms which may explain the maintenance of normal sodium and potassium concentrations. Some of the possible hypotheses include increased dietary sodium intake, increased renin concentrations (compensated failure of the zona glomerulosa), partial sparing of the zona glomerulosa, mutation of the ACTH receptor gene, disparity in the rate of destruction of glucocorticoid and mineralocorticoid secreting cells and influence of concurrent disease such as HT (Oelkers, 1992; Frank et al., 2013). In this case, the owner was not aware of a higher sodium intake and the dog had been partially anorectic for a long time. Other hypotheses, and particularly the influence of concurrent HT, could not be excluded. Nonetheless, it can be concluded that the appearance of normal sodium and potassium values does not always reflect a normal function of the zona glomerulosa and that further research on large scale is required.

In this case, a concurrent diagnosis of primary hypothyroidism (HT) was made, based on low TT4 and high TSH concentrations. When the dog became ill, that was forty-five weeks before admission, with complaints of partial anorexia, vomiting, diarrhea and weakness, blood examinations were performed and showed increased canine TT4 value (Table 1). This increased TT4 value may have been caused by anti-thyroid hormone antibodies (Thacker et al., 1992). These antibodies may occur in 2% of dogs with clinical signs of lymphocytic thyroiditis and in 15% of dogs with HT (Nachreiner et al., 2002). Anti-thyroid hormone antibodies and TSH were not measured in this dog. Therefore, it is uncertain if the dog had already been suffering from clinical HT at that time point. Nevertheless, it was certainly suffering from a polyendocrine disorder at the day of presentation. The developing time between the first and the

second endocrinopathies may vary with an average of four months (Blois, 2011). In this dog, both diseases were diagnosed simultaneously, so it was impossible to determine which disease had developed first. The appearance of multi-endocrinopathy is rare in the dog, with a prevalence of only ~5% of the dogs with HA (Peterson 1996; Scott-Moncrieff, 2015a). An immune-mediated etiology is suspected in these polyglandular syndromes (Scott-Moncrieff, 2010; Blois, 2011; Scott-Moncrieff, 2015a; Scott-Moncrieff, 2015b). The most common combinations of immune-mediated endocrine disorders in dogs with multiple endocrinopathies have been reported to be HT and diabetes mellitus (28%) and HT and HA (23%) (Lathan and Tyley, 2005; Blois, 2011). The presence of multiple endocrine disorders in dogs resembles polyglandular deficiency syndrome in humans, which is further divided in three types (Neufeld et al., 1980). The combination of primary HA, primary HT and/or insulin-dependent, diabetes mellitus is known as type II polyglandular autoimmunity or Schmidt's syndrome. This syndrome has already been described (18 cases) in small animal veterinary medicine (Bowen et al., 1986; Bartges and Nielson, 1992; Kooistra et al., 1995, Lifton et al., 1996; Melendez et al., 1996, Smallwood and Barsanti, 1995; Adissu and Foster, 2015). In ten of the eighteen reported cases, an atypical HA was described in combination with HT. The diagnosis of a polyglandular syndrome may be assumed by demonstrating circulating antiadrenal and anti-thyroid antibodies or by histology of glandular biopsies (Blois et al., 2011). One canine case with both anti-adrenal and anti-thyroid antibodies has been reported (Bowen et al., 1986). In two cases, autopsy and histology revealed an immune-mediated glandular destruction (Kooistra et al., 1995; Adissu and Foster, 2010). In the present case, antibodies were not measured. Since the dog was doing perfectly well, biopsies for histology were not advised. The signalment, clinical history, the abnormalities found on physical and blood examinations (typical of primary HA and primary HT) and on medical imaging in combination with the immediately positive response to treatment all indicated polyendocrinopathy, more specifically the Schmidt's syndrome.

The treatment of atypical HA, without electrolyte abnormalities, initially consists of the supplementation of glucocorticoids alone (0.1 to 0.22 mg/kg/day prednisolone) (Scott-Moncrieff, 2015a). The therapy should lead to rapid, total, clinical improvement, and the dose should be gradually tapered to maintenance rate (Scott-Moncrieff, 2015a). Previously, it had been assumed that the supplementation of mineralocorticoids was unnecessary because the function of the zona glomerulosa, which produces mineralocorticoids, was thought not to be affected (Kintzer and Peterson, 1997; Scott-Moncrieff, 2015a). However, knowing that serum aldosterone concentrations do not always remain within normal limits, this theory is questioned (Baumstark et al., 2014). In human medicine, the decision to supplement mineralocorticoids or not is based on the measurement of renin concentrations (Stewart and Krone, 2011). In veterinary medicine however, the measurement of renin concentration is not widely available. Therefore, it is often advised to only supplement glucocorticoids. Moreover, rapid and complete clinical improvement is seen in dogs treated with only glucocorticoid supplementation. In addition, drugs for mineralocorticoid supplementation might be costly and not always easily available (Baumstark et al., 2014; Scott-Moncrieff, 2015a). In the present case, prednisolone therapy was started at 0.14 mg/kg BID and gradually tapered, because of pup, until 0.1 mg/kg SID (Table 3). After two weeks of therapy, the dog was already doing much better and after eight weeks, the general condition of the dog was considered normal. Nonetheless, at the first recheck appointment, a lone atrial fibrillation (LAF) was noticed on the control ECG. This LAF was not present on the day of admission. LAF may be associated with endocrinopathies, such as (atypical) HA and HT, although a cause-and-effect relationship has not been clearly established yet (Gerritsen et al., 1996; Takemura et al., 2002; Riesen and Lombard., 2006). In this case, it was difficult to determine which one of the two endocrinopathies had been the possible cause of the LAF. However, HT seems to be more likely because the treatment for HT had only been started since one week, and the HT had not yet been controlled at the time of LAF diagnosis. One year later the clinical and laboratory findings were completely normalized and LAF was not present anymore.

A good follow-up of dogs with atypical primary HA is mandatory. Blood examinations have to be re-evaluated regularly because of the risk of progression to complete adrenal failure (Scott-Moncrieff, 2015a). The destruction of the adrenal cortex is thought to be caused by an immune-mediated adrenalitis, which may progress to the zona glomerulosa of the adrenal cortex (Schaer et al., 1986; Lifton et al., 1996; Lathan and Tyley, 2005). This progression leads to complementary mineralocorticoid deficiency, and additional supplementations with mineralocorticoids to the prednisolone supplementation will be required (Scott-

Moncrieff, 2010). However, this progression is difficult to predict in the individual patient. Some dogs do not progress during years of monitoring and others suddenly do (Lifton et al., 1996; Thomson et al., 2007; Scott-Moncrieff, 2010; Baumstark et al., 2014). A retrospective case study showed 12.5% chance of progression (Lifton et al., 1996). Moreover, most of the dogs that progress, do so within the first year after diagnosis (Rogers et al., 1981; Lifton et al., 1996a normal Na:K ratio ( $> 27$ ; Thompson et al., 2007). Therefore, electrolyte concentrations should be monitored every one to three months for at least the first year after diagnosis (Kintzer and Peterson, 1997; Scott-Moncrieff, 2010; Scott-Moncrieff, 2015a). Owners of these dogs should adequately be informed, so they can recognize the first clinical signs of mineralocorticoid deficiency and contact the veterinarian (Baumstark et al., 2014), because rapid supplementation of mineralocorticoids may be of vital importance (Scott-Moncrieff, 2015a). The dog in this case was regularly reevaluated for more than a year but the electrolytes always stayed within normal limits.

In addition to the HA, this dog was also diagnosed with HT and thus with a polyglandular syndrome. In these cases, it is important to treat every glandular deficiency separately (Baumstark et al., 2014). Although an immune-mediated etiology is suspected, it is not advised to start immunosuppressive drug therapy in these syndromes (Scott-Moncrieff, 2015a). Furthermore, it should be borne in mind that the treatment of one glandular deficiency might influence the other. For example, supplementation with thyroid hormones in untreated Addison patients, may precipitate an Addison crisis because the normalization of the slower metabolism associated with HT leads to increased corticosteroid demands (Bowen et al., 1986; Scott-Moncrieff, 2015a). In the present case, a very low dose of levothyroxine was therefore started only ten days after the prednisolone supplementation was initiated. The levothyroxine dose was gradually increased to avoid worsening of the cardiac problems and HA (Table 3). Although the dog was doing clinically better within short term, initially, the skin and coat problems worsened and it took nine months before skin and coat could be considered normal again. Nonetheless, this response and reaction to levothyroxine therapy can be considered normal for a hypothyroid dog. It has been documented that initially, the hair coat may appear to worsen (Credille et al., 2001), and that it may take several months of therapy for complete regrowth and progression of skin quality (Scott-Moncrieff, 2015b).

## CONCLUSION

The dog of the present case was suffering from waxing and waning, vague complaints for more than a year before it was diagnosed with atypical primary HA and primary HT. Atypical HA is more challeng-



ing to diagnose than typical HA, since the typical abnormal sodium-to-potassium concentration ratio is absent. This emphasizes the fact that normal serum electrolytes are not a reliable parameter to exclude HA. Moreover, in case of a dog with a chronic history of vague complaints, with an absent stress leukogram and which does not react properly on symptomatic treatment, high suspicion should arise for (atypical) HA. An unexpected finding in this case was the decreased aldosterone concentrations despite the normal electrolytes, as described in other cases. Further research in atypical HA patients is required.

In addition, the dog was also diagnosed with primary HT. The polyendocrinopathy, which was seen in this dog has seldom been described in veterinary medicine and is similar to a polyglandular syndrome type II (Schmidt's syndrome) described in humans.

## REFERENCES

- Addisu H.A., Foster R.A., (2010). Lymphocytic adeno-hypophysitis and adrenalitis in a dog with adrenal and thyroid atrophy. *Veterinary Pathology* 47, 1082-1085.
- Bartges J.W., Nielson D.L., (2015). Reversible megaesophagus associated with atypical primary hypoadrenocorticism in a dog. *Journal of the American Veterinary Medical Association* 201, 889-891.
- Baumstark M.E., Sieber-Ruckstuhl N.S., Müller C., Wenger M., Boretti F.S., Reusch C.E., (2014). Evaluation of aldosterone concentrations in dogs with hypoadrenocorticism. *Journal of Veterinary Internal Medicine* 28, 154-159.
- Behrend E.N., Kooistra H.S., Nelson R., Reusch C.E., Scott-Moncrieff J.C.R., (2013). Diagnosis of spontaneous canine hyperadrenocorticism: 2012 ACVIM Consensus Statement (Small Animal). *Journal of Veterinary Internal Medicine* 27, 1292-1304.
- Blois S.L., (2011). Multiple endocrine diseases in dogs: 35 cases. *Journal of the American Veterinary Medical Association* 238, 1616-1621.
- Bowen D., Schaer M., Riley W., (1986). Autoimmune polyglandular syndrome in a dog: a case report. *Journal of the American Animal Hospital Association* 22, 649-654.
- Credille K., Slater M., Moriello K., Nachreiner R.F., Tucker K.A., Dunstan R.W., (2001). The effects of thyroid hormones on the skin of beagle dogs. *Journal of Veterinary Internal Medicine* 15, 539-546.
- Frank C.B., Valentin S.Y., Scott-Moncrieff J.C.R., Miller M.A., (2013). Correlation of inflammation with adrenocortical atrophy in canine adrenalitis. *Journal of Comparative Pathology* 149, 268-279.
- Gerritsen R.J., Van Den Bront W.K., Stokhof, A., (1996). Relationship between atrial fibrillation and primary hypothyroidism in the dog. *Veterinary Quarterly* 18, 49-51.
- Kintzer P.P., Peterson M.E. (1997). Primary and secondary canine hypoadrenocorticism. *The Veterinary Clinics of North America. Small Animal Practice* 27, 349-357.
- Kooistra H.S., Rijnberk A., Van den Ingh T.S., (1995). Polyglandular deficiency syndrome in a Boxer dog: thyroid hormone and glucocorticoid deficiency. *Veterinary Quarterly* 17, 59-63.
- Lathan P., Tyley J., (2005). Canine hypoadrenocorticism: pathogenesis and clinical features. Compendium, an in-depth look: Canine hypoadrenocorticism, 110-120. Accessed at 15 December 2014 on [http://www.globalveterinaria.com/php/journal-club/meses/noviembre/HIPOADRENOCORTICISMO\\_FISIO.pdf](http://www.globalveterinaria.com/php/journal-club/meses/noviembre/HIPOADRENOCORTICISMO_FISIO.pdf)
- Lennon E.M., Boyle T.E., Hutchins R.G., Friendenthal A., Correa M.T., Bissett S.A., Moses L.S., Papich M.G., Birkenheuer A.J., (2007). Use of basal serum or plasma cortisol concentrations to rule out a diagnosis of hypoadrenocorticism in dogs: 123 Cases (2000-2005). *Journal of the American Veterinary Medical Association* 231, 413-416.
- Lifton S.J., King L.G., Zerbe C.A., (1996). Glucocorticoid deficient hypoadrenocorticism in dogs: 18 cases (1986-1995). *Journal of the American Veterinary Medical Association* 209, 2076-2081.
- Melendez L.D., Greco D.S., Turner J.L., Hay D.A., Van-Liew C.H., (1996). Concurrent hypoadrenocorticism and hypothyroidism in 10 dogs. *Journal of Veterinary Internal Medicine* 10, 182.
- Nachreiner R.F., Refsal K.R., Graham P.A., Bowman M.M. (2002). Prevalence of serum thyroid hormone autoantibodies in dogs with clinical signs of hypothyroidism. *Journal of the American Veterinary Medical* 220, 466.
- Neufeld M., Maclaren N.K., Blizzard R.M., (1980). Auto-immune polyglandular syndrome. *Pediatric Annals* 9, 154-162.
- Oelkers W, Diederich S.B., Bähr V., (1992). Diagnosis and therapy surveillance in Addison's disease: rapid adrenocorticotropin (ACTH) test and measurement of plasma ACTH, renin Activity, and aldosterone. *Journal of Clinical Endocrinology & Metabolism* 75, 259-264.
- Pikula J., Pikulova J., Bandouchova H., hajkova P., Faldyna M., (2007). Schmidt's syndrome in a dog: a case report. *Veterinarni Medicina* 52,419-422.
- Riesen S.C., Lombard C.W., (2006). ECG of the month. *Journal of the American Veterinary Medical Association* 229,1890-1892.
- Rogers W., Straus J., Chew D., (1981). Atypical hypoadrenocorticism in three dogs. *Journal of the American Animal Hospital Association* 179, 155-158.
- Sadek D., Schaer M., (1996). Atypical Addison's disease in the dog: a retrospective survey of 14 cases. *Journal of the American Animal Hospital Association* 32, 159-163.
- Schaer M., Riley W.J., Buergelt C.D., Bowen D.J., Senior D.F., Burrows C.F., Campbell G.A., (1986). Autoimmunity and Addison's disease in the dog. *Journal of the American Animal Hospital Association* 22, 789-794.
- Scott-Moncrieff J.C.R., (2010). Hypoadrenocorticism. In: Ettinger S.J., Feldman E.C. (Editors). *Textbook of Veterinary Internal Medicine*. Seventh edition, volume 2, Saunders/Elsevier, St-Louis, p. 1847-1857.
- Scott-Moncrieff J.C.R., (2015a). Hypoadrenocorticism. In: Feldman E.D., Nelson C.E., Reusch C.D., Scott-Moncrieff J.C.R. (Editors). *Canine and Feline Endocrinology*. Fourth Edition, Saunders Elsevier, St-Louis, p. 485-520.
- Scott-Moncrieff J.C.R., (2015b). Hypothyroidism. In: Feldman E.D., Nelson C.E., Reusch C.D., Scott-Moncrieff J.C.R. (Editors). *Canine and Feline Endocrinology*. Fourth edition, Saunders Elsevier, St-Louis, p. 77-135.
- Sieber-Ruckstuhl N.S., Boretti F.S., Wenger M., Maser-Gluth C., Reusch C.E., (2006). Cortisol, aldosterone, cortisol precursor, androgen and endogenous ACTH concentrations in dogs with pituitary-dependant hyper-

- adrenocorticism treated with trilostane. *Domestic Animal Endocrinology* 31, 63-75.
- Smallwood L.J., Barsanti J.A., (1995). Hypoadrenocorticism in a family of Leonbergers. *Journal of the American Animal Hospital Association* 31, 305.
- Stewart P.M., Krone N.P., (2011). The adrenal cortex. In: Melmed S., Polonsky K.S., Larsen P.R., Kronenberg H.M. (Editors). *Williams Textbook of Endocrinology*. Twelfth edition, Saunders/Elsevier, Philadelphia.
- Takemura N., Nakagawa K., Hirose., (2002). Lone atrial fibrillation in a dog. *Journal of Veterinary Medical Science* 64, 1057-1059.
- Tacher E.L., Refsal K.R., Bull R.W., (1992). Prevalence of autoantibodies to thyroglobulin, thyroxine or triiodothyronine and relationship of autoantibodies and serum concentrations of iodothyronines in dogs. *American Journal of Veterinary Research* 53, 449.
- Thompson A.L., Scott-Moncrieff C.J.R., Anderson J.D., (2007). Comparison of classic hypoadrenocorticism with glucocorticoid-deficient hypoadrenocorticism in dogs: 46 cases (1985-2005). *Journal of the American Veterinary Medical Association* 230, 1190-1194.

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