Case Study 1
“Classic” hyperadrenocorticism history

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History

A 13 year old male neutered Cairn terrier was presented for work up of polyuria, polydipsia, polyphagia and elevated liver enzyme activity. His body condition score was 6/9.

The combination of these classical symptoms made hyperadrenocorticism (HAC) very likely. Primary liver disease was considered unlikely as an increase in appetite and body weight would not be typical.

Initial diagnostics

- Laboratory results (table 1)
  - ↑Alkaline Phosphatase (AP)
  - ↑Alanine Aminotransferase (ALT)
  - Hypercholesterolemia
  - Proteinuria

Differential diagnosis

Primary polydipsia:

- Psychogenic (only in the dog)
- Impact on the thirst center
  - Stimulation (liver failure, hyperthyroidism, polycythemia, hypercalcemia, hypokalemia)
  - Hypothalamic lesion (trauma, encephalitis)

Primary polyuria:

- ADH-mediated (antidiuretic hormone = vasopressin)
  - Central diabetes insipidus
  - Nephrogenic diabetes insipidus
    - Primary nephrogenic diabetes insipidus
    - Secondary nephrogenic diabetes insipidus (E. coli infection of the urogenital tract (pyelonephritis, cystitis, prostatitis, pyometra), hypercalcemia, hypokalemia, hypercortisolism)

Table 1: Overview of selective laboratory parameters and hormone testing

Parameter including reference ranges	Result
Hematocrit (l/l) 0.35–0.58	0.55
Leukocytes (x10^9/l) 5–16	12.1
Thrombocytes (x10^9/l) 180–550	485
Alanine Aminotransferase (u/l) 18–110	145
Alkaline Phosphatase (u/l) 13–152	421
Cholesterol (mmol/l) 3.51–9.51	11.32
Triglycerides (mmol/l) 0.31–2.83	2.95
Glucose (mmol/l) 3.79–6.58	5.95
Sodium (mmol/l) 146–165	159
Potassium (mmol/l) 3.5–5.6	4.9
Urine specific gravity >1.030	1.014
Urine protein:creatinine ratio <0.5	2.3
Cortisol basal nmol/l (µg/dl)	123 (4.45)
Cortisol 1h after ACTH stimulation test nmol/L (µg/dl) <500 (<18)	601 (21.8)

- Influence of osmotic solids
  - Decreased in the renal medulla
    - Sodium (hypoadrenocorticism, medullary washout, low sodium diet)
    - BUN (medullary washout, liver failure)
  - Increased in the urine
    - Drugs (mannitol, glucose-containing fluids)
    - Sodium (hypoadrenocorticism)
    - BUN (postobstructive diuresis, renal failure)
    - Glucose (diabetes mellitus, Fanconi syndrome, proximal tubular dysfunction)
- Loss of nephrons
  - Chronic renal failure
  - Acute renal failure (ischemia, infection (Leptospirosis), toxins (ethylenglycol, grapes/raisins (dogs), lilies (cats), drugs (NSAIDs))
  - Other causes (anticonvulsives (phenobarbital), hypertension (pressure diuresis))

Increased AP:

- Increased release from cells (altered bone metabolism, damage of liver and bile duct cells)
- Glucocorticoid isoenzyme-induced

Increased ALT:

- Damage of liver cell membrane (hepatitis, FIP (cats), lymphoma, carcinoma, hepatolipidosis (cats), drugs (NSAIDs, doxycycline), toxins, secondary diseases (hypoxia, endocrinopathies))
- Severe damage of muscle cells (myositis, trauma)

Hyperlipidemia:

- Postprandial
- Secondary to other diseases, e.g. endocrinopathies (hyperthyroidism, diabetes mellitus, HAC), pancreatitis, nephrotic syndrome
- Drugs (glucocorticoids, antiepileptic drugs)
- Primary (idiopathic)

Proteinuria (significant):

- Glomerular
  - Reversible (influence of glucocorticoids, fever, exercise, hypertension)
  - Irreversible (glomerulonephritis, amyloidosis)
- Pre-glomerular
  - Multiple myeloma/plasmacytoma
  - Increased formation of low molecular proteins
- Post-glomerular
  - Pyuria, contamination
  - Hematuria

Additional diagnostics

- **ACTH stimulation test:**
  Cortisol 1h post ACTH stimulation: 601 nmol/l (reference range <500 nmol/l).

  ACTH stimulation test was diagnostic for HAC. An abdominal ultrasound was performed to clarify the etiology.
- **Ultrasound report:**
  Liver hyperechogenic and presence of gallbladder sludge.
  Adrenomegaly (right 0.78 cm, left 0.8 cm).
- **Blood pressure measurement:**
  Normal (average of 130 mmHg over five consecutive measurements).
  Long-term complications of hyperadrenocorticism include development of systemic hypertension. Possible pathophysiological mechanisms include activation of the RAAS system (renin angiotensin aldosterone system) and an increased vascular sensitivity towards catecholamines.

The absence of unilateral adrenal disease suggested pituitary-dependent HAC in this dog.

Treatment

- Trilostane (Vetoryl®; Dechra Veterinary Products): 2 mg/kg SID[1]
- Rechecks were performed according to the instructions provided by the manufacturer after 10 days, 4 weeks and thereafter every 3 months. On every recheck, polydipsia and polyuria were assessed and an ACTH stimulation test was performed.
- Vetoryl dose was increased to 3 mg/kg SID at the second visit.

ALT returned to physiological levels during treatment. There was a significant decrease of AP, cholesterol and proteinuria; however those parameters remained slightly elevated. This is frequently observed in patients with HAC.

Important findings

This case illustrates the classical symptoms of a patient with HAC:

- Polydipsia
- Polyuria
- Polyphagia
- Increase in AP (present in 95% of cases)
- Mild increase in ALT (present in 50% of cases)
- Proteinuria (present in 70% of cases)

Polyuria and polydipsia

HAC causes secondary nephrogenic diabetes insipidus which leads to polyuria with consecutive polydipsia.

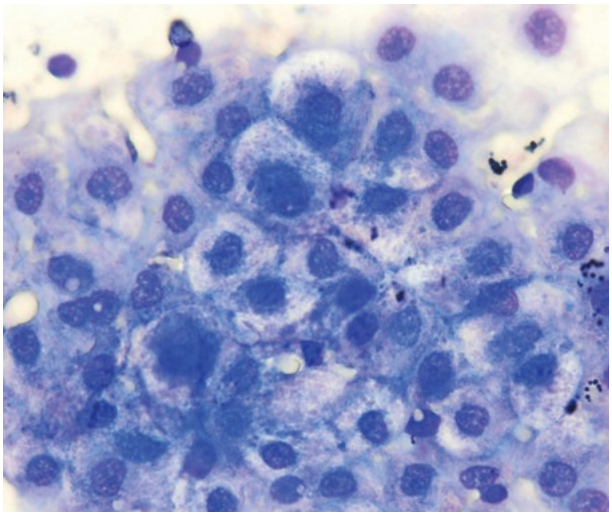
Polyphagia

Glucocorticoids trigger the formation of neuropeptide Y which drives the sensation of hunger.

AP and ALT elevation

AP elevation is caused by a glucocorticoid-induced formation of an AP isoenzyme. ALT increases because glycogen storage in the liver leads to liver cell damage. Glycogen is a polysaccharide and its formation in the liver is triggered by glucocorticoids (picture 1).

Liver size enlarges and develops a hyperechogenic appearance on ultrasound – sometimes an inhomogeneous pattern is observed.



Picture 1: Fine needle aspirate of the liver.

Cytologic description: hepatocyte cytoplasm contained numerous small fine vacuoles and was foamy in appearance (cytoplasmic rarefaction) due to glycogen storage.

Proteinuria

Approximately 70% of affected patients have proteinuria. A significant decrease of the urine protein:creatinine ratio is observed during trilostane treatment.

ACTH stimulation and LDDST tests

The ACTH stimulation test was used as a screening test here. However compared to the LDDST the ACTH stimulation test has an inferior sensitivity. The LDDST is considered to be the screening test of choice unless iatrogenic HAC is suspected[2]. The ACTH stimulation test is considered to be of less use for the diagnosis of spontaneous HAC.

1 Wehner *et al*. Association between ACTH stimulation test, clinical signs, and laboratory parameters in dogs with hyperadrenocorticism treated with trilostane. Abstract presented at the 23rd ECVIM-CA Congress, Liverpool, 12th-14th September 2013.

2 Behrend *et al* (2013) Diagnosis of Spontaneous Canine Hyperadrenocorticism: 2012 ACVIM Consensus Statement (Small Animal) *JVIM* **27**: 1292-1304.

The treatments and doses described in these case studies are entirely at the discretion of the author and are based on their own considerable clinical experience. It is the responsibility of individual prescribing veterinary surgeons to ensure that they comply with local veterinary medicine regulations.

VETORYL: Vetoryl contains Trilostane UK POM-V IE POM

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