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## **Idiopathic hypercalcaemia and idiopathic hypokalaemia in cats.**

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### **IDIOPATHIC HYPERCALCAEMIA (IHC)**

Introduction: IHC is a syndrome in cats with abnormally high blood total (tCa) and/or ionised calcium (iCa) for which all published causes of persistent hypercalcaemia have been eliminated following extensive investigations and long-term follow up. These causes include chronic kidney disease (CKD), neoplasia (lymphoma, squamous cell carcinoma, bronchogenic carcinoma, multiple myeloma, osteosarcoma, fibrosarcoma), primary hyperparathyroidism (rare), hypervitaminosis D (plants, rodenticide, antipsoriasis cream), chronic granulomatous disease and hypoadrenocorticism (very rare). The extensive investigations include haematology, biochemistry, urinalysis, endocrinological testing (PTH, 25-hydroxyvitamin D, calcitriol, PTHrp) and diagnostic imaging.

Clinical and clinico-pathological findings: Up to half of cats with IHC have no clinical signs (especially in the early stages of the disease) and ionised hypercalcaemia often is detected during routine laboratory testing for health check-ups and pre-anaesthetic screenings. Cats of all ages may be affected and there is no sex predisposition. In symptomatic cats clinical signs include mild weight loss, lethargy, anorexia, vomiting, diarrhoea and constipation. Pollakiuria, stranguria and haematuria are seen if urolithiasis is also present.

In most cases the tCa is around 3 mmol/l (not higher than 3.6mmol/l), iCa between 1.4 and 1.9 mmol/l and serum phosphorus within normal limits (unless concurrent CKD is present). In most cats, PTH concentrations are within the reference interval (often lower end), the PTHrP is undetectable while the ionized

magnesium, 25-hydroxyvitamin D and calcitriol concentrations are usually within normal limits.

Measurement of tCa and iCa: In cats, measurement of tCa cannot be reliably used to predict the concentration of the metabolically active iCa. It has been shown that only 30% of cats with ionised hypercalcaemia also have increased tCa concentrations. For this reason screening cats for calcium metabolic disorders is better served by the measurement of iCa. Large fluctuations in tCa and iCa concentrations can be observed in some cats with IHC. In addition, it has been reported that iCa concentrations can fluctuate into and above the reference interval, especially when the hypercalcemia is marginal in magnitude.

Ionized calcium and tCa concentrations can be measured using in-house hand-held or bench-top analysers or by external laboratories (special requirements for measuring iCa in postal samples). Serum or heparinised plasma samples can be used for tCa measurement but for iCa, ideally, a sample should be collected anaerobically. Exposure to air and loss of CO<sub>2</sub> can result in a more alkaline pH of blood or serum promoting more calcium binding to albumin and subsequently lower iCa concentrations. Whole blood or heparinised plasma are also acceptable samples for analysis of iCa although pH and iCa are more stable in serum.

Treatment: It has been suggested that multiple underlying causes or pathomechanisms (e.g. genetic predispositions, epigenetic changes altering calcium metabolism and hormonal control) will be discovered for feline IHC. However, as at present the pathogenesis of IHC is unknown and there is no specific treatment. It is controversial, if asymptomatic cats with mild ionised hypercalcaemia should be treated. Even so, treatment should start when iCa continues to increase and/or clinical signs become obvious. Dietary modification (wet rather than dry diets, high-fibre diets, renal diets, diets developed to prevent calcium oxalate urolithiasis), treatment with bisphosphonates (e.g. alendronate) or prednisolone can be considered.

## IDIOPATHIC HYPOKALAEMIA

Introduction: Over 90% of the potassium in the body is located within cells.

Hypokalaemia implies either normal total body potassium but with a transient translocation of potassium from the extracellular to the intracellular space or depletion of the total body potassium. Hypokalaemia in cats is most commonly due to:

- a) potassium translocation from extracellular into intracellular fluid spaces resulting from alkalaemia, administration of insulin or glucose containing fluids (including those without potassium) and profound catecholamine release
- b) increased potassium loss via the kidneys, particularly associated with diuresis or via the gastrointestinal tract, particularly resulting from vomiting (especially of stomach contents) or diarrhoea. Loss is exacerbated in cats fed potassium deficient diets containing urinary acidifiers.

The most common diseases associated with hypokalaemia in cats are chronic renal failure, systemic viral or bacterial infections, gastrointestinal disease, neuromuscular/CNS disease and hepatic disease.

Periodic hypokalaemic polymyopathy: This syndrome develops in cats 2-10 months of age and is characterised by recurrent episodes of limb muscle weakness, head and neck ventroflexion, increased serum CK, AST and ALT activities and hypokalaemia ( $K^+ < 3.0$  or  $2.5$  mmol/l according to some experts). This disease was first reported in 1983 and since then all cases have been observed mainly in Burmese and Tonkinese cats although there is a strong possibility for the problem to develop in breeds that have been based on Burmese outcrossings (e.g. Burmilla). For almost 30 years this syndrome was considered an example of idiopathic hypokalaemia until 2012 when it was shown that this disease is a very specific potassium wasting nephropathy which is caused by a mutation in the gene coding for the enzyme lysine-deficient 4 protein kinase (WNK4). This enzyme regulates complex pathways that collectively control sodium and potassium transportation. Ultimately, this mutation alters the function

of WNK4 somehow causing sufficient urinary loss of potassium to result in symptomatic hypokalaemia.

Diagnosis and treatment: A PCR test on an EDTA blood sample or cheek swab is used to test for the mutation. In suspect cases, the test can diagnose this inherited hypokalaemia even in cats with normal serum potassium concentration. In addition, the test can identify the cats that are heterozygous for the defective gene (i.e., are carriers). Enteric-coated sustained-release potassium chloride tablets with food are used to manage Burmese cats with hypokalaemia.

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