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<b>TITLE OF CASE</b>
Juvenile hyperthyroidism in a dog
<b>SUMMARY</b>
Hyperthyroidism is the most common endocrinopathy in cats and most cases are caused by multinodular hyperplasia or follicular cell adenoma, although thyroid carcinomas occur infrequently. Hyperthyroidism is rare in dogs and most cases are caused by functional thyroid carcinomas. There are case reports of canine hyperthyroidism secondary to exogenous sources and rarely thyrotoxicosis can be seen with therapeutic doses of levothyroxine prescribed for hypothyroidism. A case of juvenile hyperthyroidism has been reported in the cat and a histopathological diagnosis of diffuse thyroid hyperplasia was made. This is the first reported case of functional eutopic thyroid tissue in a young dog. Histopathological examination reported bilateral hyperplastic change in the thyroid glands, similar to the case of feline juvenile hyperthyroidism.
<b>BACKGROUND</b>
Hyperthyroidism is rare in dogs. Cases have been reported from exogenous sources such as accidental ingestion of levothyroxine medication, ingestion of raw food diets containing thyroid tissue (Kohler <i>et al</i> , 2012) or ingestion of faeces from a patient receiving levothyroxine supplementation (Shadwick <i>et al</i> , 2013). Rarely, dogs can also demonstrate signs of thyrotoxicosis when given small amounts of levothyroxine for the management of hypothyroidism and the reason for this sensitivity is unknown. Most cases of naturally occurring canine hyperthyroidism have been due to the presence of a functional thyroid adenocarcinoma (Barber 2007), although functional thyroid adenomas have also been reported (Lawrence <i>et al</i> , 1991). Thyroid neoplasia usually arises from eutopic tissue but it may also arise from ectopic thyroid tissue. Approximately 50% of healthy dogs have ectopic thyroid tissue that remains at the level of the thyroglossal duct and/or descends with the heart during embryonic development. There are several case reports of dogs with tumours originating from such ectopic thyroid tissue within the thorax, from thyroglossal duct remnants and at the base of the tongue (Stassen <i>et al</i> , 2007). Affected dogs may present due to clinical signs associated with a space-occupying lesion within the thorax or signs associated with the heart (Constantino Casas <i>et al</i> , 1996 & Kang <i>et al</i> , 2012) or more rarely due to thyrotoxicosis (Rijnberk 1981 & Stassen <i>et al</i> , 2007). A dog with hyperthyroidism has also been reported associated with probable struma cordis (Olsen <i>et al</i> , 2007). Naturally occurring canine hyperthyroidism, without the presence of thyroid neoplasia, has not been previously reported.
<b>CASE PRESENTATION</b>
An entire female 24-week-old Petit Basset Griffon Vendéen puppy was presented to the primary veterinarian with polyuria and polydipsia. The dog had been in the owner's possession for six weeks and pollakiuria and increased thirst relative to her sibling was noted. The dog's behaviour was also felt to be markedly different to that of her sibling with constant activity and restlessness, vocalising, inability to settle or to sleep. The body condition score was also reduced compared with the male sibling, despite an excellent appetite. General physical examination was unremarkable.
<b>INVESTIGATIONS</b>
An in-house blood test (Idexx SNAP T4) demonstrated an elevated thyroxine (TT4) concentration [103nmol/l; Reference Interval (RI) 14-52nmol/l]. Blood was submitted to a referral laboratory (Axiom Veterinary Laboratory) for confirmation. This confirmed an elevated thyroxine concentration (93.1nmol/l; RI 15-40nmol/l), elevated free thyroxine by equilibrium dialysis (fT4d 68.5pmol/l; RI 6.6-40pmol/l) and normal thyrotropin (TSH) concentration 0.27ng/ml (RI 0.01-0.6ng/ml). On presentation at the University of Bristol Small Animal Teaching Hospital the dog was very bright, responsive and excitable in nature. Rectal temperature was slightly increased (39.0°C) and there was moderate tachycardia (120-140 beats/minute) and panting. Physical examination revealed saliva staining of all four feet, but the examination was otherwise unremarkable. The dog weighed 9.0 kg and was in lean body condition (score 3/9). Routine haematological examination was within normal limits. Serum biochemistry documented a very mild hypoalbuminaemia (31.5g/l; RI 32-38g/l) and hypoglobulinaemia 20.9g/l (RI 20-35g/l) consistent with the age of the dog. Age-related increases in alkaline phosphatase activity (122 IU/l [RI 0-110]), hypercalcaemia (2.96mmol/l [RI 2.3-2.6mmol/l]) and hyperphosphataemia (2.45mmol/l [RI 0.75-1.25mmol/l]) were also documented. While hospitalised the dog drank water at the rate of 65ml/kg/24hour and there was frequent passage of small volumes of urine. Urinalysis demonstrated pH 6.2, absence of proteinuria (urine protein : creatinine ratio 0.08; RI <0.5) and specific gravity of 1.018. Urine sediment examination found no inflammatory cells. Urine culture was negative. A persistently elevated thyroxine measurement was documented (70.7nmol/l; RI 10-40) and TSH was within normal limits 0.1ng/ml (RI 0-0.6).

A computed tomography scan was performed under anaesthesia with contrast and no ectopic thyroid tissue was identified, the thyroid glands were subjectively slightly larger than normal and more ill-defined. They were mildly heterogenous with a mildly decreased attenuation before contrast administration. The pituitary gland was 4-5mm in height and appeared normal following contrast administration.

A technetium scan was performed and demonstrated a bilateral increase in uptake of technetium by the thyroid glands compared with the parotid salivary glands (Figure 1). Each thyroid gland was well circumscribed and the uptake and size appeared largely symmetrical. The left thyroid to salivary gland ratio (T:S ratio) was 3.45 and the right T:S ratio was 2.76 (normal value 2.2). The changes seen were consistent with bilateral hyperplasia. There was no ectopic tissue identified.

The thyroxine levels of two of the patient's siblings were measured to compare age and breed-matched values. These were documented as 26.3nmol/l and 36.3nmol/l (10-50nmol/l, Idexx Laboratories). Blood from the patient had persistently high thyroxine 74.4nmol/l (RI 10-40nmol/l), and fT4d 48.3pmol/l (RI 6.6-40pmol/l). TSH was still within normal limits 0.25ng/ml (RI 0-0.6) and tri-iodo thyronine (T3) was 2nmol/l (RI 0.3-2.5nmol/l). There was no evidence of lymphocytic thyroiditis with a normal level of thyroglobulin autoantibodies 4% (RI 0-35%).

#### **DIFFERENTIAL DIAGNOSIS**

<p><b>TREATMENT</b></p> <p>Methimazole (Felimazole; Dechra) 2.5mg <i>per os</i> once daily was prescribed and the thyroxine level was measured 3 weeks later. This showed mild reduction from 74.4nmol/l to 56.4nmol/l (RI 10-40nmol/l) and so the methimazole dose was increased to 2.5mg <i>per os</i> twice daily. One month later the thyroxine concentration had increased to 77.7nmol/l despite the increase in dose. The dog's behaviour was increasingly restless and excitable and although she had gained 1.7kg her body condition was still lean (score 3/9). It was decided to proceed to bilateral thyroidectomy.</p> <p>At surgery, both glands appeared enlarged and were highly vascular at the cranial pole. Intracapsular excision was performed bilaterally and samples were submitted for histopathology. Histopathological examination revealed similar changes in both left and right thyroid glands. The majority of the tissue within the glands was histologically normal active thyroid tissue. However, there were occasional large follicles with focal mild epithelial infolding suggestive of early hyperplastic change.</p>
<p><b>OUTCOME AND FOLLOW-UP</b></p> <p>Six days post-operatively, the thyroxine concentration was &lt;3.9nmol/l (RI 10-40) and TSH was markedly elevated in response 2.37ng/ml (RI 0-0.6). Six weeks post-operatively the hypothyroidism persisted (TT4 6.4nmol/l; RI 10-40) and the TSH was further increased 3.24ng/ml (RI 0-0.6). By this stage the dog had gained weight (to 13.3kgs), was lethargic and sleeping more. The polyuria and polydipsia had resolved. She also experienced her first oestrus.</p> <p>The thyroid status was evaluated a further two months later demonstrating euthyroidism TT4 14.3nmol/l (RI 10-40), but still markedly elevated TSH 4.15ng/ml (RI 0-0.6). Ongoing monitoring over the subsequent six months revealed persistence of the low normal TT4 concentration (10.2nmol/l and 11.3nmol/l; RI 10-40), but that the TSH concentration remained elevated (4.1ng/ml and 3.28ng/ml; RI 0-1.6). Given the persistent elevation in TSH, weight gain in the dog (up to 16kgs) and increased body condition (score 6/9), levothyroxine (Soloxine; Virbac) was prescribed at 0.02mg/kg/day. After three weeks of medication, the TT4 concentration measured 4 hours post pill was increased to 111nmol/l (RI 10-40). A dose reduction was advised (0.01mg/kg/day) and thyroid status was re-evaluated. A euthyroid state was achieved and this has been maintained in the upper half of the reference interval for three years (40.3ng/ml, RI 10-55 when last measured). T3 was also within the reference interval 37.4ng/dl (RI 20-206) three years post-operatively. Throughout this period, there has been no polyuria or polydipsia. The dog was neutered after a second oestrus and her weight has been maintained at 14kgs (condition score 5/9).</p>
<p><b>DISCUSSION</b></p> <p>This dog presented because of abnormal drinking and urination patterns and for a restless and excitable nature. It was also noted that the dog was in leaner body condition than her sibling. Repeated tests confirmed an elevated thyroxine concentration. Baseline thyroxine levels are affected by many factors (Scott-Moncrieff, 2015) and these were all considered: repeat measurements were obtained to try to eliminate random fluctuations or spurious results; there had been no previous evidence of oestrus activity; there was no known exposure to medication; the dog was in lean body condition; and both this patient and her sibling had been fed a commercially available dry kibble puppy food with a labelled iodine content well within recommended ranges<sup>1</sup>. Small breed or body size is known to have an inversely proportional effect on thyroxine levels. Age has a similar effect, with neonates having increased thyroxine levels. We collected age- and breed-matched samples to provide a relevant reference interval for comparison.</p> <p>The possibility of a biochemical abnormality without true hyperthyroidism was also considered. A dysproteinaemia (altered concentration of thyroid hormone binding proteins or change in affinity in T4 binding) could result in an elevated T4 concentration. However, the fT4d was elevated on two occasions which is not consistent with a dysproteinaemia. The T4 : T3 ratio was elevated in this patient which may be seen with deiodinase type 1 and 2 dysfunction. A reduced ability to convert T4 to T3 leads to a compensatory increase in T4 in such cases. However, deiodinase deficient patients should be phenotypically euthyroid which was not the case with this dog.</p> <p>The lack of elevation in T3 could also be interpreted as an absence of physiological hyperthyroidism, given this is the only metabolite with nuclear action. However, the patient appeared clinically hyperthyroid, histology was supportive of hyperplastic tissue and the clinical signs resolved post-operatively.</p> <p>In human cases of hyperthyroidism due to TSH stimulation, the ratio of T3 to T4 in thyroidal secretion is increased. TSH receptor stimulation alters the iodotyrosine coupling reaction to favour T3 and increases the activity of deiodinase type1 promoting conversion of T4 to T3 (Maia et al, 2011). TSH driven hyperthyroidism causes diffuse follicular cell hypertrophy and hyperplasia and increased vascularity in both humans and animals that can be identified with histology. Sustained release of TSH causes thyroid follicular epithelial cells to increase in height and become more columnar and there is enhanced endocytosis of colloid and collapse of follicles (Rosol &amp; Gröne, 2016). Dynamic testing to confirm a TSH-mediated process was not pursued given the normal TSH and T3 results and lack of diffuse histological change consistent with TSH stimulation.</p> <p>In people, hyperthyroidism is less common in children than adults. Thyrotoxicosis in children is most commonly due to Graves' disease (&gt;80%). The transient, toxic phase of Hashimoto's thyroiditis, activating</p>

TSH receptor mutations, McCune Albright syndrome, bacterial thyroiditis, subacute thyroiditis, pituitary adenoma and exposure to excessive amounts of iodine or medication are other potential causes (Williamson & Greene, 2010).

Graves' disease is characterised by hyperthyroidism, due to circulating antibodies against the thyrotropin (TSH) receptor, which results in activation of the thyroid cells and increased production and release of thyroid hormone. It results in a diffuse goitre and exophthalmos clinically. Children with other autoimmune diseases (eg. Type 1 diabetes) have a higher incidence of Graves' disease. Signs in children are often non-specific and relate to behaviour with attention difficulties and hyperactivity (Williams *et al*, 2013). TSH levels are decreased secondarily to the high T3 and T4 levels but TSH receptor antibodies in serum are specific for this diagnosis. Histologically, there is diffuse hyperplasia and hypertrophy of follicular cells with increased vascularity and lymphocytic infiltrate. There is no species-specific test available to measure TSH receptor antibodies and definitively diagnose an equivalent to Graves' disease in domestic animals. However, in this case the absence of lymphocytes or diffuse columnar follicular epithelial cells on histological examination are not consistent with this aetiology.

Hashimoto's thyroiditis occurs secondarily to autoimmune lymphocytic infiltration of the thyroid gland. The acute infiltration can cause apoptosis of follicular cells and rapid release of thyroid hormone resulting in transient hyperthyroidism. However, many cases are euthyroid or hypothyroid. The ophthalmological changes seen with Graves' disease may be less severe with Hashimoto's thyroiditis. Decreased TSH and increased T4 and T3 levels are present and lymphocytic infiltration is observed on histopathological examination. There was no evidence of thyroiditis histologically in our case.

Non immune-mediated causes of hyperthyroidism are rare in children but include activating TSH receptor genetic mutations and McCune Albright syndrome. Bacterial thyroiditis is also rare but the destruction of follicular cells causes release of thyroid hormone. The condition is characterised by fever, pain in the thyroid gland and also a sore throat. Abscess formation can develop. Subacute thyroiditis occurs infrequently in children and develops as a post-viral inflammation of the thyroid gland. Pituitary neoplasia is also reported but the TSH-secreting adenomas and more likely to be macroadenomas and patients have concurrent neurological deficits (pressure on the optic nerve). There were no clinical signs consistent with bacterial thyroiditis or pituitary neoplasia in the case described. A genetic mutation remains a possible explanation for her signs.

In domestic animals, thyroid gland hyperplasia is usually seen with iodine deficient diets, dietary iodide excess, goitrogenic compounds or enzyme defects in the biosynthesis of thyroid hormones (congenital goitre). In all of these conditions inadequate thyroid hormone synthesis and low blood levels of T4 and T3 are detected by the hypothalamus, stimulating the pituitary to release more TSH, which results in hyperplasia and hypertrophy of the follicular cells (Scott-Moncrieff).

Hyperplasia is not typically associated with hyperthyroidism in domestic animals other than in the cat. In older dogs, cats and horses nodular hyperplasia is observed. These appear as multiple nodules within the thyroid gland and may result in an irregular contour of the gland. In older dogs and horses the nodular goitre is non-functional and an incidental lesion identified at post-mortem. In cats, the multinodular follicular cell hyperplasia is typically functional. The clinical syndrome of hyperthyroidism in older cats is usually due to either multinodular hyperplasia or follicular cell adenoma. Histologically, hyperplastic nodules are multiple, generally poorly encapsulated, have a variable microscopic appearance and do not compress adjacent parenchyma. Follicular adenomas tend to be well demarcated, partially or fully encapsulated, uniform microscopically and compress the surrounding parenchyma due to expansile growth but the distinction may be challenging in some cases (Rosol & Gröne, 2016).

In this puppy there was no evidence of multinodular hyperplasia or changes consistent with follicular adenoma or carcinoma. The changes observed histologically resemble those in the only case report of juvenile hyperthyroidism in a cat (Gordon *et al*, 2003).

In this case, the cat presented at 8 months of age and had been adopted along with two litter mates. The patient concerned had been smaller in size and more active than its litter mates since birth. Interestingly, the feline case presented with more intermittent gastrointestinal signs (diarrhoea) and dyspnoea than the urinary signs described in our case. Further investigations revealed increases in ALKP and phosphorus consistent with the age at presentation. ALT activity was increased and attributed to hepatocyte damage secondary to the enteropathy. Blood results confirmed persistently increased T4 and also an increase in T3. TSH was not measured. Scintigraphy was performed and revealed bilateral increased uptake and no ectopic tissue identified. The cat was treated with unilateral thyroidectomy, to obtain a thyroid biopsy, and post-operative methimazole. Histological examination confirmed diffuse thyroid hyperplasia. Five months later the cat was treated with radioactive iodine due to poor control of the hyperthyroidism medically. The clinical signs did resolve but the cat was hypothyroid following treatment and required supplementation with levothyroxine to manage the lethargy and weight gain.

The puppy described here also presented at a young age for signs typically associated with older cats and the clinical presentation of hyperthyroidism (polyuria, polydipsia, restless behaviour and poor weight gain). Thyroid imaging and scintigraphy studies showed increased uptake by bilaterally enlarged thyroid glands. Active, hyperplastic thyroid follicles were identified on histological examination and bilateral thyroidectomy resolved the presenting signs. Post-operatively, lethargy and weight gain consistent with clinical hypothyroidism were observed and required treatment.

<p><b>LEARNING POINTS/TAKE HOME MESSAGES</b></p> <ul style="list-style-type: none"> <li>• This is the first case of functional eutopic thyroid tissue in a young dog</li> <li>• Although rare, canine juvenile hyperthyroidism due to thyroid hyperplasia can occur</li> <li>• Typical clinical signs of hyperthyroidism are seen (polyuria, polydipsia, restless behaviour)</li> </ul>
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<p><b>FIGURE/VIDEO CAPTIONS</b></p> <p>Figure 1: Technetium scan - Dorsoventral view demonstrating increased uptake bilaterally by the thyroid tissue.</p>
<p><b>OWNER'S PERSPECTIVE</b></p>
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