PAPER

Cluster of cases of congenital feline goitrous hypothyroidism in a single hospital

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Objectives: To describe the clinicopathological findings and outcomes of cases of feline congenital hypothyroidism diagnosed in a single veterinary hospital in Santiago, Chile.

Materials and Methods: Medical records were searched for cases of congenital hypothyroidism over an 18-month period. Inclusion criteria were a diagnosis of congenital hypothyroidism based on consistent historical and clinical findings, a low or low-normal serum total T4 and elevated serum canine TSH (cTSH).

Results: Six unrelated cats ranging in age from 4 to 19 months met the inclusion criteria. The most common historical signs were small stature and lethargy. All cats had disproportionate dwarfism, delayed tooth eruption, retained deciduous teeth, bilateral palpable goitres and low rectal temperatures. Other findings were bradycardia, obesity, poor hair coat and focal alopecia on the ventral aspects of the elbows and hocks. In all cases, cTSH was markedly elevated. Sequential changes noted after the initiation of therapy included normal T4 after 6 weeks, improved hair coat and increased physical activity by 8 weeks, normal cTSH by 10 weeks and normal physical appearance and dentition after 4 months. Goitres shrank markedly but remained palpable. Hypothyroidism was well managed clinically in all cases 2 years after diagnosis except for one cat that died of unrelated causes.

Clinical Significance: This is the first report to describe a cluster of congenital hypothyroidism cases in non-related cats that were presented over a short period of time. Growth defects resolve with treatment, even in cats diagnosed after puberty. Larger, prospective multi-centre studies are warranted to determine the incidence of congenital hypothyroidism in cats.

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INTRODUCTION

Feline hypothyroidism is most frequently an iatrogenic consequence of therapy for hyperthyroidism (Welches *et al.* 1989). Spontaneous hypothyroidism is uncommon, with only 11 cases of adult-onset disease (Rand *et al.* 1993, Blois *et al.* 2010, Galgano *et al.* 2014, Kent *et al.* 2016, Peterson *et al.* 2018) and approximately 65 cases of congenital hypothyroidism reported (Arnold *et al.* 1984, Peterson 1989, Sjollema *et al.* 1991, Tanase *et al.* 1991, Jones *et al.* 1992, Peterson *et al.* 1994, Stephan & Schütt-Mast 1995, Schumm-Draeger *et al.* 1996, Firth *et al.* 2000, Tobias & Labato 2001, Mazrier *et al.* 2003, Crowe 2004, Szabo & Wells 2007, Traas *et al.* 2008, Quante *et al.* 2010, McGhie & Thompson 2011, Lim *et al.* 2014, Peterson 2015, Van Bergen *et al.* 2016, Jacobson & Rochette 2018).

Congenital hypothyroidism is caused by developmental failure of the thyroid gland (thyroid dysgenesis) (Tanase *et al.* 1991, Traas *et al.* 2008) or by impaired thyroid hormone production (thyroid dyshormonogenesis) (Jones *et al.* 1992, Mazrier *et al.* 2003). Clinical signs of congenital hypothyroidism are related to dysfunction of physiological processes mediated by thyroid hormones, including muscle and brain development, energy balance and normal growth (Peterson 2019).

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Congenital hypothyroidism in cats has mainly been reported in the USA and Europe, with cases also reported in New Zealand, Australia, South Africa, Turkey and Japan (Tanase *et al.* 1991, Jones *et al.* 1992, Traas *et al.* 2008, McGhie & Thompson 2011). It has been suggested that congenital hypothyroidism is an under-recognised disorder of cats as routine screening for the disease is not performed (Traas *et al.* 2008, Bojanic *et al.* 2011, Lim *et al.* 2014, Peterson 2019).

OBJECTIVE

The objective of this retrospective case series was to describe the clinicopathological findings and outcomes of cases of feline congenital hypothyroidism diagnosed in one veterinary hospital in Santiago, Chile, over an 18-month period.

MATERIALS AND METHODS

The electronic patient medical records system of a University Veterinary Teaching Hospital in Santiago, Chile was searched for cases of feline congenital hypothyroidism between July 1, 2017 and January 1, 2018. All feline medical records were searched by two operators using the key words congenital hypothyroidism, hypothyroidism, dwarfism and cretinism in pre-diagnosis or diagnosis fields. One operator searched the data, and the other one analysed the medical records obtained to determine if inclusion criteria were met. Inclusion criteria were a diagnosis of congenital hypothyroidism based on consistent historical and clinical findings and a low or low-normal serum total T4 and an elevated serum cTSH, measured using a chemiluminescent enzyme immunoassay (CEIA) Immulite Total T4 and Immulite Canine TSH (Siemens Health Care Diagnostic Products), respectively. Data extracted from the medical records included signalment, information about diet, historical and clinical findings, clinicopathological findings, treatment and outcome.

RESULTS

During the study period, 1800 feline cases were seen in total, excluding revisits. Six cases met the inclusion criteria. All cats were unrelated and ranged in age from 4 to 19 months at diagnosis. All cats were fed with a variety of commercial balanced and complete diets (Purina Cat Chow and ProPlan, Nestle Purina Petcare; Royal Canin, Mars) from the age of weaning.

The most common historical findings were small stature and lethargy/mental dullness. The most common clinical abnormalities were disproportionate dwarfism with a large head, a short wide neck, short body and short thick limbs. Facial dysmorphism was characterised by a broad head with a flat face. Other common findings were obesity, retained deciduous teeth and/or delayed teeth eruption, palpable bilateral mobile goitres (10–15 mm) that were visible in two cases, bradycardia and hypothermia. Table 1 summarises age at presentation, historical and clinical signs and their duration, and results of thyroid hormone testing are summarised in Table 2. Additional case details are provided below.

Case 1

Two 4-month-old indoor domestic shorthair (DSH) male siblings from the same litter were presented to be neutered. Both cats were considered healthy by their owners. Mentation, dentition, size and clinical findings were normal in one of the cats (BCS 5/9, bodyweight 2.8 kg, heart rate (HR) 180 bpm). Its sibling was bright and active but had a broad head with a flat face (Fig 1) and was smaller with a higher body condition score (BCS 7/9), lower bodyweight (2.2 kg), lower HR (160 bpm) and thicker

Table 1. Age at diagnosis, historical findings and clinical signs in six cats with primary goitrous hypothyroidism

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at first presentation (months)	**4**	**5**	**7**	**8**	**12**	**19**
Historical signs						
Small stature noticed by owner	–	+	+	+	+	+
Lethargy	–	–	+	+	–	+
Weight gain	–	–	–	+	–	–
Inappetence	–	–	+	–	–	–
Constipation	–	–	+	–	+	–
Physical examination findings						
Body condition score	7/9	7/9	4/9	7/9	5/9	7/9
Bodyweight (Kg)	2.2	1.38	1.75	3.8	2.9	3.0
Disproportionate dwarfism	+	+	+	+	+	+
Facial dysmorphism (broad, flat face)	+	+	+	+	–	+
Retained deciduous teeth/eruption delay	+	+	+	+	+	+
Palpable bilateral goitre	+	+	+	+	+	+
Thyroid gland diameter right/left (mm)	10/10	10/12	8/8	12/12	15/15	15/15
Heart rate ≤ 140 bpm	–	–	+	–	+	+
Hypothermia (Temperature ≤ 37.8)	+	+	+	+	+	+
Unkempt/dry coat	–	–	+	+	+	+
Alopecia over pressure points	–	+	–	–	+	+
Dehydration	–	–	+	–	–	–
Palpably distended colon	–	–	+	–	–	–

Table 2. Results of serial serum endocrine tests at diagnosis and after initiation of therapy

Case	Hormones	Time after starting levothyroxine (weeks)			
		0	4–6	8–10	108
1	T4 (μg/dL, RI* 0.6–3.6 μg/dL)	0.4	1.9	2.7	2.7
	TSH (ng/mL, RI* 0.06–0.32 ng/mL)	3.6	3.6	0.07	0.07
2	T4 (μg/dL)	0.5	1.4	0.9	0.9
	TSH (ng/mL)	12	12	0.3	0.32
3	T4 (μg/dL)	0.8	1.4	1.7	2.0
	TSH (ng/mL)	7.5	6.0	0.28	0.2
4	T4 (μg/dL)	0.4	0.6	2.2	ND†
	TSH (ng/mL)	2.7	2.7	0.25	ND†
5	T4 (μg/dL)	1.0	1.4	2.1	2.0
	TSH (ng/mL)	3.0	2.9	0.12	0.18
6	T4 (μg/dL)	0.8	1.3	1.5	2.8
	TSH (ng/mL)	12	12	0.3	0.32

*RI: reference interval
†ND: not done

limbs. Other abnormalities included low rectal temperature (37.5°C), lethargy, palpable symmetric goitres, delayed eruption of premolar teeth (#506-#508, #606-#608, #707, #708, #807, #808) and partially erupted deciduous canines (#504, #604, #704, #804) (Floyd 1991) (Fig 1) (Table 1).

Abdominal palpation was unremarkable. Results of a complete blood count (CBC) and serum biochemistry panel were normal. Urine specific gravity (USG) was normal (> 1.060) with inactive sediment. Serum total T4 was low, and TSH was markedly elevated (Table 2).

Case 2

A 5-month-old female DSH cat was presented because of its small size compared with its female litter mate, noticed by its owners from 2 months of age. Although smaller in stature, it had a large head with a flat, rounded face and was heavier (bodyweight 1.38 kg vs 1.23 kg), with a lower HR (160 bpm vs 180 bpm) and rectal temperature (37.7° vs 38.3°C) than its sibling. It also had palpable bilateral asymmetric enlargement of the thyroid lobes, delayed eruption of premolar teeth similar to Case 1 and alopecia on the ventral aspects of both hocks (Table 1). Serum total T4 was low, and TSH was markedly elevated (Table 2).

Case 3

A 7-month-old female DSH cat was presented for lethargy, constipation and anorexia of 2 weeks' duration. It had experienced recurrent episodes of constipation since it was 2 months old. Clinical findings included disproportionate dwarfism, lethargy, dehydration, an unkempt coat and a distended abdomen (Fig 2). Rectal temperature was 36.5°C, and HR was 140 bpm. Bilateral symmetric goitres were palpable (Table 1), and on abdominal palpation, the colon was distended with firm faeces. There were retained canine (#504, #604, #704, #804) and premolar (#506, #507, #606, #607, #707, #708) deciduous teeth and incisor (#501-#503, #601-#603, #701-#703, #801-#803) tooth eruption delay (Fig 2).

Serum total T4 was low-normal, and TSH was markedly elevated (Table 2). Abdominal radiographs revealed megacolon and evidence of delayed ossification, including short vertebral bodies, widened growth plates in the proximal tibiae and femoral condyles and absent patellae.

Case 4

An 8-month-old male DSH cat was presented with a history of lethargy and weight gain compared with its litter mate since it was 3 months old. The cat remained in one location in the house for most of the day and did not play. On physical examination, the cat was small, obese (BCS 7/9) and had a broad, flat face and other features of disproportionate dwarfism (Fig 3). Other abnormalities included a markedly unkempt and dry hair coat, partially erupted deciduous premolars similar to Case 1 (Fig 3), palpable symmetric bilateral goitres (12 mm), bradycardia (150/min bpm) and hypothermia (37.0°C). Abdominal palpation was normal (Table 1). Serum total T4 was low, and TSH was elevated (Table 2).

Case 5

A 12-month-old male DSH cat was presented with a history of small size compared with its litter mate and recurrent episodes of constipation since it was 4 months old. It had disproportionate dwarfism, a dry hair coat with focal alopecia on the ventral aspects of both tarsi and elbows, delayed eruption of the molar teeth (#109, #209, #309, #409) and large visible and palpable bilateral symmetric goitres and was bradycardic (120 bpm) and hypothermic (37.7°C). Abdominal palpation was normal (Table 1). Abdominal radiographs were declined by the owners. Serum total T4 was low-normal, but TSH was elevated (Table 2).

Case 6

A 19-month-old male neutered DSH cat was presented with a history of lethargy and small stature, noticed since it was 7 months old. It had a broad head, short and wide neck, square body and short thick limbs. There were partially erupted canines (#304, #404), incisor teeth (#301-#303, #401-#403) and premolars (#106-#108, #206-#208) (Fig 4). The cat also had bradycardia (132 bpm), hypothermia (37.5°C), visible and palpable symmetrical bilateral goitres and alopecia of pressure points (tarsus and elbows). Abdominal palpation was normal (Table 1). Serum total T4 was low-normal, and TSH was markedly elevated (Table 2). Results of a serum biochemistry panel were within reference intervals. On urinalysis sediment was benign, USG was >1.040, and urine protein/creatinine ratio (UPC) was within reference limits (<0.2).

Treatment and outcome

After diagnosis, all cats received oral levothyroxine supplementation (median 13.5 μg/kg twice daily, range 10–20 μg/Kg) as a tablet (Eutirox®) administered on an empty stomach and were rechecked at 3–4-week intervals to evaluate response to therapy. Blood samples were taken 4 hours after levothyroxine supplementation, and serum T4 and cTSH were measured. Levothyroxine doses were adjusted as necessary to maintain an absence of clinical

FIG 1. Case 1, a 4-month old male DSH kitten with congenital hypothyroidism was presented to be neutered with its litter mate. The cat had delayed eruption of its canine and premolar teeth (a) a broad, flat face (b) and was smaller with a high body condition score (7/9) compared with its litter mate (c)

FIG 2. Case 3, a 7-month-old female DSH with disproportionate dwarfism. Note the broad, flat face and unkempt coat (a), retained deciduous canine teeth (b, c) and delayed eruption of incisors and premolars (c)

FIG 3. Case 4, an 8-month-old male DSH cat with disproportionate dwarfism. Note the broad, flat face, thick limbs and unkempt coat (a) and partially erupted premolar teeth (b)

signs of hypothyroidism and serum T4 and Thyroid Stimulating Hormone (TSH) concentrations within reference ranges (median 16 µg/kg twice daily, range 14–20 µg/Kg). Results of total T4 pre- and post-treatment and TSH are presented in Table 2 and Fig 6.

All cats responded to treatment. Four to eight weeks after starting levothyroxine, all owners reported an improvement in their cat's hair coat quality and increased physical activity. Heart rate and temperature were normalised after 8 weeks. Alopecia resolved after 8–12 weeks. A normalised physical appearance, including normal stature and eruption of permanent teeth, was apparent after 16 weeks of treatment. Thyroid glands decreased in size considerably in all cases (~80%) but remained palpable

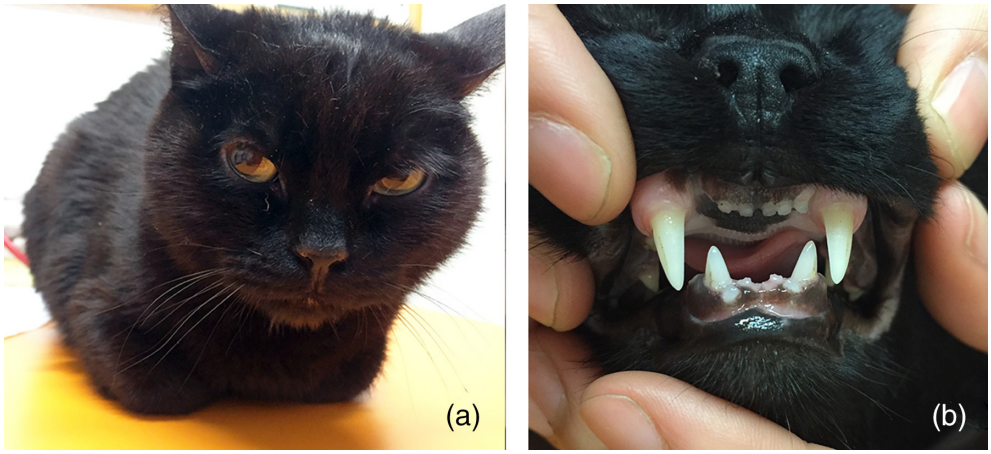

FIG 4. Case 6, a 19-month-old male neutered DSH cat with disproportionate dwarfism. The cat had a markedly flat and broad head (a), as well as a short and wide neck, square body and short thick limbs. There were partially erupted canines (#304, #404) and incisor teeth (#301, #302, #303, #401, #402, #403) (b)

FIG 5. Case 1 after treatment, 16 weeks after diagnosis (a) and 2 years after diagnosis (b). The affected cat is on left showing normalisation of disproportionate dwarfism, and its litter mate is on the right

(2–3 mm) even after total T4 and cTSH fell within reference intervals. In all cases, serum total T4 was within the reference interval 4–6 weeks after starting treatment, but TSH remained high until weeks 8–10.

Two years after starting therapy, five of the six cats remained clinically stable with thyroid hormone values within reference intervals, and no sequelae of hypothyroidism were apparent (Fig 5). One of the cats died of unrelated causes (trauma).

DISCUSSION

This is the first report of congenital hypothyroidism diagnosed in young cats in Chile. Interestingly, we identified six cases over an 18-month period, adding support to the suggestion that congenital hypothyroidism is more common than previously thought and also raising questions about the underlying cause of disease in these cats. To ascertain the true incidence of this disease and the potential effects of certain exposures resulting in case clustering, epidemiological studies involving large patient medical record datasets in different countries are warranted.

The discrepancy in size between four of the cases of congenital hypothyroidism described here and an unaffected litter mate they were each domiciled with was one factor that alerted the owner or attending veterinarian that the affected cat was physically abnormal. At the time of presentation, all six cats showed signs of disproportionate dwarfism, had retained deciduous teeth and/or eruption delay and had bilateral goitres, all signs observed in pre-

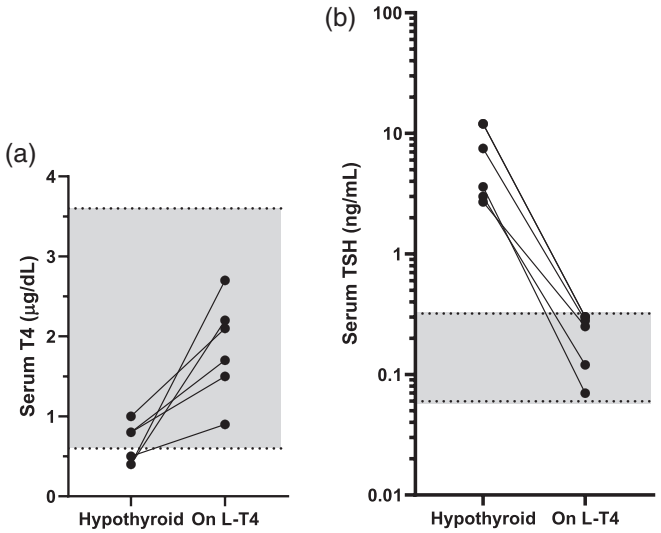

FIG 6. Serum T4 (a) and cTSH (b) at diagnosis and 8–10 weeks after therapy with twice daily oral levothyroxine administered on an empty stomach

vious reports of feline hypothyroidism (Tanase *et al*. 1991, Jones *et al*. 1992, Crowe 2004, Traas *et al*. 2008, Quante *et al*. 2010, McGhie & Thompson 2011). Mental dullness and constipation, both signs typical of the condition, were documented in only two cases here (Peterson 2019). Severe megacolon in Case 3 resolved after thyroid hormone supplementation, as has been described in other cases (Quante *et al*. 2010, Lim *et al*. 2014).

In addition to disproportionate dwarfism, the finding of a low or low-normal HR, together with low-normal or low rectal temperature, was helpful clinical information to rank congenital hypothyroidism as a major differential diagnosis and to justify thyroid hormone testing. Other differential diagnoses for dwarfism and facial dysmorphism in cats include hyposomatotropism, lysosomal storage diseases (*e.g*. mucopolysaccharidosis) and portosystemic shunt. In congenital hypothyroidism, delayed epiphyseal ossification is a common radiographic finding and was present in the case here that had radiographic examination.

A poor hair coat (unkempt and dry) was observed in all cases here but was not investigated further. Dermatological abnormalities in congenital hypothyroidism are usually attributed to retention of the juvenile haircoat, progressive alopecia and a lack of primary guard hairs (Bojanic *et al*. 2011). Seborrhoea is also reportedly common (Lim *et al*. 2014). The focal lesions of alopecia over "pressure points," present in three of our cases, has not been described previously.

Cases 5 and 6 had visible goitres, likely reflecting the long-time course of disease in these older cats. Although both had disproportionate dwarfism, which is usually noticeable by 2 months of age, and one had recurrent episodes of constipation since 4 months of age, neither were presented by their owners until much later. Acquired goitrous hypothyroidism could not completely be ruled out as dietary testing for iodine levels or goitrogens was not performed, but this was considered unlikely due to the presence of signs from a young age, and both cats were fed different commercial diets that meet the requirements of the Association of American Feed Control Officials.

Three other cases of congenital hypothyroidism diagnosed in older cats have also been reported, including a 3-year-old cat with severe constipation and megacolon that was referred for subtotal colectomy (Crowe 2004, Szabo & Wells 2007, Peterson 2015). In two of those cases, a definitive diagnosis of hypothyroidism was not obtained as cTSH levels or scintigraphy was not performed, but the diagnosis was supported by radiographic findings of epiphyseal dysgenesis of the vertebral bodies, pelvis and tibiae (Crowe 2004, Szabo & Wells 2007). The third case, in a 12-month old DSH, was similar to the cases reported here with disproportionate dwarfism, an unkempt coat, severe lethargy and bilateral palpable goitres. In that case, the results of thyroid scintigraphy performed after the administration of sodium ^{99m}Tc-pertechnetate were consistent with thyroid dyshormonogenesis, with greatly increased uptake of the radionuclide by the hyperplastic goitre (Peterson 2015). Scintigraphy would have been useful to support a diagnosis of thyroid dyshormonogenesis in the cases described here but was unavailable.

Congenital dyshormonogenic hypothyroidism with goitre secondary to thyroid peroxidase (TPO) deficiency and impaired iodine organification has been reported in related DSH and Abyssinian cats, with a suspected autosomal recessive mode of inheritance (Sjollema *et al*. 1991, Jones *et al*. 1992). This mechanism and mode of inheritance has been confirmed in two canine breeds (Toy Fox and Rat Terriers) with congenital goitrous hypothyroidism, and confirmatory genetic tests are available (Pettigrew *et al*. 2007, Dodgson *et al*. 2012). Another cause of congenital goitrous hypothyroidism in shi-tzu dogs is an iodide transport defect due to an autosomal recessive homozygous single nucleotide polymorphism in the *SLC5A5* gene that encodes for the sodium/iodine symporter (Soler Arias *et al*. 2018).

In animals with congenital goitrous hypothyroidism, TSH secretion is upregulated in response to low T4 and T3 concentrations, resulting in thyroid gland hyperplasia. This condition has also been described in puppies born to dams ingesting iodine-deficient diets or goitrogens during pregnancy and in pups fed a diet with excessive or deficient iodine content from the age of weaning (Nuttall 1986, Castillo *et al*. 2001a, 2001b, Mooney 2016). The congenital goitrous hypothyroidism of cats in this case series could have been caused by genetic defects in hormone synthesis and/or could be a consequence of being born to iodine-deficient queens. Dietary iodine deficiency or excess in pregnant women can result in congenital transient hypothyroidism (Grob *et al*. 2012). Dietary and medical histories of the queens of the cases reported here were not available, and congenital goitrous hypothyroidism in cats due to iodine-imbalanced diets of queens has not yet been reported.

Non-goitrous cases of congenital hypothyroidism have also been reported in cats, including thyroid hypoplasia and thyrotropin resistance (Tanase *et al*. 1991, Traas *et al*. 2008). Approximately half of all cases of feline congenital hypothyroidism are goitrous (Sjollema *et al*. 1991, Jones *et al*. 1992, Peterson *et al*. 1994, Mazrier *et al*. 2003, Jacobson & Rochette 2018), and the new cases here support that hypothyroidism with goitre is the most common form of congenital hypothyroidism in cats.

Abnormalities in haematology, serum biochemistry or urinalysis were not present in either cat in which these tests were

performed, although hypercholesterolemia, azotaemia and mild anaemia can be present in congenital hypothyroidism (Peterson 2019). Decreased glomerular filtration rates have been documented in cats with iatrogenic hypothyroidism (Williams *et al*. 2010). There is one report of a cat with congenital hypothyroidism in which azotaemia and proteinuria were suspected to be associated with impaired renal development and function due to low thyroid hormones (Lim *et al*. 2014).

The combination of consistent clinical findings, low or low-normal T4 and elevated cTSH confirmed a diagnosis of primary hypothyroidism in these cases. Some cats with mild hypothyroidism can maintain serum T4 in the lower end of the reference range (0.8–1.5 µg/dL) (Peterson 2019). Free T4 was not measured as an equilibrium dialysis assay was not available.

All of the cats in this report had a good response to therapy with oral levothyroxine, and the timing of resolution of clinical signs was similar to previous reports, with improvement after 4 weeks of therapy and normal clinical appearance and thyroid hormones after 16 weeks (Quante *et al*. 2010, Van Bergen *et al*. 2016). Interestingly, although goitres markedly shrank in all cases, none completely resolved. This is in contrast to a previous report of congenital goitrous hypothyroidism in cat where complete resolution of the goitre was observed after levothyroxine therapy (Peterson 2015). It has recently been shown that, while healthy cats can have wide inter-individual biological variation in serum TSH concentrations, most maintain serum TSH in the lower third of the population-based reference interval (<0.1 ng/mL) (Prieto *et al*. 2020). While serum TSH was suppressed into the reference range in our cases, in only one of the six cats was it suppressed to the lowest third of the reference interval. Thus, in at least some of the cats, it is possible that a higher dose of levothyroxine may have resulted in complete resolution of the goitre.

Findings in these cases were consistent with primary goitrous congenital hypothyroidism due to thyroid dyshormonogenesis. All cases responded to levothyroxine supplementation, with T4 and cTSH normalisation and resolution of clinical signs after 16 weeks. Feline congenital hypothyroidism can be well managed over time with oral levothyroxine.

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Conflict of interest

No conflicts of interest have been declared.

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