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Congenital Thyroid Hypoplasia and Seizures in 2 Littermate Kittens

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Two male littermate kittens (Kitten A and B) were examined at 14 weeks of age because of straining to defecate in the litter box. According to the owner neither kitten was seen having a bowel movement during the prior 2 weeks, but they were still eating, drinking, and urinating appropriately.

The kittens were adopted at 8 weeks of age and were possibly the result of a father-daughter mating. The queen's mother was a purebred Abyssinian, who was allowed to roam outdoors, and was likely bred by the only feral tom known to reside in the neighborhood, producing a total of 15 known offspring in several litters. One of the offspring, the mother of these kittens, was also allowed outdoors where she was possibly impregnated by her father. This queen had a total of 10 kittens from 2 litters including these 2 affected, 2 clinically normal kittens, and 6 kittens of unknown clinical status but presumed unaffected. The owner of the mother of these affected kittens reported that the queen was on a premium commercial cat food with no supplements and suffered no apparent health problems during the pregnancy and nursing period. The 2 affected kittens tested negative for feline leukemia virus infection and were given routine vaccinations. There was no history of previous illnesses.

At initial examination, both kittens had disproportionally short legs, abducted elbows, rounded and flattened faces (Fig 1), and were severely obstipated. Their facial structure and dentition resembled that of a 4-week-old kitten. They were not yet playing with toys or each other. During examination they appeared mentally dull and responded slowly to stimuli. Kittens A and B weighed 0.73 and 0.95 kg, respectively, when a normal weight for a domestic shorthair kitten of that age is approximately 1.5 kg. Their vital signs were normal, but abdominal palpation caused discomfort and revealed distention due to a very large colon filled with firm feces.

Radiographs showed widened bone growth plates inappropriate for their age, as well as shortened long bones and wide vertebral bodies. Several tarsal and carpal bones were not visible due to delayed mineralization and Kitten A had a physeal fracture of the sternum causing deformation. These changes are diagnostic of epiphyseal dysgenesis and typical of congenital hypothyroidism (CH). Megacolon, filled with fecal material, was also evident as well as excess gas in the stomach and small intestines (Fig 2).

Serum total T₄ concentrations were lower than the detectable limits of the assay (≤ 0.4 $\mu\text{g/dL}$; normal adult values = 1–4 $\mu\text{g/dL}$) in both kittens. Fecal examinations were negative for parasites. They were administered levothyroxine^a (0.05 mg q12h PO), lactulose^b (1 mL q8h

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^aSoloxine, Daniels, Fort Worth, TX

PO), and several warm water enemas. Both kittens required 5 visits over the following 2 weeks for enemas until they could defecate normally.

At 4 months of age, serum T₄ levels 4 hours after supplementation were 1.9 and 1.8 µg/dL, Kitten A and B, respectively. The thyroxine was increased to 0.1 mg q 12h PO to adjust for growth and to maintain their values in the adult range.

At 5 months of age, while on thyroid hormone supplementation, Kitten B began having episodes of shivering and trembling reported by the owner to be possible seizures. Because these episodes progressed in frequency to at least 1 per day, the kittens were referred.

Presented at 6 months of age (24 weeks) to the Pediatrics and Genetics Clinic at the University of Pennsylvania Veterinary Hospital (as part of the NIH Referral Center for Animal Models of Human Disease), the kittens were evaluated as part of a protocol for clinical workup and study of genetic diseases in dogs and cats as approved by the Institutional Animal Care and Use Committee. Both kittens had features consistent with cretinism including short stature, abducted elbows resulting in a bowlegged stance, rostral-caudally shortened faces, and mental dullness. Adult tooth eruption was delayed and they had slightly enlarged soft abdomens and, although they had body condition scores of 6/9, they were underweight for their age at 2.44 kg (Kitten A) and 2.64 kg (Kitten B). Vital signs were normal and thyroid glands were not palpable in either kitten.

Both kittens responded, but slowly, to name and noises and thus were apparently able to hear. They used the litter box and ate normally, but did not exhibit normal play behavior for 6-month-old kittens. Kitten A would slowly swat a ball a few times before wandering slowly away. Kitten B displayed additional cognitive dysfunction by being slower to respond to his name and noises, uninterested in playing with toys and not responding to his brother's attempts at play. He also had subtle evidence of rear limb ataxia and would occasionally crossover the hind paws. Both kittens responded to petting by purring and appeared to be content. No seizure-like episodes were observed in either kitten during the 1st 2 weeks of close observation. Following initial workup, Kitten A was adopted by a veterinarian at the hospital.

CBC and serum chemistry panels were within normal limits. A thyroid panel was performed at the Michigan State Animal Health Diagnostic Laboratory (thyroxine supplementation had been withdrawn 2 weeks before presentation), and repeated 2 weeks later, at 26 weeks, to include a serum TSH concentration, which was high in both kittens (Table 1).

Two weeks after admission, Kitten B was found shivering. He appeared duller and more lethargic than usual and was rapidly open mouth breathing. He was in good body condition at 2.8 kg, but his body temperature was 105.7°F. Attempts to resolve the hyperthermia with ice packs, cold-water baths and fans failed, but within 3 hours of administration of meloxicam^c (0.1 mg/kg for a total dose of 0.25 mg SC) it resolved. A CBC, serum chemistry panel, and serum creatine kinase activity were within normal limits for his age. He did not have any further seizure activities or hyperthermia, but remained lethargic and inappetent until the next morning. Although no cause for the hyperthermia and behavioral changes was observed, a seizure was suspected given his previous history. Six days later a veterinary nurse witnessed him having a generalized seizure and he was euthanized due to a very long (12 hours) postictal phase including vomiting and diarrhea.

^bEnulose, Barre, Baltimore, MD

^cMetacam, Boehringer Ingelheim Vetmedica Inc, St Joseph, MO

Kitten A continued to do well for the next month despite lack of thyroid supplementation. Thyroid axis and potential iodine uptake testing was planned after which thyroxin supplementation would have been reestablished. Although he had no prior history of seizures, he experienced a generalized seizure progressing to respiratory arrest at 32 weeks of age, and because he could not be revived enough to function without respiratory support, he was euthanized.

Complete necropsies on both kittens revealed thyroid glands that were indistinct from the surrounding tissue, thin, soft and light red-brown. The inability to distinguish and separate the glands from the surrounding fatty tissue (Fig 3) prevented accurate measurements. The intestines showed no evidence of the previously diagnosed megacolon. All other body tissues appeared grossly normal.

Histologically, follicles were greatly reduced in number and size in the severely hypoplastic thyroid glands of both kittens. Most were lined by low cuboidal or flattened epithelial cells and some were filled with brightly eosinophilic colloid material (Fig 4). There were multifocal clusters of very small follicles, which were empty of colloid and were lined by larger cuboidal epithelial cells with light eosinophilic or cleared cytoplasm. Kitten A also had interspersed thymic remnants within the area of the thyroid.

No neurologic cause for seizures could be determined by necropsy; however, Kitten B had mild leptomenigeal edema and the lymph nodes showed evidence of lymphoid hyperplasia. Both kittens had evidence of pulmonary edema likely due to the recent seizure activities. No other histologic abnormalities were found.

Discussion

CH has been reported in many species and can be due to dysfunctions at several sites including the thyroid, pituitary, or hypothalamus. While cretinism (developmental delays, short stature, and mental retardation) and megacolon of unknown cause, goiter and thyrotrophin resistance have been previously described in cats,^{d,1-6} we report here on 2 littermate kittens with similar signs due to severe congenital thyroid hypoplasia. The possible inbred parentage, the age of onset, similarity of disease course in 2 littermates, and presence of healthy kittens in the same litter all suggest a hereditary versus an acquired form of CH, although an acquired form cannot be excluded.

While common in humans, the frequency and importance of CH in kittens remain unknown, but may be underreported and misdiagnosed as idiopathic megacolon and other skeletal anomalies. Once megacolon, short stature, and mental dullness are recognized as clinical signs of CH, a diagnosis of hypothyroidism is easily made in a kitten based on a serum T₄ level at or below the normal adult range. A full thyroid profile including serum TSH concentrations can further classify the disease: TSH is expected to be high in CH not originating in the hypothalamus or pituitary gland. Although the assay is not validated for the cat, the assay for canine TSH has recently been demonstrated to detect feline TSH (http://www.animalhealth.msu.edu/FAQ/Endocrinology/Thyroid_Feline.php#04). The normal range of thyroid hormone levels in kittens is not well established. In most mammals including children, the normal range is slightly higher than adults. However in 1 study, kittens approached the upper end of the normal adult range but did not go above the range as seen in other species.^e

^dMazier H, French A, Ellinwood NM, et al. Goiterous congenital hypothyroidism caused by thyroid peroxidase deficiency in a family of domestic shorthair cats. *J Vet Intern Med* 2003;17:395-396 (ACVIM abstract)

^eZerbe CA, Casal ML, Jczyk PF, Refsal KR, Nachreiner RF. Thyroid profiles in healthy kittens from birth to 12 weeks of age. *J Vet Intern Med* 1998;12: 212 (ACVIM abstract # 58)

CH can be divided into 2 main categories: goiterous (thyroid dyshormonogenesis) or nongoiterous (thyroid dysmorphogenesis). Both forms typically have a genetic basis albeit acquired causes such as iodine deficiency or excess, toxins, immune-mediated or radioactive iodine exposure must also be considered.⁷

Thyroid dyshormonogenesis is caused by mutations in the genes encoding the protein “machinery” of thyroid hormone production (eg, thyroglobulin, thyroid peroxidase, sodium/iodide symporter, and others). Because thyroid hormones are not produced, decreased feedback to the hypothalamus and pituitary causes increased stimulation of the gland and hyperplasia of the glandular tissue ensues (goiter) as is seen in most previous reports of CH in dogs and cats.^{d,1,2,8,9} Although much less common than acquired hypothyroidism, goiterous CH has been reported in various dog breeds, including Toy Fox⁸ and Rat⁹ terriers where a nonsense mutation in the thyroid peroxidase gene was discovered. Goiterous CH has also been reported in kittens and preliminary studies indicated organification defects.^{d,1,2} In one of these reports, Abyssinian kittens were unable to incorporate iodine into thyroglobulin.¹ Although the kittens described in this report have an Abyssinian grandmother they did not have goiter and thus had a different basis of disease.

Hereditary thyroid dysmorphogenesis represents by far the more common cause of CH in children,¹⁰ and the kittens of this report could have a similar genetic defect in thyroid development. The classic clinical signs of cretinism seen in children (developmental delays, short stature, and mental retardation) were also displayed in these kittens. However, constipation and megacolon, which are common, yet unexplained, presentations of hypothyroid kittens,^{1,3,11} are not reported in affected children.

Hypothalamic and pituitary forms of hypothyroidism have been rarely reported in companion animals as single defects¹² as well as part of more complex endocrinopathies, for example, dwarf German Shepherds with pituitary cysts.¹³ In the kittens reported here, the high serum TSH levels point to an error within the thyroid gland itself, but TSH mutations that render the hormone nonfunctional could also be possible. Because TSH levels were already high and glandular mass was very low, a diagnostic trial with TSH was not attempted and would have been unlikely to be effective.

Thyroid dysmorphogenesis in other species includes defects in genes encoding or related to thyroid transcription factor-1, and -2, paired box gene 8, the TSH receptor, and signal transduction pathways downstream of the TSH receptor.^{14,15} These defects result in agenesis, hypoplasia (which accounts for approximately 16% of hypothyroid children¹⁶⁻¹⁸), and rarely in ectopic thyroid glands. Sequencing of the cDNAs involving any of these candidate genes and other genes more rarely involved in disease has not been attempted in these kittens and hence the molecular basis of this severe congenital thyroid hypoplasia remains unknown.

While CH can be effectively treated when recognized early, and the clinical signs of cretinism and megacolon can be reversed, the development of generalized seizures represented an additional clinical feature and led to the demise of both kittens reported here. The generalized seizures in the kittens of this report, if related, are likely unique to this form of congenital thyroid hypoplasia, as they have not been observed in children or animals with CH. In human medicine, seizures have been reported in a few cases of congenital and acquired hypothyroidism, but a direct association to the primary disease or any particular defect has not been documented.¹⁹⁻²¹ The fact that kittens with the goiterous form of hypothyroidism do not exhibit seizure activity, despite similarly severe mental retardation as seen in humans and the kittens reported herein, and that both kittens of this report developed seizures, when on or off thyroid supplementation, suggests that a pleiotropic effect of a single gene defect could be involved and thus may represent a specific syndrome. However, a coincidental disease and an

early onset nonreversible seizure focus could not be excluded albeit no gross or histopathologic brain lesions were identified in either kitten.

In contrast to human patients with CH, constipation and the development of megacolon, as seen in these kittens, seems to represent a common manifestation in hypothyroid kittens as seen in previously described goiterous hypothyroid kittens.^{d,1,2} The mechanism of constipation and megacolon remains unknown, but may involve defective innervations as well as pelvic deformities. Because dullness and mildly stunted growth of a hypothyroid kitten may not be recognized by owners as a disease process, the major presenting complaint of owners of kittens due to any cause of hypothyroidism may be constipation, as reported here and previously. While idiopathic megacolon has a poor prognosis in cats, megacolon and constipation associated with CH are reversible after initial intensive therapy to evacuate the colon followed by simple daily thyroid hormone supplementation until the kittens are grown. Young adult and older hypothyroid cats do not appear to experience signs of hypothyroid-associated megacolon and constipation.

In conclusion, screening of kittens with suspicious clinical signs for CH, regardless of the presence or absence of goiter, is recommended. The disease can be easily diagnosed and in most cases easily treated with thyroid hormone supplementation and acute management of constipation, unless complicated by unexplained seizures as uniquely seen in the kittens of this report.

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References

1. Jones BR, Gruffydd-Jones TJ, Sparkes AH, Lucke VM. Preliminary studies on congenital hypothyroidism in a family of Abyssinian cats. *Vet Rec* 1992;131:145–148. [PubMed: 1329305]
2. Sjollem BE, den Hartog MT, de Vijlder JJ, et al. Congenital hypothyroidism in two cats due to defective organification: Data suggesting loosely anchored thyroperoxidase. *Acta Endocrinol (Copenhagen)* 1991;125:435–440.
3. Tanase H, Kudo K, Horikoshi H, et al. Inherited primary hypothyroidism with thyrotrophin resistance in Japanese cats. *J Endocrinol* 1991;129:245–251. [PubMed: 1904088]
4. Firth MF, Fondacaro JV, Greco DS. Challenging cases in internal medicine: What's your diagnosis? *Vet Med* 2000;95:606–614.
5. Szabo SD, Wells KL. What is your diagnosis? Congenital hypothyroidism. *J Am Vet Med Assoc* 2007;230:29–30. [PubMed: 17199487]
6. Tobias S, Labato MA. Identifying and managing feline congenital hypothyroidism. *Vet Med* 2001;96:719–726.
7. Buyukgebiz A. Newborn screening for congenital hypothyroidism. *J Pediatr Endocrinol Metab* 2006;19:1291–1298. [PubMed: 17220056]
8. Fyfe JC, Kampschmidt K, Dang V, et al. Congenital hypothyroidism with goiter in toy fox terriers. *J Vet Intern Med* 2003;17:50–57. [PubMed: 12564727]
9. Pettigrew R, Fyfe JC, Gregory BL, et al. CNS hypomyelination in Rat Terrier dogs with congenital goiter and a mutation in the thyroid peroxidase gene. *Vet Pathol* 2007;44:50–56. [PubMed: 17197623]
10. Macchia PE. Recent advances in understanding the molecular basis of primary congenital hypothyroidism. *Mol Med Today* 2000;6:36–42. [PubMed: 10637573]
11. Greco DS. Diagnosis of congenital and adult-onset hypothyroidism in cats. *Clin Tech Small Anim Pract* 2006;21:40–44. [PubMed: 16584030]
12. Mooney CT, Anderson TJ. Congenital hypothyroidism in a boxer dog. *J Small Anim Pract* 1993;34:31–35.

13. Kooistra HS, Voorhout G, Mol JA, Rijnberk A. Combined pituitary hormone deficiency in German Shepherd dogs with dwarfism. *Domest Anim Endocrinol* 2000;19:177–190. [PubMed: 11064220]
14. Genetics Home Reference. Congenital hypothyroidism20064http://ghr.nlm.nih.gov/
15. Sasaki N, Hosoda Y, Nagata A, et al. A mutation in *Tpst2* encoding tyrosylprotein sulfotransferase causes dwarfism associated with hypothyroidism. *Mol Endocrinol* 2007;21:1713–1721. [PubMed: 17456791]
16. Gaudino R, Garel C, Czernichow P, Leger J. Proportion of various types of thyroid disorders among newborns with congenital hypothyroidism and normally located gland: A regional cohort study. *Clin Endocrinol (Oxford)* 2005;62:444–448.
17. Macchia PE, Lapi P, Krude H, et al. PAX8 mutations associated with congenital hypothyroidism caused by thyroid dysgenesis. *Nat Genet* 1998;19:83–86. [PubMed: 9590296]
18. Vono-Toniolo J, Kopp P. Thyroglobulin gene mutations and other genetic defects associated with congenital hypothyroidism. *Arq Bras Endocrinol Metabol* 2004;48:70–82. [PubMed: 15611820]
19. Asami T, Sasagawa F, Kyo S, et al. Incidence of febrile convulsions in children with congenital hypothyroidism. *Acta Paediatr* 1998;87:623–626. [PubMed: 9686652]
20. Aszalos Z. Some neurological and psychiatric complications in the disorders of the thyroid gland. *Orv Hetil* 2007;148:303–310. [PubMed: 17344150]
21. al-Qudah AA. Screening for congenital hypothyroidism in cognitively delayed children. *Ann Trop Paediatr* 1998;18:285–288. [PubMed: 9924583]

Fig 1. Photographs of affected littermate kittens. Kitten A (photos A and B) and Kitten B (photos C and D) at 14 weeks of age. Note the disproportionate dwarfism typical of cretinism.

Fig 2. Radiographs of Kitten A at 14 weeks of age. Note the wide growth plates with delayed ossification. Vertebral bodies (photos A and D) are widened and square. Carpal (photo C) and tarsal (photo D) bones also have delayed ossification. Megacolon (A,D) and a fracture of a sternbrae through the growth plate (D) can also be seen.

Fig 3. Gross pathology of Kitten B cervical region. On postmortem examination severely hypoplastic thyroid glands were paper-thin, pale brown, and indistinct from surrounding tissues (arrow).

Fig 4. Histopathology of normal and affected thyroid glands. Histology at 2 different magnifications, showing a normal age-matched thyroid gland (**A, C**) compared with an affected thyroid gland (**B, D**). Follicles in the affected glands are decreased in both density and size.

Table 1

Serial serum thyroid testing from 2 kittens with congenital hypothyroidism ($\mu\text{g/dL}$).

Age (Weeks)	Kitten A/B		Normal Ranges
	24	26	Adult
Total T4	7/2	2/4	10-55
Total T3	0.4/0.9	0.4/0.4	0.6-1.4
Free T4	0/0	2/0	10-50
Free T3	2.0/3.2	1.8/1.8	1.5-6.0
TSH	ND	312/205	0-21

Tests run at the Diagnostic Center for Population and Animal Health at Michigan State University. The reference ranges given by the laboratories are for adult animals.

ND, not done.