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Goiter with Vascular Anomalies in a Litter of Polish Lowland Sheepdogs

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Abstract

At approximately 4–5 mo of age, three Polish Lowland sheepdog puppies from a single litter of eight puppies presented to their respective primary veterinarians with bilateral subcutaneous masses in their ventral cervical regions. Evaluation, including thyroid function testing, surgical exploration with resection, computed tomography, and angiography, identified the masses as enlarged thyroid glands with severely dilated and abnormal vasculature in the regions of the glands. The dogs were also found to have serum concentrations of thyroid hormones that were below the reference ranges. None of the three dogs showed clinical signs of hypothyroidism, except for the presence of goiter. One dog also had a patent ductus arteriosus that was surgically repaired. All dogs were clinically normal at 2 yr of age. This is the first report of major vascular anomalies associated with goiter in any species. The mechanism is unknown.

Introduction

A goiter is an enlargement of the thyroid gland, which may or may not be associated with abnormal thyroid function. Congenital goitrous hypothyroidism (CGH) has been described in humans, dogs, cats, and other species.^{1–7} In humans, congenital hypothyroidism (CH) occurs at a frequency of 1 in 3,000 live births.⁷ Approximately 10–15% of human cases of CH are attributed to mutations in genes that encode enzymes required for normal thyroid hormone synthesis, resulting in CGH.⁷ Severe loss-of-function mutations are recognized in the neonatal period whereas other mutations develop later in childhood, either as goitrous hypothyroidism or familial euthyroid goiter.^{8,9}

The development of a goiter depends on the etiology of the hypothyroidism, and can be either inherited or acquired. Acquired goitrous hypothyroidism can be congenital (e.g., teratogenic) or develop later in life (e.g., iodine deficiency). If the hypothalamic-pituitary-thyroid axis is intact, thyroid stimulating hormone (TSH) binding to its receptor is appropriate, and the defect in hormonogenesis lies within the thyroid gland. In the latter case, a goiter will develop as the result of increased TSH secretion secondary to lack of

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negative feedback from plasma thyroxine (T₄) and triiodothyronine (T₃). Iodine excess or deficiency and exposure to specific drugs and foods have also been associated with both goiter development and hypothyroidism in humans and dogs.^{10–12} The purpose of this study was to describe three puppies with goiter and hypothyroidism. To the authors' knowledge, goiter with associated vascular anomalies described in the puppies of this report is unique for any species.

Case Report

Three puppies, one intact female and two intact males, from a litter of eight Polish Lowland sheepdogs were presented to The Center for Veterinary Care in Millbrook, NY (cases 1 and 2) and The Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania (case 3) for bilateral, subcutaneous, soft-tissue masses on their ventral necks. The remaining littermates (three males and two females), as well as the parents, were reportedly unaffected. According to the breeder, there were no reported health (including goiter) problems noted in any relatives or previous litters of either the bitch or sire. The bitch was clinically normal and had been fed a commercial dog food^a during pregnancy and nursing. She had been treated with enrofloxacin^b for 9 days shortly after breeding to treat a vaginal discharge, which resolved within 1–2 days of initiating treatment. No other medications, vaccines, or supplements were given to the bitch during her pregnancy (according to the breeder). All puppies in the litter were fed a commercial puppy diet^c and developed appropriately without any notable size or activity differences among the puppies. After being adopted, all puppies reportedly appeared clinically normal for their age until the time of regular wellness exams when subcutaneous masses in the ventral cervical region were recognized in three puppies by their respective veterinarians.

When examined at 4.5 mo, 5.5 mo, and 5.5 mo of age, respectively, the three affected puppies appeared to be of normal stature and proportions, had normal body condition scores, had hair coats normal for age and breed, had appropriate dental development for their age, and were bright and alert. They remained clinically normal throughout their respective clinical evaluations. Cases 2 and 3 each had bilateral masses measuring approximately 4 cm × 4 cm × 3 cm. The subcutaneous masses were mobile and were located in the area of the thyroid glands. Case 1 initially had a similar, unilateral mass, but re-evaluation by the veterinarian revealed that the puppy actually had bilateral masses. All three puppies had mild, generalized, cardiomegaly on thoracic radiographs with enlargement of the right ventricle. In all three puppies, the cervical, thoracic, and lumbar vertebral bones appeared normal for their age. The growth plates, epiphyses, and shape and radiodensity of the proximal humeri visible on thoracic radiographs appeared normal for dogs of their respective ages.

Serum thyroid hormone concentrations were below the reference ranges in all three puppies compared with the laboratories' adult reference ranges (Table 1). Case 1 had total and free T₄ concentrations below the reference ranges when tested 4 days after surgical removal of the masses. Cases 2 (preoperative assay) and 3 also had total and free T₄ concentrations below the reference ranges. Case 3 also had a TSH concentration above the reference range (Table 1). Percentages of autoantibodies for T₄, T₃, and thyroglobulin were all within the reference ranges. All puppies were supplemented with thyroxine^d at a dose of 0.02 mg/kg *per os* q 12 hr.

^aPro Plan Adult Chicken and Rice Formula; Nestle Purina PetCare Company, St. Louis, MO

^bBaytril; Bayer Animal Health, Shawnee Mission, KS

^cPro Plan Puppy Lamb and Rice Formula; Nestle Purina PetCare Company, St. Louis, MO

^dSoloxine; Virbac Animal Health, Inc., Fort Worth, TX

Surgical evaluation of the ventral cervical region of case 1 was performed, which revealed bilateral, kidney-shaped masses (each measuring 4 cm × 4 cm × 3 cm) with an approximately 5 mm isthmus connecting the caudal poles. The masses, along with the highly abnormal vasculature, were excised. On the right side of the neck was an approximately 3 mm long nonpulsating, dilated blood vessel identified in the area of the carotid artery and jugular vein. The blood vessel was double ligated at the level of the carotid artery and jugular vein.

Histopathology of the excised masses revealed thyroid tissue with marked follicular hyperplasia, which was consistent with goiter. No evidence of parathyroid tissue was found (Figure 1). This puppy recovered well from surgery. The only complication was postoperative hypocalcemia that was controlled with oral calcium^e and calcitriol supplementation^f.

Case 2 also had bilaterally enlarged thyroid glands identified during exploratory surgery. The left thyroid gland was supplied by >10 (rather than 1) arterial branches from the thyroid artery. In addition, the caudal aspect of the left gland had multiple large veins. An approximately 1.2 cm vascular dilation was noted near the left cranial thyroid artery, which appeared to be part of the arterial supply of the thyroid gland. Double ligatures were placed around the vascular dilation. Retrograde jugular pulses were noted initially, which resolved with ligation of the dilated blood vessel. The surgeon did not report similar findings on the right side.

Histopathologic examination of the excised left thyroid gland revealed mild to moderate hyperplasia of follicular cells, which was consistent with goiter. Case 2 recovered uneventfully.

At 6 mo of age, after initial identification of the masses, case 3 presented to Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania for additional diagnostic testing of the goiter and associated vasculature prior to intervention. A previously performed ventral cervical ultrasound had revealed the two cervical masses to be thyroid glands that measured approximately 5 cm × 2 cm × 2 cm with tortuous blood vessels in the area of the glands and possible arteriovenous (AV) communication between the jugular veins and carotid arteries bilaterally. Physical examination revealed the enlarged thyroid glands with no fremitus over the glands and no bruit ausculted over the glands. A grade 1/6 systolic murmur was ausculted over the left heart base. Fine-needle aspiration of the goiters revealed only red blood cells.

A dual-phase computed tomographic angiogram of the thyroid region, performed under general anesthesia, showed both thyroid glands to be markedly enlarged (5 cm × 2.5 cm × 2.5 cm, Figure 2). Both common carotid arteries were dilated caudal to the level of the origin of the cranial thyroid arteries, but they were drastically reduced in size cranial to the origin of the cranial thyroid arteries. The cranial thyroid arteries were dilated and branched into multiple subsegments that supplied various areas of the enlarged thyroid glands. During the arterial phase of the study, the left internal jugular vein was mildly dilated compared with the right; however, the left internal jugular vein remained smaller than the carotid artery. There was early contrast-enhancement of the left internal jugular vein compared with the right; however, no clear, dilated, or tortuous vessel was seen between the thyroid artery or its branches and the left internal jugular vein. No anomalous vessel was seen entering the external jugular vein.

^eTums; GlaxoSmithKline; Brentford, Middlesex, United Kingdom

^fRocaltrol; Validus Pharmaceuticals, Parsippany, NJ

Echocardiographically, case 3 had features consistent with a left-to-right shunting patent ductus arteriosus (PDA). Abdominal ultrasonography revealed prominent splenic or hepatic lymph nodes and a prominent portal vein and caudal vena cava. The puppy was prescribed a thyroxine supplement^d (0.02 mg/kg *per os* q 12 hr). One month later, at 7 mo of age, case 3 remained clinically normal without any treatment (except for the thyroxine supplementation). Repeat cervical ultrasound revealed that the thyroid glands were unchanged, and both the carotid arteries and the internal jugular veins were enlarged and appeared tortuous. The vessels could be followed and were seen branching within the glands, with no obvious AV fistulae or focally dilated vessel. No arterial pulses were demonstrated in what were assumed to be venous branches of the blood vessels.

Repeat thoracic radiographs of case 3 revealed persistent left and right heart enlargement, a mild bulge of the main pulmonary artery, and prominent pulmonary veins and arteries. A grade 1/6 systolic murmur was again ausculted over the left heart base. It is unclear why the murmur was not louder or continuous in light of the echocardiographic findings of a left-to-right shunting PDA. Following coil embolization of the PDA, brachiocephalic artery and aortic root angiograms were performed with the dog in both dorsal recumbency and obliqued dorsal recumbency. This allowed visualization of the right and left common carotid arteries, arterial blood supply to the thyroid gland, and venous drainage from the head and rostral neck. Although the internal and external jugular veins were distended, neither early venous phase nor tortuous vessel anatomy was noted to support the presence of AV malformations.

Following supplementation with thyroxine, despite not increasing the dose as their body weights increased as they grew, all three puppies maintained normal total and free T₄ concentrations and either normal or undetectable TSH concentrations when tested posttreatment (Table 1). Moreover, all three puppies continued to develop normally without any change in goiter size if not previously surgically excised.

Discussion

This clinicopathologic report describes goiter and vascular engorgements surrounding the thyroid glands in three puppies of a litter of eight Polish Lowland sheepdogs. CGH has been reported with thyroid organification defects in toy fox terriers and rat terriers, Abyssinians, and domestic shorthairs as a result of a thyroid peroxidase deficiency.^{1,2,5,6,13,14} Although the puppies in this report had serum thyroid concentrations below the reference ranges and one puppy also had a serum TSH concentration mildly above the reference range, those three puppies did not show the classic clinical features of CH (known as cretinism), such as dwarfism, dullness, and skeletal deformities.

Neoplasia, such as a thyroid adenoma and carcinoma, was an unlikely consideration for those puppies due to their young age and the presence of the masses in multiple puppies of the same litter. Histopathology of samples from cases 1 and 2 was consistent with thyroid hyperplasia (i.e., goiter, Figure 1). Postdiagnosis, the swellings did not grow in the two puppies that were not treated with thyroidectomy, and all three puppies were doing well at the time this report was written (when the puppies were 2 yr of age). Thus, thyroidectomy was retrospectively not necessary, and fine-needle aspiration and/or incisional biopsy could have been considered prior to surgical excision.

Either lack of or excess dietary iodine and exposure to certain drugs, foods, and nutritional supplements have also been associated with goiter development and hypothyroidism in humans and dogs.^{10–12} During pregnancy, the bitch of the litter was reportedly fed a commercial diet without supplementation, which likely excluded a dietary cause. However,

there have been reports of excessive iodine in commercially prepared dog foods, leading to hypothyroidism.¹² The bitch was treated with enrofloxacin^b during the first part of her pregnancy, which could have caused the developmental abnormalities. The safety of enrofloxacin in pregnant dogs has been evaluated in a small number of dogs, specifically poodles infected with *Brucella canis*. At standard doses, treatment-related effects on the offspring were not noted, but specific testing for abnormal thyroid function was not performed.¹⁵ Enrofloxacin has been reported to cross the placenta in rabbits, but has not been specifically studied in dogs.¹⁶ Similarly, deficiencies in vitamins or nutrients, such as iodine, cannot be ruled out as contributing factors affecting thyroid development in this litter. One would have expected all puppies to be affected by a drug given to the bitch; however, certain teratogens, such as thalidomide, do not affect all animals in a litter equally.¹⁷

All three puppies had palpable, bilateral goiters, but none of those dogs had other physical signs of hypothyroidism. They were of normal size, had normal skeletal development, and were behaviorally appropriate (active and playful) as expected for their age. According to the breeder's communications with all owners of the dogs of this litter, the three affected puppies were similar in size and stature as their unaffected littermates.

Although CGH has been reported in several breeds of dogs, the puppies of this litter were incidentally found to have neck masses rather than showing any other clinical signs of hypothyroidism, which is different from previously reported dogs. It is not likely that the same type of organification defect (i.e., thyroid peroxidase deficiency) exists in this family because the dogs would have been expected to show clinical signs of hypothyroidism.^{1,2} The mechanism for why goiters developed, but other clinical signs did not, remains unclear based on the evaluation of those three puppies. Specific testing for defects in thyroid organification, such as a perchlorate discharge test or thyroid peroxidase enzyme assay, was not performed in the puppies due to high costs, unavailability, and/or radioactivity concerns.

It is possible that the defect affecting thyroid hormone synthesis in those puppies was partial and allowed some effective thyroid hormone to provide its normal functions on the body. It is also conceivable that the puppies were born with normal thyroid function, but that some defect led to progressive loss of function, which might explain the serum hormone concentrations below the reference ranges with a lack of clinical signs. Although all puppies had serum thyroid hormone concentrations that were below the reference ranges, only one puppy had a serum TSH concentration that was above the reference range, which normalized following thyroid hormone supplementation. In case 3, resolution of the mild hyperthyrotropinemia (Table 1) indicates normal pituitary feedback and therefore excludes thyroid hormone resistance as the cause of thyromegaly.¹⁸

These puppies, at least in part, fit the criteria for the human syndrome of euthyroid goiter, which is characterized by various degrees of thyroid gland enlargement without clinical and laboratory evidence of thyroid dysfunction and inflammatory processes. Euthyroid goiters are suspected to develop due to a complex interaction between underlying genetic determinants and environmental factors. A strong influence of genetic susceptibility has been suggested by early development of euthyroid goiter in clusters of individuals within families.⁹ Genetic abnormalities in genes important for thyroid function and physiology would be plausible in this family of puppies. Variations in genetic alterations might explain that the dogs of this report had laboratory data consistent with hypothyroidism, but did not exhibit clinical signs aside from goiter.

To the authors' knowledge, vascular anomalies have not been associated with either goiter or normal thyroid glands in dogs. In humans, vascular complications in the cervical region,

especially involving the thyroid gland and its accompanying vessels, are also extremely rare.¹⁹ In one report of a person with an aneurysm of the vasculature near or within the thyroid gland, the abnormal vasculature was neither associated with hypothyroidism nor goiter.¹⁹ All puppies described herein had grossly abnormal vasculature around their thyroid glands that was either noted during surgery or via CT and angiography scans. In the one dog that underwent advanced imaging studies (case 3), true AV communications could not be documented, but may have remained undetected by the imaging techniques performed. Venous outflow from the thyroid gland in case 3 appeared to be increased at the level of the jugular veins, but it was not possible to specifically visualize the thyroid vein and capillary blood flow. Thus, the vascular anomalies with goiter are unique for any species.

TSH is considered a thyroid-specific growth factor and could be considered to play a role in increasing thyroid gland growth and angiogenesis; however, only one of the two tested puppies had a slightly high serum TSH value.²⁰ Vascular endothelial growth factor (VEGF) is a specific mitogen for endothelial cells and has been identified as a mediator of angiogenesis in the thyroid gland.^{20–22} It has been reported that human thyroid follicles increase VEGF mRNA in response to TSH, and VEGF has been detected in enlarged thyroid glands of benign and malignant etiology.²⁰ Finally, TSH was found to be a stimulator of VEGF.²⁰ It is therefore possible that elevated TSH concentration secondary to a lack of negative feedback from T₃ and T₄ is the cause of not only goiter formation but also abnormal blood vessel growth via cytokines, such as VEGF, leading to the appearance of enlarged and/or dilated thyroid arteries and veins. However, this does not explain why adult dogs with acquired hypothyroidism do not reportedly have anomalous vasculature associated with their thyroid glands considering that 76% of dogs with acquired hypothyroidism reportedly have serum TSH concentrations that are above reference ranges.²³ Thus, other mediators may also be involved.²²

The question arises as to whether goiter led to abnormal development of the associated thyroid vasculature, a vascular anomaly led to abnormal development of the thyroid gland, or the goiter and vascular anomalies are unrelated phenomena in these dogs. Dilation of the jugular veins without AV communication makes it less likely that a blockade of venous outflow led to a decreased amount of T₃ and T₄ in the circulation and thus increased serum TSH concentrations, leading to goiter formation. Moreover, one puppy had a second vascular anomaly in the form of a PDA. Because PDAs are one of the most common congenital cardiovascular anomalies in dogs, the PDA may be an unrelated congenital anomaly in this dog.²⁴ However, it could also be considered additional evidence for a primary problem in vascular development.

Although one puppy in this report had complete surgical excision of its ventral neck masses and ligation of the anomalous vessels, this did not appear to be necessary as the lesions were identified as nonmalignant and nonprogressive. To diagnose either hypothyroidism or goiter, complete serum thyroid panels, imaging studies, and either fine-needle aspiration or incisional biopsy are initially recommended. Finally, as this could likely be a genetic disorder, it is recommended to not breed the parents or any of the affected or unaffected littermates.

Conclusion

This report presents three cases of goiter and severe vascular anomalies in a litter of Polish Lowland sheepdogs without signs of hypothyroidism. These anomalies may have either a hereditary or acquired basis. Whether there is a primary defect in the vascular development process, a primary inborn error in thyroid metabolism, two separate developmental defects, or any effect of enrofloxacin during pregnancy remains unknown.

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Glossary

AV	arteriovenous
CGH	congenital goitrous hypothyroidism
CH	congenital hypothyroidism
PDA	patent ductus arteriosus
T₃	total triiodothyronine
T₄	total thyroxine
TSH	thyroid stimulating hormone
VEGF	vascular endothelial growth factor

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FIGURE 1. Hyperplasia of thyroid follicular cells resulting in formation of irregular cysts, follicles, packets, and rows separated by thin fibrovascular trabeculae, consistent with hyperplastic goiter. Hematoxylin and eosin staining, original magnification $\times 40$

FIGURE 2.

Ventral view of a computed tomographic angiography during the arterial phase showing volume rendering in the area of the thyroid. Cranial is to the top, and left is to the right. Note the enlarged thyroid glands and enlarged cranial and caudal thyroid arteries feeding the thyroid glands.

Serum Thyroid Hormone and Thyroid Stimulating Hormone Concentrations for Cases 1–3

TABLE 1

Case	Age (months)	Timing relative to treatment	Total T ₄	Free T ₄ [*]	Free T ₃	TSH
1	5.5	Four days postoperatively	<2.6	<2	ND	ND
	6.5	During thyroxine supplementation	23	22	ND	ND
2	5.5	Prior to treatment	9	1	5.4	21
	6.5	During thyroxine supplementation	25	15	ND	UD
3	5.5	Prior to treatment	3	3	2.4	40
	9	During thyroxine supplementation	30	13	3.8	12
Reference ranges	Adult		15–67 nmol/L	8–40 pmol/L	4.5–12 pmol/L	0–37 mU/L

* Measured by equilibrium dialysis

Note: Percentages of T₃, T₄, and serum thyroglobulin autoantibodies were all within the reference ranges for adult dogs. ND, not done; T₃, total triiodothyronine; T₄, total thyroxine; TSH, thyroid stimulating hormone; UD, undetectable.