This is a translated version of the Japanese article, CAP March 2016, pp. 95-98.
CAP is a veterinary magazine published by Midori Shobo Co.,Ltd.

Let's think again
The diagnosis of hypothyroidism
- Utilization of in-house rapid diagnostic assays -

Naohito Nishii, DVM, PhD
Laboratory of Veterinary Internal Medicine, Faculty of Applied Biological Sciences, Gifu University

Introduction

Hypothyroidism is an endocrine disorder which is often diagnosed in dogs. Since this disease is accompanied by especially non-specific clinical symptoms, it may be overlooked or, conversely, over-diagnosed. Hypothyroidism can be easily treated with the administration of thyroid hormone preparations, while, if the disease is mistakenly diagnosed, unnecessary drug treatment may be continued for the entire life of dogs.

Recently, a wide variety of diagnostic tools for canine hypothyroidism has been developed, which has allowed us to easily assess hormone concentrations in blood. In particular, in-house assay instruments can swiftly produce measurement results and provide great convenience and benefits to veterinarians, pets and owners. However, while such tools are convenient, we should remember the fact that they may entail the risk of increasing misdiagnosis due to wrong usage. In the present article, we would describe methods for diagnosing hypothyroidism using T4/TSH in-house rapid diagnostic assays.

Pathologies of canine hypothyroidism

In most cases, canine hypothyroidism is primary hypothyroidism, which is a disorder of thyroid gland itself. Secondary hypothyroidism, which is associated with the disorder of, for example, the pituitary gland and the resultant decrease in TSH secretion, is infrequently observed. About half of the cases of primary hypothyroidism are those of lymphocytic thyroiditis which is associated with infiltration of inflammatory cells (mainly, lymphocytes) and the other half or so are cases of idiopathic thyroid gland atrophy which is not accompanied by inflammatory cell infiltration. In addition, there may be infrequent cases of destruction of the thyroid gland tissue due to tumors or traumas. In dogs with lymphocytic thyroiditis, autoantibodies such as thyroglobulin auto-antibody (TgAA) and anti-T4antibody are detected, so the possibility that it is an autoimmune disease has been indicated. On the other hand, the cases of idiopathic thyroid gland atrophy have not been elucidated.

Table 1 Staging of hypothyroidism (hypothesis proposed by Graham et al.)

Stage		Clinical signs/ symptoms	T4,FT4	TSH	TgAA
I	Subclinical thyroiditis	–	Normal	Normal	+
II	Subclinical hypothyroidism	–	Normal	Increased	+
III	Hypothyroidism (Lymphocytic thyroiditis)	+	Decreased	Increased	+
IV	Non-inflammatory atrophic hypothyroidism	+	Decreased	Increased	–

This table is cited and edited from the literature No.1

Graham et al.[1] have proposed the hypothesis that lymphocytic thyroiditis and idiopathic thyroid gland atrophy correspond to a pathologic sequence and that lymphocytic thyroiditis may eventually progress to a state called idiopathic thyroid gland atrophy. Based on this hypothesis, four stages of canine hypothyroidism have been established (Table 1). Stage I represents hypothyroidism which is associated with TgAA positivity but with normal thyroid functions. Stage II represents TgAA-positive hypothyroidism associated with destruction of the thyroid gland, which is compensated by excessive TSH secretion. Stage III represents TgAA-positive hypothyroidism associated with clinical symptoms due to decreased functions of the thyroid gland, which corresponds to the so-called "lymphocytic thyroiditis". Finally, Stage IV represents TgAA-negative hypothyroidism, corresponding to idiopathic thyroid gland atrophy.

In fact, when investigating the disposition of age at the onset of Stage I-II, Stage III (hypothyroidism due to lymphocytic thyroiditis) and Stage IV (hypothyroidism due to idiopathic thyroid gland atrophy), respectively, it has been found that age corresponding to the peaks of incidences of Stage I-II, Stage III and Stage IV are about 2 years, 4 years and 7 years, respectively, which indicates that pathologic stage may advance with increasing age at the onset. While this finding is merely a circumstantial evidence, it may indicate the possibility that canine hypothyroidism may progress from Stage I to, eventually, Stage IV.

When we should suspect hypothyroidism?

As stated above, clinical symptoms of canine hypothyroidism are very non-specific, so the diagnosis of the disease is sometimes difficult. In this section, we would discuss with what clinical symptoms, we should suspect hypothyroidism. However, please take note of the fact that, in this section, we want not only describe clinical symptoms indicative of the presence of hypothyroidism but also emphasize that care should be exercised in diagnosing hypothyroidism in the absence of such clinical symptoms. If a dog does not present any clinical symptoms which should be frequently observed in hypothyroidism, we should carefully examine again whether the dog is really suffering from hypothyroidism.

• Point 1　Dermatologic symptoms

In most dogs with hypothyroidism, some dermatologic symptoms are observed (Table 2). Such dermatologic symptoms may be manifested as marked endocrine alopecia (such as symmetrical alopecia and pigmentation) as well as mild seborrhea.

• Point 2　Hyperlipidemia

In about 75% of dogs with hypothyroidism, hyperlipidemia (hypercholesterolemia and hypertriglyceridemia) is observed.

• Point 3　Decreased physical activity and obesity

In about half of dogs with hypothyroidism, decreased physical activity and obesity are seen. However, these clinical symptoms are fairly non-specific, and we should take note the fact that the incidences of decreased physical activity caused by other diseases and simple obesity are much higher.

Other abnormalities seen in hypothyroidism

Hypothyroidism may cause facial nerve palsy, vestibular disorder, and other peripheral nerve disorders (Table 2). In addition, the possibility that hypothyroidism may be associated with other secondary symptoms such as megaesophagus, laryngeal paralysis, and myasthenia gravis has been suggested, although no causal relationship between hypothyroidism and such symptoms has been definitively elucidated.[3-5] In dogs with these abnormal symptoms, possibility of the presence of hypothyroidism should be assessed, but diagnosis should be given with great caution.

Circumstances requiring thyroid hormone measurement

Concentration of thyroid hormones in blood can be easily measured. In particular, we can get values of thyroid hormone concentration only by setting samples on an assay device and pushing the start button or by sending samples to an external laboratory. Through such simple procedures, we can get the values of hormone concentration. However, the most important responsibility of veterinarians is the proper interpretation of measurements obtained in such testing. Since thyroid hormone concentration in blood is susceptible to various pathologic states, measurement without any clear diagnostic strategy will lead to misdiagnosis. We do not recommend measuring thyroid hormone concentrations in blood (whether measurement is done for T4/ FT4 or other hormones) as a part of health check-up for dogs. The reasons for this strategy include the fact that the incidence of hypothyroidism in dogs is not so high, and most dogs which are subjected to health check-up will have normal thyroid gland function, leading to low diagnostic efficiency, as well as the fact that abnormal values for thyroid hormone concentration in blood may be obtained due to the effects of other diseases (euthyroid sick syndrome). Therefore, we recommend that measurement of thyroid hormone concentration in blood should be performed only in dogs presenting with some clinical symptoms indicative of hypothyroidism.

Table 2　Clinical symptoms of canine hypothyroidism

Clinical signs/symptoms		Incidence
Dermatological symptoms	endocrine alopecia, seborrhea	88%
Obesity		49%
Decreased physical activity		48%
Weakness		12%
Neurological symptom	facial nerve palsy, vestibular disorder, and other peripheral nerve disorders	9%
Reproductive disorder		<2%
Cardiovascular symptom	Bradycardia	10%

Cited with modification from Literature No. 2.

Exclusion of euthyroid sick syndrome

The diagnosis of hypothyroidism is complicated by the fact that abnormal thyroid hormone concentration in blood may be caused by other diseases or medication. Such pathologic status is called euthyroid sick syndrome, in which low thyroid hormone concentrations are obtained but no abnormality of the thyroid gland is present. In particular, debilitating disease or inflammatory disease accompanied with loss of appetite tends to affect thyroid gland hormone concentrations in blood. Hyperadrenocorticism is a frequent cause of euthyroid sick syndrome, and its clinical symptoms are sometimes confused with those of hypothyroidism, requiring great attention. In dogs presenting with certain symptoms such as polydipsia/polyuria and elevated alkaline phosphatase in blood, the possibility of hyperadrenocorticism should be carefully examined. In addition, simple hypothyroidism is associated with values of leukocyte count and CRP in blood within the reference range, so, if values of these parameters are high, possibility of extensive, latent inflammatory disease should be considered. Of course, the possibility that a dog may concurrently develop non-thyroid disease as mentioned above and hypothyroidism cannot be eliminated, but the probability of the presence of euthyroid sick syndrome is much more higher. In addition, administration of certain drugs such as prednisolone tends to decrease thyroid hormone levels in blood. If a dog is given such a drug, thyroid hormone levels in blood (whether measurement is done for T4/ FT4 or other hormones) should be assessed with special caution and, if possible, measurement should be performed after the discontinuation of such medication.

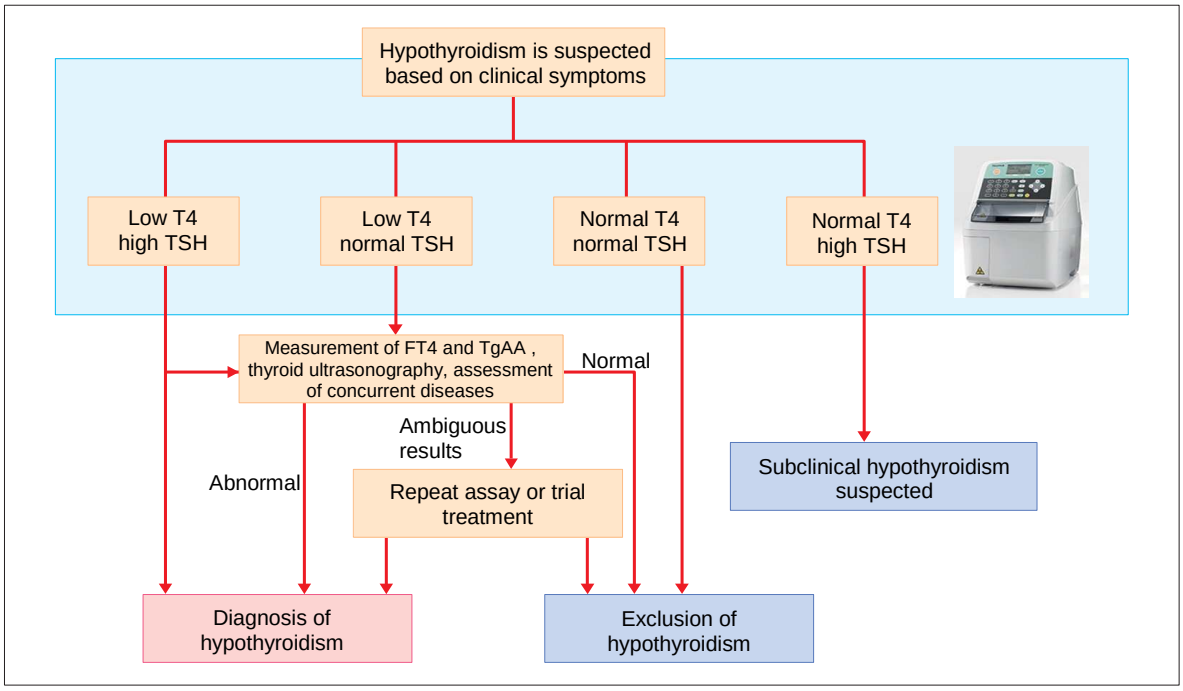

Figure 1 Diagnosis of hypothyroidism using an in-house rapid diagnostic assay system

First, T4 and TSH concentrations should be measured in a clinic to assess the possibility of hypothyroidism. Then, based on the results of measurement, the next diagnostic/therapeutic strategy should be determined and implemented.

If you cannot definitively judge whether the thyroid function is normal or not by any means, you can choose from two options. The first option is a repeat testing at a later date and the second option is assessment of response to treatment given on a trial basis. If the second option is chosen, treatment should be continued for at least 2-3 months and, if symptoms have not been improved, the treatment should be discontinued. If possible, even when symptom improvement has been observed, treatment should be stopped once to check for the recurrence of the same symptoms, which may lead to more reliable diagnosis. When you intend to initiate any treatment on a trial basis, it is important for you to notify this strategy to the owner and avoid chronic administration for an unknown period of time.

Significance of in-house rapid diagnostic assay

As a instrument for in-house rapid diagnostic assay of thyroid functions in animals, FUJI DRI-CHEM IMMUNO AU10V (Fuji Film Corporation) is available. This device is a convenient tool in that it can measure concentration of T4 or TSH in blood in about 10 minutes. For the assessment of thyroid functions, measurement of only T4 concentration in blood is insufficient because its concentration may be greatly affected also by euthydroid sick syndrome. Therefore, TSH concentration in blood should be concurrently measured when you intend to make a diagnosis (Figure 1). A low T4 concentration and high TSH concentration strongly indicate the presence of hypothyroidism. However, the possibility that a dog with a non-thyroid disease may have similar assay results cannot be excluded. Therefore, we recommend initiation of treatment with thyroid hormone preparations followed by careful judgement about responses to such treatment, or concurrent use of other tools such as FT4/TgAA measurement and thyroid ultrasonography to make more reliable diagnosis. We believe that, at a minimum, FT4, which is associated with higher diagnostic specificity than T4,[6] should be measured. If a dog has a low T4 concentration and a normal TSH concentration , careful examination should be performed in consideration of the possibility of euthyroid sick syndrome. On the other hand, if both T4 and TSH concentrations are normal, the possibility of hypothyroidism can be excluded. In this case, clinical symptoms observed are caused by other disease than hypothyroidism, so assays for the diagnosis of such a disease should be considered. If a dog has a normal T4 concentration and a high TSH concentration, the dog may be given the diagnosis of subclinical hypothyroidism in accordance with the classification established by Graham et al. However, in 12% of dogs with non-thyroid disease, high TSH concentration values are obtained.[2] Therefore, dogs in which only TSH concentration is increased may be more likely to have non-thyroid disease.

However, even if we can easily measure hormone concentrations, implementation of excessive assays may entail the risk of misdiagnosis. To begin with, in most cases, the urgency of diagnosing hypothyroidism is not high. In other words, you do not necessarily need to make a diagnosis of hypothyroidism and swiftly start treatment at the initial visit. This does not mean that the significance of instruments for in-house rapid assay is small. In fact, such instruments may play two significant roles. The first role is the diagnostic exclusion of hypothyroidism. Dogs may develop various diseases which are manifested as clinical symptoms common to those of hypothyroidism, including diseases which should be diagnosed and treated without delay. If you can assess thyroid functions using in-house assay instruments and swiftly judge that “the thyroid functions are normal”, you will be able to proceed to the next diagnostic plan without delay, representing a great advantage. The second role of instruments for in-house rapid disgnostic assay is the monitoring of hypothyroidism during treatment (Figure 2). In particular, in cases where little improvement in clinical symptoms has been seen despite drug treatment, you can swiftly get assay results for T4 and TSH concentrations in blood using in-house rapid diagnostic assay instruments to judge whether the dose of drugs is sufficient and, if

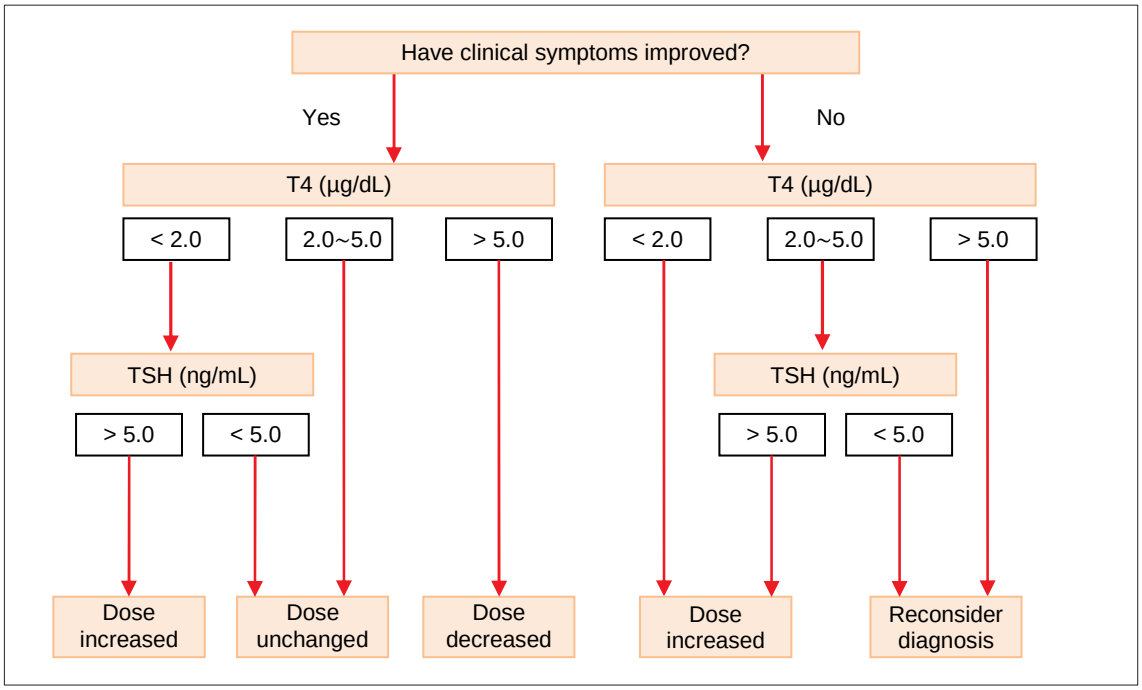

Figure 2 Monitoring and dose adjustment in treatment for hypothyroidism

Measurement of T4 and TSH concentrations in blood should be performed 4-6 hours after the administration of a T4 preparation. Possible time points when measurement should be conducted include the following: (1) 6-8 weeks after the initiation of treatment; (2) when no improvement in clinical symptoms is seen; and (3) when a symptom indicative of hyperthyroidism is observed.

necessary,
you can adjust the drug dose without delay and can ultimately reduce the burden on owners due to clinic visits.

Conclusion

While an increasingly wide variety of instruments/techniques for diagnosing canine hypothyroidism has been developed year by year, other efficient use of such instruments/techniques is dependent on the ability of veterinarian. We should comprehensively review and properly assess assay results to make reliable diagnosis.

References

1) Graham PA, Refsal KR, Nachreiner RF. Etiopathologic findings of canine hypothyroidism. *Vet Clin North Am Small Anim Pract*. 37, 617-631, 2007.
2) Feldman EC, Nelson RW, Reusch CE, Scott-Moncrieff JC and Behrend EN. Canine and feline endocrinology 4th ed. Elsevier, St. Louis, 2015.
3) Fracassi F, Tamborini A. Reversible megaoesophagus associated with primary hypothyroidism in a dog. *Vet Rec*. 168, 329b, 2011.
4) Bruchim Y, Kushnir A, Shamir MH. L-thyroxine responsive cricopharyngeal achalasia associated with hypothyroidism in a dog. *J Small Anim Pract*. 46, 553-554, 2005.
5) Panciera DL. Conditions associated with canine hypothyroidism. *Vet Clin North Am Small Anim Pract*. 31, 935-950, 2001.
6) Peterson ME, Melián C, Nichols R. Measurement of serum total thyroxine, triiodothyronine, free thyroxine, and thyrotropin concentrations for diagnosis of hypothyroidism in dogs. *J Am Vet Med Assoc.* 211, 1396-1402, 1997.

[Author's Profile]

Naohito Nishii
Associate Professor, Gifu University

Specialty:
- Internal medicine, Endocrinology

Brief record :
- Associate Professor, Laboratory of Veterinary Internal Medicine, Faculty of Applied Biological Sciences, Gifu University (2012 to present)
- Junior Associate Professor, Laboratory of Veterinary Pharmacotherapeutics, Faculty of Agriculture, Tottori University (2008-2012)
- PhD in Veterinary Sciences, United Graduate School of Veterinary Science, Gifu University (2008)
- Resident veterinarian, Private Veterinary Clinic (2001-2004)
- Bachelor of Veterinary Science, Division of Veterinary Medicine, Faculty of Agriculture, Gifu University (2001)

Affiliation societies:
- The Japanese Society of Veterinary Science
- Japan Veterinary Medical Association
- Japanese Society of Clinical Veterinary Medicine

Translation by FUJIFILM Corporation, May 2016.
(http://www.fujifilm.com/products/medical/)