Neurologic Manifestations of Hypothyroidism in Dogs

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Abstract: Hypothyroidism is a common endocrine disease in dogs. A variety of clinicopathologic abnormalities may be present; however, neurologic deficits are rare. In some instances, neurologic deficits may be the sole manifestation of hypothyroidism. Consequently, the diagnosis and management of the neurologic disorders associated with hypothyroidism can be challenging. This article describes several neurologic manifestations of primary hypothyroidism in dogs; discusses the pathophysiology of hypothyroidism-induced neurologic disorders affecting the peripheral and central nervous systems; and reviews the evidence for the neurologic effects of hypothyroidism.

The reported prevalence of hypothyroidism in middle-aged to older dogs is 0.2% to 0.8%. The clinical syndrome results from a deficiency of the active thyroid hormones triiodothyronine ($T_3$) and thyroxine ($T_4$), which are synthesized in the thyroid gland from the protein thyroglobulin. All circulating $T_4$ is derived from the thyroid gland, but 80% of $T_3$ is produced by nonthyroidal tissues after deiodination of $T_4$. The thyroid gland synthesizes thyroid hormone after being stimulated by thyroid-stimulating hormone (TSH), which is released from the adenohypophysis (pituitary gland) in response to thyrotropin-releasing hormone (TRH) released by the hypothalamus. Hypothyroidism may be due to dysfunction of the hypothalamus, pituitary gland, or thyroid gland. The most common presentation occurs in adult dogs with disease affecting the thyroid gland (primary hypothyroidism), with 50% of these dogs having evidence of lymphocytic thyroiditis and 50% having idiopathic atrophy of the thyroid gland. Lymphocytic thyroiditis is an autoimmune disease in which (1) lymphocytic-plasmacytic infiltrates exist within the glandular tissue and (2) circulating autoantibodies directed against thyroglobulin, $T_4$, or $T_3$ are present. Certain breeds, such as pointers, English setters, boxers, and beagles, are predisposed to having antithyroid hormone antibodies. However, the presence of autoantibodies does not confirm the presence of clinical hypothyroidism.

With idiopathic atrophy of the thyroid gland, the parenchyma is replaced with adipose tissue. Clinical signs are a result of decreased synthesis and secretion of $T_3$ and $T_4$.

Nonneurologic Clinical Signs and Diagnosis of Hypothyroidism

A variety of clinicopathologic abnormalities are present in affected dogs. Typical physical manifestations include dermatologic changes such as nonpruritic, symmetrical truncal and distal tail alopecia and superficial pyoderma. Other physical examination findings include bradycardia, lethargy, weight gain, and hypothermia. Anestrus, testicular atrophy, loss of libido, and gynecomastia have also been reported.

A complete blood count may reveal a nonregenerative anemia that is the result of reduced erythropoietin production consequent to reduced $T_4$ levels. Hypercholesterolemia is often present and is primarily due to the role of thyroid hormone in stimulating lipid synthesis, mobilization, and degradation via its actions on hepatic and lipoprotein lipase as well as on hepatic low-density lipoprotein (LDL) receptors. In 20% to 30% of hyperthyroid dogs, the serum creatine kinase level is elevated due to hypothyroid myopathy or changes in muscle metabolism; creatine kinase activity has been shown to be inversely proportional to thyroid hormone activity in humans.

Therapy for hypothyroidism is straightforward and involves thyroid hormone supplementation. However, in some instances, the diagnosis can be challenging, as a number of non–thyroid-related diseases affect thyroid hormone metabolism. As a result, serum concentrations of $T_4$ may be low despite normal thyroid function. This is referred to as euthyroid sick syndrome. Similarly,
drugs may alter thyroid hormone metabolism, which can result in an inaccurate diagnosis of hypothyroidism (TABLE 1). Among commonly used medications, phenobarbital and corticosteroids may alter thyroid hormone levels. Likewise, trimethoprim-sulfonamides can result in true hypothyroidism. A definitive diagnosis of hypothyroidism is established by demonstrating a serum fT4 concentration below 90% of the reference range, in addition to clinical suspicion of disease. Endogenous TSH levels can help strengthen the diagnosis and are 80% diagnostic for hypothyroidism; however, measurement of endogenous TSH concentration is more specific in the presence of a low fT4 level than if interpreted alone. Ultimately, the decision to treat dogs suspected of being hypothyroid depends on the clinical signs, combined with the results of thyroid function testing. A complete thyroid panel, including measurement of total thyroxine (TT4), fT4 and TSH, is recommended. Affected dogs are treated with synthetic T4 at a dosage of 0.02 mg/kg twice daily. Six to 8 weeks should be allowed to observe an improvement in clinical signs, and lethargy and dullness may improve sooner than dermatologic and reproductive abnormalities. Neurologic signs may show improvement rapidly. However, cases of myopathy may take weeks to months to improve.

### Pathogenesis of Hypothyroid-Induced Neurologic Signs

Neurologic signs occur in 7.5% of hypothyroid dogs. Neurologic deficits may implicate the involvement of the peripheral nervous system and the central nervous system (CNS). A causal relationship between hypothyroidism and neurologic dysfunction has not been definitively established; however, the literature strongly suggests that hypothyroidism plays a role in the development of neurologic deficits. Although not fully understood, the pathophysiologic mechanisms underlying the development of neurologic signs may involve, among other processes, alterations in axonal transport and ischemia.

### Abnormal Axonal Transport

Thyroid hormone induces activity of adenosinetriphosphatase (ATPase), which is used by the sodium/potassium pumps necessary for axonal transport of ATP and molecular proteins. Consequently, in hypothyroidism, ATPase activity is decreased, resulting in a decreased activity of these pumps. Additionally, thyroid hormone influences the expression of dynein and tubulin proteins, which are involved with microtubule functions necessary for axonal transport. Altered microtubule formation and function can lead not only to slowed axonal transport, but also to degradation of the axon and impaired regeneration.

### Ischemia

Ischemic events are some of the most frequently cited causes of CNS signs in hypothyroid dogs, but they have also been postulated to play a role in clinical signs related to the peripheral nervous system. In hypothyroid animals, ischemia and secondary infarction of tissue may be the result of atherosclerosis. Hyperlipidemia, which is the accumulation of plasma lipid and cholesterol, occurs commonly in dogs with hypothyroidism and is secondary to a reduction in the uptake of triglycerides due to T4 deficiency. Atherosclerosis is characterized by thickening of the tunica media/interna of arterial walls, associated with lipid deposition. Smooth muscle and lipid-filled macrophages known as foam cells proliferate in the tunica media/interna, and a fibrous plaque forms around a core of lipid (atheroma). In humans, plasma LDL concentrations have been positively correlated with the risk of developing atherosclerosis. Several reasons may explain this correlation. LDLs easily penetrate the subintimal space of vessels, have greater susceptibility to oxidation than other plasma lipoproteins, bind intimal proteoglycans, are toxic to endothelial cells, and stimulate the production and secretion of plasminogen activator inhibitor 1 and thromboxane by endothelial cells. LDLs also bind to scavenger receptors, thereby contributing to the formation of foam cells.

### Table 1. Commonly Used Medications in Veterinary Neurology and Their Effect on Thyroid Axis Testing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Mechanism</th>
<th>Effect on Thyroid Testing</th>
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<tbody>
<tr>
<td>Phenobarbital</td>
<td>Anticonvulsant</td>
<td>Increases hepatic metabolism, decreases T4 5’ deiodinase activity</td>
<td>Decreased TT4, Decreased fT4, Increased TSH</td>
</tr>
<tr>
<td>Potassium bromide</td>
<td>Anticonvulsant</td>
<td>Suspected to interfere with iodide transport</td>
<td>None</td>
</tr>
<tr>
<td>Carprofen</td>
<td>Antiinflammatory</td>
<td>Displaces thyroid hormone from serum-binding proteins, decreases hepatic uptake</td>
<td>Decreased TT4, Decreased fT4, Decreased TSH</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Antiinflammatory</td>
<td>Decreases TSH secretion, T4 5’ deiodinase activity, and T4-binding globulin levels</td>
<td>Decreased TT4, Decreased fT4, Increased TSH</td>
</tr>
<tr>
<td>Opioids</td>
<td>Analgesia</td>
<td>Unknown</td>
<td>Decreased TT4, Decreased fT4, Decreased TSH</td>
</tr>
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</table>

fT4 = free thyroxine, TSH = thyroid-stimulating hormone, T4 = thyroxine, TT4 = total thyroxine.
Although dogs with naturally occurring hypothyroidism are relatively resistant to the development of atherosclerosis, dogs made hypothyroid through thyroid ablation or thyroidectomy that are fed a diet high in cholesterol may develop atherosclerosis. Hypothyroidism is the most common cause of atherosclerosis in dogs, but plaques may also form in dogs with hypertension, diabetes mellitus, and hyperlipidemia. Cerebrovascular accidents may also be caused by intravascular neoplasia or underlying diseases that cause hypercoagulability, such as hyperadrenocorticism, pheochromocytoma, diabetes mellitus, cardiac disease, and protein-losing enteropathy/nephropathy.

Dogs that have hyperlipidemia and develop atherosclerosis have increased lipoprotein levels, primarily in the β and α2 fractions consistent with LDLs, which may suggest an underlying pathogenesis for ischemia and infarction similar to that in humans. Additionally, an increase in triglyceride and cholesterol concentrations increases blood viscosity and the risk of thromboembolic events. Multifocal thromboemboli and lipid emboli involving the brain and muscle tissue have been observed antemortem and at necropsy in hypothyroid dogs.

Miscellaneous Causes
Secondary immune-mediated demyelination of nerves, primary inherited Schwann cell demyelination, and deposits of glycoprotein around nerves have been reported in humans and dogs, and nerve compression by myxedematous deposits has been described in humans and dogs. Lipid granulomas have been reported in cats with hyperchylomicronemia. Affected cats have elevated cholesterol and LDL levels, which is a condition also seen in hypothyroid dogs. The pathogenesis for these findings remains undefined.

Peripheral Nervous System Disorders
The most commonly encountered neurologic disorders related to hypothyroidism include neuropathic and myopathic disease. In both, neurologic examination abnormalities may include abnormal postural reactions, decreased patellar and withdrawal reflexes, and decreased muscle tone and atrophy.

Generalized Polynuropathy
Hypothyroidism is associated with polynuropathy. Large and giant-breed dogs are usually affected and can present with pelvic limb paresis progressing to tetraparesis over the course of 1 to 2 months. Neurologic deficits include postural reaction deficits, hyporeflexia, hypotonia, and muscle atrophy. The diagnosis of hypothyroid-induced polynuropathy begins with documenting hypothyroidism in a dog with signs of neuromuscular dysfunction. More definitive diagnosis includes electrophysiological testing. Electromyography (EMG) may reveal fibrillation potentials, positive sharp waves, increased insertional activity, and complex repetitive discharges from the proximal appendicular muscles. Since these findings can be present with disorders of nerve or muscle, more suggestive evidence of polynuropathy is found with direct evoked motor potentials, in which motor nerve conduction velocities are decreased and, in some cases, conduction blocks exist. It is important to note that affected dogs may have concurrent myopathy. Histopathologic demonstration of wallerian degeneration with intercalated internodes and myelin irregularities in nerve tissue provides definitive evidence of a polynuropathy.

Ultrasoundography of the vasculature supplying the affected limbs may detect thrombi. In one study, emboli were identified in the internal iliac and the femoral arteries of hypothyroid dogs.

Response to thyroid supplementation is often rapid in dogs with a polynuropathy. Affected dogs may show improvement in 24 hours, with complete resolution occurring within 1 to 2 months.

Myasthenia Gravis
In humans, a link between hypothyroidism and myasthenia gravis (MG) has been reported. Approximately 10% to 20% of people with MG also have thyroid disorders. Hypothyroidism also has been observed in dogs with MG. It is hypothesized that the auto-antibodies directed at the acetylcholine (ACh) receptor cross-react with self-antigens present in the thyroid gland. Embryologically, the thyroid gland arises from the endoderm of the floor of the foregut and migrates caudally. Ectopic migration may result in the presence of myoepithelial cells expressing ACh receptors, the target for autoantibodies in MG, in thyroid tissue. Such a pathogenesis has been documented for disorders of the thymus. The occurrence of hypothyroidism before development of MG or vice versa has not been studied, and a causal relationship in dogs remains to be established.

Cranial Nerve Disorders
Isolated or multiple cranial neuropathies involving the vestibular branch of the vestibulocochlear nerve, the facial nerve, and the sensory branch of the trigeminal nerve may be observed in dogs with hypothyroidism. However, other cranial nerves can also be affected.

There are many reports of hypothyroid dogs with facial nerve dysfunction. Facial nerve paralysis is present in up to 70% of dogs with hypothyroidism and nerve dysfunction. Neurologic abnormalities may include decreased or absent palpebral reflexes, lip droop, ear droop, or decreased tear production. Unilateral or bilateral facial paresis/paralysis was reported in four dogs in which clinical signs improved over a 2-week period during which thyroid supplementation was administered. In another study, absent corneal and palpebral reflexes were observed in 88% of hypothyroid dogs examined over a 3-year period. Unilateral facial nerve paralysis in hypothyroid dogs has been reported. In addition to typical neurologic defects, bilateral stapedial reflex deficits were detected by impedance audiometry, and EMG revealed fibrillation potentials and positive sharp waves in the facial muscles in two dogs in one report. Both dogs experienced improvement in facial nerve paralysis after 2 weeks of thyroid hormone supplementation and were free of neurologic deficits by 4 weeks.

Myxedematous deposits surrounding the nerves as they pass through the internal acoustic meatus have been suggested as a likely
cause for facial neuropathies. Decreased vascular perfusion of the inner ear may also be a cause of facial neuropathies in hypothyroid dogs. The inner ear is supplied by the labyrinthine artery, which travels along the cochlear aqueduct. This artery is contained in a confined space that may be subject to perfusion injury secondary to hyperlipidemia and increased blood viscosity. In addition to facial nerve paralysis, deficits relating to the parasympathetic branch of the facial nerve may be present.

**Peripheral Vestibular Disease**

Peripheral vestibular dysfunction may occur secondary to hypothyroidism. Signs of peripheral vestibular dysfunction include head tilt, vestibular ataxia, and rotary or horizontal nystagmus. While not specific for hypothyroid-induced dysfunction, brainstem auditory evoked response testing reveals abnormal conduction in dogs with peripheral vestibular disease. In one dog with hypothyroidism and signs of peripheral vestibular disease with no other identified cause, bilateral stapedial reflexes were also dampened. Given the prevalence of otitis media/interna, all dogs with signs of peripheral vestibular dysfunction should undergo an otoscopic examination. Otoscopic examination, radiographs of the tympanic bullae, and computed tomography or magnetic resonance imaging (MRI) of the head should be performed to exclude otitis media/interna and other otic diseases from consideration.

**Glossopharyngeal/Vagal Neuropathies**

Cricopharyngeal achalasia in a hypothyroid dog has been described in which dysphagia and pytalism resolved after 6 days of treatment with synthetic thyroxine. A focal neuropathy involving the pharyngeal branches of the glossopharyngeal and vagus nerves was suspected.

**Laryngeal Paralysis**

Laryngeal dysfunction has been reported in dogs with hypothyroidism. In a study of 140 dogs with laryngeal paralysis, 30 dogs were diagnosed with hypothyroidism based on results of a measurement of T₄, fT₄, and TSH levels or a TSH stimulation test. However, treatment for laryngeal paralysis usually entails surgical intervention, and response to thyroid hormone supplementation alone has not been widely reported. In one study of 66 hypothyroid dogs, two dogs had laryngeal paralysis that was not corrected by treatment with thyroid supplementation.

**Megaesophagus**

While megaesophagus has been thought to be a consequence of hypothyroidism, recent evidence has failed to demonstrate an association between acquired megaesophagus and hypothyroidism. In one study, three dogs with megaesophagus and hypothyroidism had levels of antibodies directed against the ACh receptor that were diagnostic for MG and experienced response to cholinergic therapy. These dogs also received thyroid hormone supplementation; however, although impossible to determine, clinical improvement likely reflected a response to treatment for MG rather than thyroid supplementation. As further evidence for a lack of correlation between hypothyroidism and megaesophagus, abnormal esophageal function does not respond to thyroid hormone supplementation. Ultimately, care must be exercised when interpreting thyroid function testing in dogs with megaesophagus, as many dogs are likely to have euthyroid sick syndrome rather than hypothyroidism.

**Muscle Disorders**

Up to 40% of humans with hypothyroidism have clinical signs of skeletal muscle weakness at initial diagnosis. Similarly, dogs can present with muscle pain and stiffness as well as generalized weakness.

In one hypothyroid dog, pelvic limb paresis progressed to tetraparesis over the course of 6 weeks. The dog was unable to bear weight without assistance but had motor function. Postural reactions were normal when the dog's weight was supported. The dog was hyporeflexive and hypotonic in all four limbs. EMG revealed prolonged insertional activity, fibrillation potentials, positive sharp waves, and complex repetitive discharges, which are suggestive of a myopathy. Abnormalities were detected in the muscles of the limbs innervated by the femoral, sciatic, obturator, radial, median, and ulnar nerves. Motor nerve conduction velocity was decreased (50 m/sec in the femoral branch and 42 m/sec in the tibial branch of the sciatic nerve; normal range: 52 to 67 m/sec). A muscle biopsy revealed angular atrophy of type II muscle fibers, and some type I fibers had vacuoles containing para-aminosalicylic acid–stained material that was resistant to amylase digestion. Amylase removes glycogen within myotubules; therefore, this material was not glycogen. However, the presence of stain uptake indicated that it could be a product of glycogen metabolism. The presence of large amounts of glycogen between myofibrils has been shown in muscle biopsy samples from humans with hypothyroidism. The dog was treated with thyroid hormone supplementation and was able to walk a short distance within 1 week. By 3 months, it had a normal gait.

The pathogenesis of hypothyroid myopathy likely involves abnormal cellular metabolism. Through the process of beta oxidation, which takes place in the mitochondria, myocytes use fatty acids for energy. Carnitine is necessary to shuttle fatty acids from the cytosol into the mitochondria for beta oxidation. One possible explanation for the development of a myopathy secondary to hypothyroidism is a decreased skeletal muscle carnitine level. This may be due to decreased synthesis of de novo carnitine, leading to a shift of carnitine from skeletal muscle to the extracellular pool and subsequent increased urinary excretion. In an experimental model for hypothyroidism, affected dogs had a higher urinary excretion of carnitine and decreased levels of muscle carnitine after 6 months of uncontrolled disease compared with control dogs. Although none of the dogs developed neuromuscular signs during the 18-month time period, five out of nine dogs had abnormal EMG findings.

The same study compared histopathologic evidence of muscle pathology. At 6 months, nemaline rod inclusions and atrophy of
type II fibers were present. Although this indicates denervation injury, which may also be accompanied by type I fiber atrophy in some dogs, intramuscular nerve fibers were normal throughout the length of the study, indicating a myopathy.

Total myofiber mass between affected and control dogs was not statistically different; however, hypothyroid dogs displayed a decreased type II:type I myofiber area ratio at all of the time points in the study compared with control dogs. These changes mimicked those reported in dogs with naturally occurring hypothyroidism.6

Interference with normal carbohydrate metabolism, an increase in the proportion of slow myofibrillar proteins, abnormal oxidative phosphorylation, abnormal triglyceride turnover, and abnormal cation transfer across the sarcolemma are other proposed mechanisms of hypothyroid-induced peripheral nerve dysfunction.12 Additionally, immune-mediated depletion of myofibrillar proteins22 and deposition of glycogen between myofibers have been shown in humans.5

Owners of hypothyroid dogs often notice an increase in their dogs’ activity levels and exercise tolerance within 2 weeks of starting thyroid supplementation.8

Central Nervous System Disorders

Hypothyroidism has been associated with clinical signs of mental dullness, circling, seizures, and central vestibular signs as well as cognitive dysfunction.7 Mechanisms may include atherosclerosis, myxedema coma, or presence of a pituitary tumor. As a whole, the CNS is more resilient than other tissues to the metabolic effects of a decreased T3 level. Therefore, CNS dysfunction is a rare presentation in hypothyroid dogs and is most commonly related to ischemic pathology. However, the effects on the CNS can be profound, and clinicians should be aware of the possibility of involvement of metabolic disease as well as primary neurologic etiologies.

Central Vestibular Disease

In a recent retrospective report of 10 dogs with central vestibular signs and confirmed hypothyroidism, signs included abnormal nystagmus, postural reaction deficits, tetraparesis/hemiparesis, and paradoxical central vestibular dysfunction (typified by a head tilt contralateral to the observed postural reaction deficits). Dogs presented with variable disease progression; two had a history of paroxysms of vestibular dysfunction on a daily or weekly basis, and eight had an acute onset of signs.30 In another case, a hypothyroid dog presented for acute onset of central vestibular dysfunction.3 Tetra-weighed MRI revealed a focal hyperintense lesion in the area of the brainstem. Clinical signs improved in 24 hours without treatment. The history, spontaneous improvement, and MRI features were suggestive of a brainstem infarction. Territorial infarction of the cerebellum has also been reported in three dogs with central vestibular signs and hypothyroidism.10

Prosencephalic Signs

Rarely, dogs may display prosencephalic signs, characterized as propulsive circling, seizures, and changes in mentation (aggression and dementia).5,7 Although there is little definitive evidence to confirm that hypothyroidism causes seizures, atherosclerosis and hyperlipidemia are potential underlying mechanisms of prosencephalic signs. Dogs with epilepsy may have euthyroid sick syndrome as a result of nonthyroidal illness as well as from the effect of anticonvulsant medications on basal thyroid hormone levels, further confounding the association between hypothyroidism and seizures.

Stupor and coma, referred to as myxedema coma, may be a result of altered neurotransmitter release and reuptake or failure of thyroid hormone transport locally within the brain. Myxedema occurs in the skin of hypothyroid dogs. Myxedema results in the accumulation of acidic and neutral mucopolysaccharides and hyaluronic acids, which bind water and result in increased thickness of the skin and other tissues.7 Signs of myxedema coma include nonpitting edema of the face and jowls, bradycardia, and profuse obtundation to coma and may also be responsible for neuronal and tissue compression.7,33,36 When performed, electroencephalography reveals extremely low-voltage, low-amplitude brain activity, which is consistent with reduced cerebral metabolism.14,32

Infarction involving the prosencephalon may also be the result of hypothyroidism. In one study, three dogs with hypothyroidism presented with circling, disorientation, stupor, and blindness. Atherosclerotic plaques and obstructions in the cerebral arterial circle were observed at necropsy.18

Similar findings have been reported in a dog with hypothyroidism that presented with a 1-day history of seizures and disorientation and a 1-year history of peripheral vestibular dysfunction.32 At necropsy, changes in the brain vasculature, including the basilar, rostral and caudal cerebellar, labyrinthine, internal carotid, and caudal, middle, and rostral cerebral arteries, were observed. In addition, parietal lobe malacia and a cholesterol granuloma were found.

Despite the essential need for energy and its high metabolic demands, the brain is relatively insensitive to metabolic changes present in other tissues in hypothyroid animals. A small number of thyroid hormone–induced genes are present in the adult canine brain, and it has been shown that the brain increases thyroid hormone uptake via an active transport process within the blood-brain barrier in times of deficiency of thyroid hormone.12 In addition, activities of deiodinases that catalyze the conversion of T3 to T4 are increased, and degradation of thyroid hormone is decreased. This allows the CNS to function at a relatively normal metabolic rate compared with peripheral tissues, even when hypothyroidism is chronic. In hypothyroid rodents, however, it has been shown that γ-aminobutyric acid (GABA) and benzodiazepine receptor density is altered, as are the reuptake of GABA and the activities of acetylcholinesterase,10 which may explain the mental dullness observed in some dogs with hypothyroidism.

Although uncommonly reported in the literature, pituitary neoplasms that cause secondary hypothyroidism can also lead to signs of mental dullness.37-40 Neurologic signs are the predominant clinical signs. In these cases, the compressive effects of the tumor on surrounding structures can cause ataxia, seizures, depression,
and head pressing. Tumors of the pituitary region may also compress the overlying diencephalon and associated ascending reticular activating system and are often associated with the most extreme cases of mental dullness. Measured TSH is low in these dogs. In addition, these tumors may alter production of TRH and, therefore, TSH. Diagnosis in these cases should be confirmed by advanced imaging.

**Conclusion**
Hypothyroidism and neurologic and muscular diseases are common conditions that are not mutually exclusive. Although thyroid hormone deficiency and clinical and biological changes within the nervous system are not definitively proven to have a cause-and-effect relationship, the clinical experiences of veterinarians, along with the extensive case reports and research in the literature, suggest a direct association. Because thyroid levels are affected by many factors that can confound the diagnosis of hypothyroidism, and because the underlying cause of neurologic syndromes can be difficult to identify, further studies need to be performed to assess the molecular basis of neurologic diseases in dogs with hypothyroidism. Future studies should be aimed at determining the effects of thyroid hormone deficiency on the peripheral nervous system, CNS, and muscles. Most of the speculation and disbelief surrounding the association between hypothyroidism and neurologic disease is based on the lack of definitive evidence that neurologic dysfunction may be induced by the metabolic changes that occur in hypothyroid dogs. Therefore, a better understanding of the nature of hypothyroidism will develop when other causes of neurologic dysfunction are thoroughly ruled out. This may require induction of hypothyroid states. Studies that conclusively determine the effects of hypothyroidism on mitochondrial function are needed. Until then, clinicians should be aware of this association and test for and potentially treat hypothyroidism in dogs with neurologic diseases and clinical signs suggestive of hypothyroidism.

**References**
1. Most dogs with hypothyroidism have _______ hypothyroidism caused by _______.
   a. primary; lymphocytic-plasmacytic thyroiditis
   b. secondary; lymphocytic-plasmacytic thyroiditis
   c. primary; lymphocytic thyroiditis or idiopathic atrophy
   d. secondary; lymphocytic-plasmacytic thyroiditis or idiopathic atrophy

2. The most appropriate diagnostic test(s) to perform in a case of suspected hypothyroidism is/are measurement of the
   a. total thyroxine (T4) level.
   b. total T4, free T4, and thyroid-stimulating hormone (TSH) levels.
   c. total and free T4 levels.
   d. total and free T4 levels, plus a TSH stimulation test.

3. What is the cause of hyperlipidemia in hypothyroid dogs?
   a. increased dietary intake secondary to polyphagia
   b. inhibition of lipoprotein lipase caused by lack of thyroid hormone
   c. decreased cholesterol uptake due to oversaturation of receptors
   d. lack of thyroid hormone–mediated uptake of plasma triglycerides

4. The pathophysiology of atherosclerotic damage is initiated by
   a. lipid deposition and thickening of the tunica media/interna.
   b. vascular dilatation secondary to nitrous oxide release.
   c. fibrosis of the muscular lining of arteries, arterioles, and capillaries.
   d. damage to endothelial lining of small vessels.

5. Which mechanism is thought to be the one by which plasma low-density lipoproteins (LDLs) cause most of the vascular damage in hypothyroid dogs?
   a. LDLs easily penetrate the subintimal space of vessels.
   b. LDLs have greater susceptibility to oxidation than other plasma lipoproteins.
   c. LDLs stimulate the production and secretion of plasminogen activator inhibitor 1 and thromboxane by endothelial cells.
   d. all of the above

6. The most common manifestation(s) of neurologic disease in hypothyroid dogs is/are
   a. central nervous system ischemic events.
   b. myxedema coma.
   c. neuropathic and myopathic disease.
   d. seizures.

7. Which describes the presentation of a dog with generalized polyneuropathy due to hypothyroidism?
   a. small-breed dog with increased patellar reflexes and tone
   b. large-breed dog with decreased patellar reflexes and normal to decreased tone
   c. large-breed dog with increased patellar reflexes and tone
   d. small-breed dog with decreased patellar reflexes and normal to decreased tone

8. Which statement is true regarding peripheral nervous system disorders in hypothyroid dogs?
   a. Generalized polyneuropathies have a poor response to T4 supplementation.
   b. Myasthenia gravis is thought to be associated with hypothyroidism due to acetylcholine antibody receptor displaying cross-reactivity with the thyroid gland.
   c. Most cases of megaesophagus resolve after a short course of treatment with T4 supplementation.
   d. A muscle biopsy is the preferred diagnostic test for generalized polyneuropathy.

9. Histopathologic evidence associated with myopathies in hypothyroid dogs may include a _______ type II:type I myofiber area ratio and _______ intramuscular nerve fiber morphology.
   a. decreased; lengthened
   b. increased; shortened
   c. increased; normal
   d. decreased; normal

10. Which is the most likely explanation for the pathophysiology of myxedema coma?
   a. altered GABA and inhibitory neurotransmitters present in the central nervous system (CNS)
   b. accumulation of neutral and acidic mucopolysaccharides and hyaluronic acids in the dermis causing tissue compression
   c. ischemic damage to specific regions of the cerebral cortex
   d. elevated ammonia levels circulating within the CNS