

# Neuromuscular manifestations of hypothyroidism in dogs

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## SUMMARY

Primary hypothyroidism in dogs has been associated with a variety of neuromuscular signs including generalised peripheral neuropathy, peripheral vestibular syndrome, facial paralysis, laryngeal paralysis, megaesophagus and myaesthesia gravis. This literature review describes the different signs and discusses where a convincing relationship with hypothyroidism can be seen and where a connection is more inconclusive.

This paper originally appeared in:

*\*Svensk veterinärtidning* (2006) **14**, p 11 - 17

## Introduction

Hypothyroidism is the most frequently diagnosed endocrinopathy in dogs (18). The disease is characterised by diminished production of the thyroid hormones thyroxine (T4) and thyronine (T3). Thyroid hormones influence a large number of metabolic processes in the body and, in the event of disorders in hormone production, symptoms can arise from a number of organ systems.

Primary hypothyroidism accounts for more than 95 percent of the cases and is usually caused by lymphocytic thyroiditis or idiopathic thyroid atrophy [13, 18]. Rarely thyrotropin (thyroid stimulating hormone, TSH) deficiency, as a result of reduced production in the pituitary gland, can result in hypothyroidism [13, 18]. Tertiary hypothyroidism, caused by a thyrotropin releasing hormone (TRH) deficiency, and congenital hypothyroidism are two other rare forms of hypothyroidism [18].

In addition to the most commonly occurring symptoms such as dermatological changes and signs of general metabolic disturbances, a number of neurological manifestations have been reported to occur in hypothyroidism in dogs. (Figure 1) Neurological symptoms of hypothyroidism can originate from the central and peripheral nervous systems as well as from the muscles. Symptoms from the peripheral nervous system which have been described are exercise intolerance, general

weakness, paraparesis and tetraparesis, and symptoms of the cranial nerves such as vestibular syndrome and facial paralysis. Laryngeal paralysis and megaesophagus have also been reported in hypothyroid dogs. In neurological manifestations of hypothyroidism, the dog may not show any of the classical symptoms such as lethargy and dermatological changes [1, 3]. Many of the signs are reversible on treatment with the synthetic

*Fig. 1. In addition to dermatological changes and general metabolic disturbances, a number of neurological manifestations have been reported in dogs with hypothyroidism.*



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\* Presented by SSAVA (Sweden)

thyroid hormone, levothyroxine.

This literature review describes hypothyroid-associated manifestations of the peripheral nervous system, which from a clinical point of view includes symptoms originating from the alpha motor neurons, nerve roots, peripheral nerves and the neuromuscular end-plate, as well as the muscles. Symptoms can also arise as a result of involvement of sensory nerves.

The purpose of this review is to illustrate that there are symptoms of hypothyroidism which differ from the classical ones.

## Aetiology and pathogenesis

Little is known about the etiology and pathogenesis of neuropathy resulting from hypothyroidism. It is unclear how a deficiency of thyroid hormones causes the changes described [5].

Under physiological conditions, the thyroid hormone stimulates mitochondrial respiratory activity and in this way aids in the production of ATP during aerobic conditions. Thyroxine seems to increase the activity of both ATP and the ATP-dependent sodium potassium pump. Hypothyroidism causes an ATP deficiency and diminished ATPase-activity impairs sodium-potassium pump activity, with a change in pump-dependant axonal transport in neurons as a result. Reduced axonal transport in sciatic nerves has been demonstrated in experiments with hypothyroid rats and is thought to lead to axonal degeneration and peripheral neuropathy [12]. Increased amounts of glycogen and glucosamino glycans in the cytoplasm, e.g. in Schwann cells and perineural cells in humans, has been described as well as signs of demyelination and axonal degeneration. The occurrence of atypical mitochondria in Schwann cells has also been reported. Axonal involvement in the form of shrunken axoplasma in myelinated fibres as well as disintegration of axonal neurotubules and neurofilaments have, in addition, been reported [5].

The pathogenesis of paralysis of cranial nerves such as the vestibulocochlear nerve and facial nerve in hypothyroidism is not clear. One possible explanation can be that the neuropathy is caused by compression as a result of myxoedematous deposits which occur in and around the affected nerves where they exit through os temporale [5, 13]. Another possible cause can be compression of nerves when they pass through myxoedematous tissue of the head and neck [5].

## Diagnostic methods

Typical clinical histories and symptoms of hypothyroidism are lethargy and weight gain, weakness, exercise intolerance and dermatological symptoms such as flaking skin, changes of the coat, alopecia and hyperpigmentation. In addition to the classical symptoms, symptoms from other organ systems have been reported, such as the nervous systems, reproductive organs, cardiovascular system and gastrointestinal organs [15, 16]. Myopathy has also been described in hypothyroidism in dogs [2, 5]

To help substantiate the diagnosis of hypothyroidism, there are a number of diagnostic aids. Haematological changes such as mild normocytic, normochromic, non-regenerative anaemia and serum biochemical abnormalities such as hypercholesterolaemia, hyperlipidaemia and hypertriglyceridaemia can indicate



*Fig.2. Haematological changes such as anaemia and biochemical changes such as hypercholesterolaemia, hyperlipidaemia and hypertriglyceridaemia can indicate hypothyroidism.*

hypothyroidism [5, 18]. (Figure 2). The serum concentrations of creatine kinase can be mildly increased in hypothyroidism [12, 15].

Measurement of TSH, free T4 and total T4 is performed to establish a diagnosis. In primary hypothyroidism, the levels of free T4 and total T4 are low and TSH elevated or normal [5, 16]. Factors such as non-thyroidal systemic diseases, breed and drug administration can influence the thyroid hormone levels and thereby make the interpretation of these functional tests more difficult [16, 17, 18]. Antithyroglobulin antibodies exist in approx. 50 percent of all dogs with hypothyroidism caused by autoimmune thyroiditis [16]. Further tests, such as TSH- respectively TRH-response test, nuclear scintigraphy and biopsies from the thyroid gland can be performed in order to establish as conclusive a diagnosis as possible [5, 16].

For symptoms from the nervous system, a neurological examination is performed to establish the localisation of the lesion and thereby the peripheral and/or central localisation. Electrophysiological testing such as electromyography (EMG) and nerve conduction studies (e.g. motor nerve conduction velocity - MNVC) can be used in diseases of the peripheral nervous system and musculature in order to establish the peripheral localisation and to differentiate a myopathy from a neuropathy.

### **Electromyography (EMG)**

Electromyography is the measurement of electrical activity within a muscle and is performed using electrodes. Mechanical stimulation, using a needle electrode, leads to depolarisation of the muscle membrane with a short burst of electrical activity, so-called insertional activity, as a result. A normal muscle at rest is otherwise electrically inactive. In pathological conditions, different forms of spontaneous electric activity can be seen following spontaneous depolarisation which progress along the muscle membranes and this spontaneous activity can be registered as different types of wave-formed curves. Fibrillation potentials and positive sharp waves can be seen

following denervation and in some cases also complex repetitive discharges. Fibrillation potentials and positive sharp waves can also be seen in certain primary muscle diseases, with complex repetitive discharges occurring foremost in primary muscle diseases [19]. The occurrence of fibrillation potentials, positive sharp waves [4, 10, 11, 12, 13] and complex repetitive discharges [12, 13] has been described in dogs with hypothyroidism.

### **Nerve conduction studies**

Nerve conduction studies measure the conduction velocity of impulses along peripheral nerves. Abnormal findings upon measurement of motor nerve conduction velocity (MNCV) have been noted in hypothyroid dogs [5, 10, 12, 13] in the form of reduced conduction velocity in e.g. the tibial nerve [10, 12], which indicates demyelination [5, 11]. Reduced conduction velocity in sensory nerves has also been reported in dogs with hypothyroidism [10].

### **Brainstem auditory evoked response (BAER)**

When the vestibulocochlear nerve is affected, hearing can be reduced. To assess hearing, a brainstem auditory evoked response (BAER, AER) can be performed. BAER records the electrical activity within the auditory pathways of the nervous system which occur as a result of a specific sound stimulus. BAER results is shown as a complex wave-formed curve [19]. Abnormal BAER-findings have been reported in hypothyroid dogs [1, 12, 13].

### **Other diagnostic aids**

Other diagnostic aids to enable differentiation of neuropathies from myopathies are histopathological and histochemical examinations of muscle and nerve biopsies [5].

In dogs with neuropathies caused by hypothyroidism, muscle biopsies can show varying degrees of neurogenic atrophy with angular atrophy of primarily type II myofibres, but also of type I myofibres [4, 5, 10, 12, 13], along with variations in fibre size [12]. In nerve biopsies, nonspecific changes such as demyelination, remyelination and axonal degeneration can be seen [4, 5, 10, 13].

In hypothyroid myopathy in dogs, oval or angular atrophic type II myofibres can be seen throughout all muscle bundles. Loss of type II myofibres has been noted in some dogs with hypothyroidism [2, 5]. Accumulation of nemaline rod inclusions in type I myofibres has been described in hypothyroid dogs [6]. None of these finding which can be seen in electrophysiological examinations or nerve and muscle biopsies are, however, pathognomonic for hypothyroidism.

## **Generalised peripheral neuropathy**

Peripheral neuropathy is a disease process localised to nerve roots or peripheral nerves. Peripheral neuropathy caused by hypothyroidism affects primarily middle-aged and older individuals [12, 13], especially of middle- to large-sized breeds [12]. Dogs with generalised peripheral neuropathy often have other signs of hypothyroidism such as dermatological changes [1, 10], weight gain and hypercholesterolaemia [5, 12]. The course of the disease is usually slowly progressive during 2 - 8 weeks [4, 10, 12, 13] and fluctuations in clinical signs are not unusual

[13]. The diagnosis of hypothyroidism is based on diminished response to TSH-stimulation in a number of studies [4, 10, 11, 12, 15].

Clinical signs include exercise intolerance, general weakness, initially mild gait deficits which can progress to paraparesis or tetraparesis, ataxia, reduced spinal reflexes and muscle atrophy [1, 4, 10, 11, 12]. Proprioceptive positioning deficits and decreased spinal reflexes are generally more evident in the hind limbs, however reduced spinal reflexes in all four limbs can occur [12, 13]. Involvement of the cranial nerves, such as trigeminal, facial and vestibulocochlear can occur [5].

The result of electrophysiological examinations is abnormal in most patients with generalised peripheral neuropathy [12, 13] with findings such as fibrillation potentials, positive sharp waves [4, 10, 11, 12, 13] and complex repetitive discharges [12, 13]. In some cases a correlation between the degree of EMG-changes and clinical symptoms [10] is absent. Reduced conduction velocity in motor nerves can be seen, indicating demyelination and supporting the diagnosis of peripheral neuropathy [5, 10, 11, 12]. Muscle biopsies show varying degrees of neurogenic atrophy [4, 10, 12, 13] while nerve biopsies show signs of demyelination and remyelination [4, 14] and axonal degeneration [4, 5, 10] which support a diagnosis of polyneuropathy with secondary neurogenic myopathy [13].

The clinical signs of generalised peripheral neuropathy caused by hypothyroidism are usually reversible after two to three months treatment using thyroid hormone supplements [4, 10, 11, 12, 13]. In one study encompassing eleven dogs with peripheral neuropathy caused by hypothyroidism, after two months of treatment using levothyroxine no clinical or neurological abnormalities were discovered in any of the dogs. Electrophysiological examinations were performed on one dog two months after the treatment was initiated and no pathological changes were discovered [12].

### **Lameness of the foreleg**

Intermittent, as well as constant, forelimb lameness is described in dogs with hypothyroidism [3, 4, 13]. In one study which included four dogs, electromyography demonstrated fibrillation potentials and positive sharp waves in both the forelimb and hind limb muscles, indicating involvement of multiple muscle groups. In these four dogs the diagnosis of hypothyroidism was based on insufficient response to TSH-stimulation. No other clinical symptoms of hypothyroidism were seen in three of the dogs. The lameness resolved after three to eight weeks of treatment with levothyroxine in all the dogs. A follow-up EMG-examination, which was performed 6 - 16 months after treatment was initiated, was normal in three of the dogs with one dog showing only mild changes. In two of the dogs, where the levothyroxine treatment was ended after six months, the lameness reappeared within two weeks. The symptoms disappeared when the levothyroxine treatment was reinitiated [3].

## **Peripheral vestibular syndrome**

Peripheral vestibular syndrome caused by hypothyroidism is seen primarily in older dogs [1, 5, 12, 13] and can occur alone or as part of generalised neuropathy [1, 5, 13]. The diagnosis of



Fig.3. Symptoms which can occur in peripheral vestibular syndrome include ipsilateral head tilt.

hypothyroidism is made as a result of reduced response to TSH-stimulation in several reports [1, 11, 12, 15].

Symptoms which can occur in peripheral vestibular syndrome include ipsilateral head tilt (figure 3), vestibular ataxia and circling, ipsilateral ventral strabismus and horizontal nystagmus with fast phase away from the affected side [1, 5, 12, 13]. Postural reactions and spinal reflexes are normal [13].

The onset of clinical signs is in most cases reported to be acute and non-progressive, however the course of the disease can in some cases be chronically progressive [1, 12, 13]. Vestibular dysfunction can be the only clinical sign of hypothyroidism [1]. Facial paralysis is reported to occur [11, 12] in approx. 70 percent [17] of hypothyroid dogs with peripheral vestibular syndrome and can be ipsilateral [5] or bilateral [13, 15]. Abnormal BAER-results such as decreased amplitude and increased latency can be seen in peripheral vestibular syndrome as a result of vestibulocochlear nerve involvement [1, 12, 13]. EMG-changes can be seen if a simultaneous generalised neuropathy exists and include fibrillation potentials and positive sharp waves in the proximal and distal extensor muscles [12, 13].

Vestibular symptoms in hypothyroidism-associated neuropathy are often completely or partly reversible within two to four months using thyroid hormone supplement therapy [1, 12, 13].

## Other neuromuscular manifestations

Hypothyroidism has in the literature been associated with facial paralysis, laryngeal paralysis, megaesophagus and myaesthesia gravis in dogs.

### Facial paralysis

Hypothyroidism has been suggested as the cause of facial paralysis, however whether a direct relationship exists is not clear. One retrospective study, which included 31 dogs with facial paralysis as a single sign, could not show a significant association to hypothyroidism, when the diagnosis of hypothyroidism was documented by TSH-response test [14]. One source indicates that facial nerve dysfunction seldom improves as a result of treatment with levothyroxine [5].

### Laryngeal paralysis

In one retrospective study which included five hypothyroid dogs with laryngeal paralysis, a complete neurological examination revealed signs of generalised peripheral neuropathy in three of the dogs. EMG and MNCV supported a general involvement of the peripheral nervous system. All five dogs were treated with levothyroxine and four of the dogs were also treated by surgery. Four of the dogs, including the dog which was only treated medically, improved [12]. In one retrospective study which included 66 dogs with hypothyroidism, two dogs with laryngeal paralysis were described as only being treated with levothyroxine. There was no improvement in the condition seen in these two dogs [15]. The diagnosis of hypothyroidism was based on a reduced response to TSH-stimulation in these studies. In one study which included 23 dogs with laryngeal paralysis, three were regarded as having primary hypothyroidism based on the appearance of low serum thyroxine (one dog) and reduced response to TSH-stimulation (two dogs) [8].

### Megaesophagus

Treatment of megaesophagus in hypothyroid dogs using levothyroxine has shown varied results. In one retrospective study which included four dogs with hypothyroidism and megaesophagus, clinical improvement was seen in only one dog [12]. In another report, four dogs with hypothyroidism and megaesophagus are described which were treated with levothyroxine. Oesophageal dilatation resolved after three months treatment in one dog and did not reappear when levothyroxine supplementation was ended [15]. In one hypothyroid dog with paraparesis, laryngeal paralysis and megaesophagus, only the paraparesis improved on treatment using levothyroxine [4]. In these three reports the diagnosis of hypothyroidism was made as a result of reduced response to TSH-stimulation. In a case-controlled study including 136 dogs with acquired megaesophagus, no statistically significant relationship between megaesophagus and hypothyroidism could be proved [9].

### Myaesthesia gravis

Acquired myaesthesia gravis (MG) has been reported in hypothyroid dogs [7, 15]. Five dogs with hypothyroidism and acquired MG are described in one of the reports [7]. The diagnosis of hypothyroidism is based on low T4-concentrations and diminished response to TSH-stimulation; myaesthesia gravis was confirmed by increased serum concentrations of acetylcholine receptor antibodies. Two dogs had clinical signs of peripheral polyneuropathy and nerve biopsies from one of the dogs showed demyelination, remyelination and axonal necrosis, which supports the diagnosis of neuropathy. These

two dogs showed clear signs of improvement when the thyroxin supplement was initiated. None of them were treated with pyridostigmine. Based on their report, the authors of the article suggest that a connection exists between hypothyroidism and acquired MG in dogs [7].

## Discussion

Hypothyroidism is an important differential diagnosis for generalised peripheral neuropathy and peripheral vestibular syndrome since it is a treatable disease and the prognosis for complete recovery is good.

The diagnosis of neuropathy caused by hypothyroidism should be based on a combination of history, clinical signs including neurological findings, haematological and biochemical changes, the result of thyroid gland function tests as well as the result of electrophysiological examinations and analysis of muscle and nerve biopsies. A large number of diseases can cause symptoms from the peripheral nervous system and there are no single changes which are pathognomonic to hypothyroid neuropathy. Factors which can prevent a definitive diagnosis being made are that electrophysiological examination methods are not generally available to all clinicians as well, as it being difficult to transport and examine muscles and nerve biopsies since the material, in many cases must be fresh. In addition, few laboratories are specialised in the examination of muscle and nerve biopsies from animals. Hypothyroidism can in itself be a diagnostic challenge since many systemic diseases and other factors, such as the administration of certain drugs, can influence concentrations of thyroid hormones in the blood. A TSH-response test may be needed in order to confirm the diagnosis of hypothyroidism in those cases where TSH and T4 results are not in accordance with the clinical picture. It may also be needed in cases with atypical symptoms, when there is simultaneous systemic disease, or when the dog is being treated with a drug which affects the thyroid hormone levels [16].

Caution should be taken in diagnosing hypothyroid neuropathy from clinical findings and low levels of T4 alone, especially in those cases where other symptoms of hypothyroidism are absent. (Figure 4).

The relationship between generalized peripheral neuropathy and hypothyroidism is convincing as many case reports exist with results showing diminished response to the TSH-response test, findings from electrophysiological examinations and analyses of muscle and/or nerve biopsies which are in agreement with that described for diseases of the peripheral nervous system in dogs [4, 10, 11, 12]. Dogs in these studies also often have other symptoms which are typical of hypothyroidism and clinical signs of generalised peripheral neuropathy that are usually reversible after two to three months treatment with thyroid hormone supplementation [11, 12, 13]. In follow-ups of treated dogs, after two months, there were no clinical or neurological abnormalities discovered and electrophysiological tests were normal [12], supporting the theory that generalised peripheral neuropathy can be caused by hypothyroidism. In those descriptions of forelimb lameness and simultaneous hypothyroidism which exist, the diagnosis of hypothyroidism is based on the reduced response on TSH-stimulation and electromyography showing fibrillation



*Fig.4. Caution should be taken when making the diagnosis of hypothyroid neuropathy from clinical findings only, such as the furcoat changes seen in the picture, and occurrences of low T4 levels.*

potentials and positive sharp waves. This is in accordance with what is described for peripheral neuropathy in hypothyroid dogs. Levothyroxine therapy led to the resolution of lameness which reappeared six months following the end of the levothyroxine therapy. This also indicates that there is a connection between hypothyroidism and the occurrence of forelimb lameness, as well as the normalisation of EMG-results following the initiation of treatment in three of the four dogs [3].

The potential association between peripheral vestibular syndrome and hypothyroidism is convincing, since there are a number of cases described where the diagnosis was based on reduced response to TSH-stimulation and electrophysiological findings, in accordance with those described for generalised peripheral neuropathy in hypothyroidism in dogs. Many dogs recover following treatment with levothyroxine [11, 12, 13], however incomplete recovery also occurs. It is however important to note that many dogs with peripheral vestibular syndrome, regardless of etiology, can compensate for the neurological deficits over time with only minimal residual symptoms, regardless of treatment. The clinical improvement is therefore not necessarily associated with levothyroxine therapy.

In EMG examinations of hypothyroid dogs with peripheral vestibular syndrome respectively forelimb lameness, fibrillation potentials and positive sharp waves in both the fore and hind leg muscles has been described. This indicates that there is good reason to suspect that both these manifestations are in many cases the only clinically visible sign of a sub-clinical generalised polyneuropathy.

The relationship between facial paralysis, laryngeal paralysis, megaesophagus, myasthenia gravis and hypothyroidism is not entirely clear.

There is no proven association which supports a connection between hypothyroidism and the occurrence of facial paralysis as a single sign in dogs [14] and one source indicate that the facial dysfunction seldom improves on treatment using levothyroxine [5] which gives some reason to question if hypothyroidism causes facial paralysis alone.

There are few reported cases of laryngeal paralysis and

megaoesophagus in hypothyroid dogs. Few of these have been treated with levothyroxine only, and the responses to levothyroxine supplementation alone are often poor. The follow-up in several cases was insufficient, which is why there is some reason to be cautious in drawing a conclusion that hypothyroidism is the cause of the symptoms. In those few hypothyroid dogs with megaoesophagus described, no or only slight improvement has been seen following treatment using levothyroxine [12, 15] which can indicate a weak relationship. Megaoesophagus can cause aspiration pneumonia, which in its turn can cause so-called euthyroid sick syndrome, i.e. when non-thyroidal systemic illness leads to reduced T4 levels. This can lead to difficulties in interpreting test results with a risk for making an incorrect diagnosis of hypothyroidism [17]. Since megaoesophagus and laryngeal paralysis can occur in a large number of neuromuscular diseases, care should be taken in making a diagnosis of hypothyroid neuropathy if this is based only on the occurrence of low thyroid hormone levels. General electrophysiological evaluation of dogs with clinical signs only of megaoesophagus or laryngeal paralysis are recommended since both conditions are often early manifestations of a general peripheral neuropathy for which the etiology can vary.

Acquired myasthenia gravis is an immune-mediated disease like many cases of primary hypothyroidism, which indicates that a common background can exist, however, whether there is a direct relationship between both diseases is not clear.

In order to investigate if there is a direct connection between hypothyroidism and the occurrence of facial paralysis, laryngeal paralysis, megaoesophagus and myasthenia gravis, more studies are required. In addition to medical history and clinical findings, haematological and biochemical analyses and thyroid function tests, the investigation should include a complete neurological examination, electrophysiological testing and biopsies from muscles and peripheral nerves in order to decide if there are changes which are in accordance with that described in hypothyroid neuropathy in dogs. A follow-up of treated patients should include renewed clinical and neurological examination, repeated electrophysiological examination and, if possible, new muscle and nerve biopsies in order to decide which effect the levothyroxine supplementation has had.

## Conclusion

Primary hypothyroidism in dogs has been associated with a variety of neurological signs, including lower motor neuron disease, peripheral vestibular syndrome, facial paralysis, laryngeal paralysis, megaoesophagus and myasthenia gravis. The relationship between hypothyroidism and polyneuropathy and peripheral vestibular syndrome is convincing, with several reports showing similar results of electrodiagnostic testing and biopsies of muscles and peripheral nerves. There is a less clear relationship between hypothyroidism and facial paralysis, laryngeal paralysis, megaoesophagus and myasthenia gravis.

Confirmation of the diagnosis is based upon neurological signs, clinicopathologic findings including low T4 concentrations and elevated TSH concentrations, alternatively diminished response to TSH-stimulation, and results of electrodiagnostic investigations and biopsies of muscles and nerves. Treatment with thyroxine supplementation is successful in most cases of

polyneuropathy and peripheral vestibular syndrome, but less so in laryngeal paralysis and megaoesophagus.

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