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ORIGINAL ARTICLE

Improvement of the clinical signs of gait abnormality after treatment with levothyroxine in a horse with shivering and hypothyroidism

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ABSTRACT

An 11-year-old Hanoverian gelding used for jumping was evaluated for gait abnormalities and hoof problems in the hindlimbs. Clinical examinations revealed signs consistent with shivers. A thyroid gland enlargement was noticed, baseline serum thyroid hormone (TH) concentrations were low, and a low response to thyrotropin-releasing hormone administration was observed. Hypothyroidism was suspected. The horse was treated with levothyroxine for 1 year. TH concentrations returned to the normal range by week 4 of treatment. Thirty weeks after the initiation of levothyroxine therapy, the gait abnormality improved. Our findings suggest that the assessment of thyroid status and especially of the subclinical thyroid gland disorders in horses affected with shivering, as well as evaluation of the effects of levothyroxine on the improvement of clinical signs could be promising in establishing the aetiopathogenesis and/or treatment of shivering in horses.

KEYWORDS

horse, shivering, hypothyroidism, neuropathy, myopathy, levothyroxine

INTRODUCTION

Equine shivering, also known as shivers, is a neuromuscular disease (Aman et al., 2018). The neurophysiological and pathological mechanisms of the disease are unknown, and no effective treatments have been reported. Hypothyroidism is poorly understood in the horse, and the prevalence of true hypothyroidism in adult horses is unknown (McFarlane and Fleming, 2015). Hypothyroidism has been thought to contribute to a variety of problems in the horse, including obesity, laminitis, anhidrosis, recurrent rhabdomyolysis and poor fertility (Toribio, 2018). There is a well-known association between the occurrence of hypothyroidism and neuromuscular manifestations. The beneficial effects of levothyroxine replacement therapy in the reduction of neuromuscular complaints have been demonstrated in humans and dogs (Jaggy et al., 1994; Duyff et al., 2000; Salvatore et al., 2014).

In this paper we describe the clinical features, diagnostic procedures, treatment and clinical outcome of a case of shivering with hypothyroidism in an 11-year-old Hanoverian

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gelding. We also discuss the possible pathophysiological association between hypothyroidism and shivering and the possible beneficial effects of levothyroxine on improvement of the clinical signs of equine shivers.

CASE HISTORY

A Hanoverian gelding (11 years old) was referred for evaluation of his slowly progressive gait abnormality and hoof cleaning or trimming problems in the hindlimbs. Based on the owner's statements, there was a problem in lifting the right hindlimb in farriery; therefore, hoof had not been properly trimmed and shoed within the last 2 years. The gelding had been purchased at 9 years old from Germany and was flown to Iran to compete at jumping class of 130 cm height during the last 2 years. No information on medical history regarding gait abnormality was provided for the owner. He used to refuse to jump and sit in a dog style posture with muscle quivering during training or jumping competitions when faced with an obstacle in a sharply curved pathway directed to the right side. No records of trauma, lameness, surgery and infectious diseases were documented in a 2-year period after importation from Germany. His ration included soaked alfalfa hay [11 kg as fed, equivalent to about 8 kg on dry matter (DM) basis], soaked concentrate (5 kg as fed, equivalent to about 3.5 kg on DM basis) and supplements of vitamins and minerals including vitamin E and selenium (VITA-E PLUS, TRM, Ireland) balanced for sport horses. The gelding's routine exercise took 40-min sessions daily. Animal welfare was satisfactory.

Clinical findings

The gelding was bright, quiet, alert, responsive and in a body condition score of 6 (on a scale of 1–9, ≤3 = underweight; 4–6 = optimal condition; ≥7 = overweight) (Henneke et al., 1983) and a cresty neck score of 2 (on a scale of 0–5, ≥3 = cresty neck) (Carter et al., 2009). The vital signs were within the reference limits. The horse was stalled in a 4 × 4 m square box. He was 180 cm in height and no obvious malconformations and evidences of old ulcers and scars were observed. Complete neurological examination demonstrated normal mentation and cranial nerve functions with no head tremor, muscle atrophy, proprioceptive ataxia or any proprioceptive deficit. The gelding showed symmetry in the head position and the posture of the neck, limbs and trunk. No abnormality was observed in manipulation of the neck and back musculature, dorsal processes of vertebrae, thorax and abdomen.

Constant semi-flexion and abduction of the right hindlimb was seen while the animal rested with the toe touching the ground and the heel raised off. The gelding often rested on the left hindlimb. Attempts to manually lift the right hindlimb were not successful due to rapid flexion and severe resistance of the limb despite sedation with detomidine hydrochloride (Calmant®, Ranvet, NSW, Australia) at 0.02 mg/kg IV. The left hindlimb could be lifted manually with reluctance and resistance. Hoof cleaning and farriery were not possible on the right hindlimb. The hindquarter muscles were rigid with tremor and hyperflexion following attempts of right hindlimb manipulation. Both hindlimbs showed hyperflexion with abduction at the first few strides of forward walking (Fig. 1). Hyperflexion and reluctance to move were also observed in backward walking. Before rapid return to the ground, the affected hindlimb remained hyperflexed in a spastic state for a few moments. The gait abnormality was intermittent and more evident on the left hindlimb during both forward and backward walking. The gelding showed a normal gait in trotting and cantering.

Radiographic examinations of the hindlimbs (stifle, fetlock, pastern and foot), ultrasonographic examination of the hindquarter muscles, transrectal ultrasonographic examination of the lumbosacral and sacroiliac joints, lumbosacral cerebrospinal fluid analyses, serum creatine kinase and aspartate aminotransferase activities, serum vitamin E and selenium concentrations and haematological parameters were in normal ranges. A glutaeal muscle biopsy was taken using a needle of 6 mm diameter to rule out other potential underlying causes such as polysaccharide storage myopathy. The biopsy sample was stained with haematoxylin and eosin, periodic acid–Schiff (PAS), and amylase–PAS stains. Histological findings did not show abnormalities in the muscle sections.

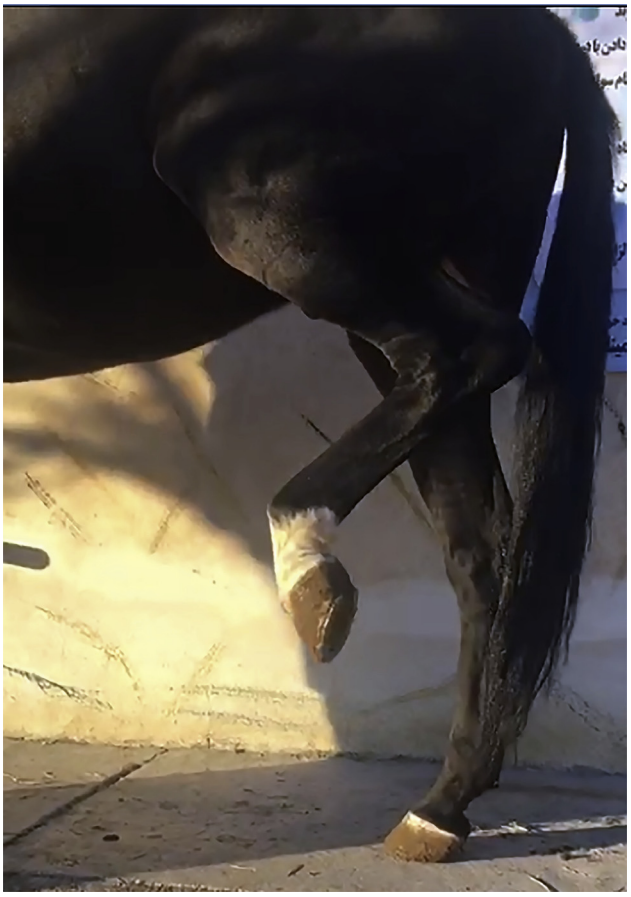

Fig. 1. Hyperflexion with abduction of the left hindlimb during forward walking

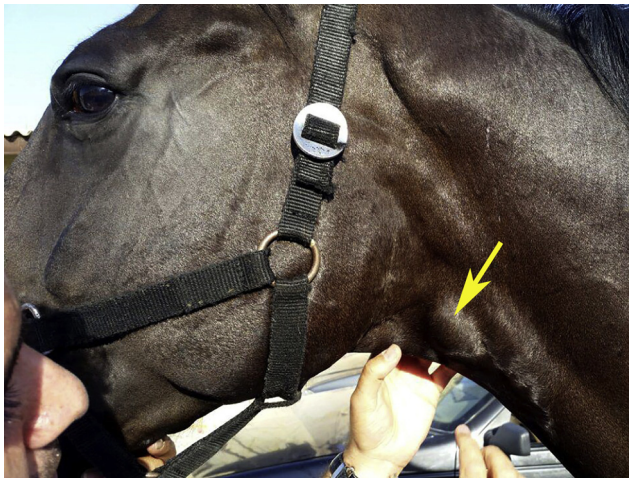

Fig. 2. Visible enlargement (arrow) of the thyroid gland (goitre)

Physical examination revealed a marked bilaterally symmetric enlargement located at the topographic area of the thyroid gland on the trachea (Fig. 2). It was readily visible, smooth, firm and ovoid to round shape. Ultrasonographic examination, using 7.5-MHz linear and 5-MHz curvilinear transducers, revealed a hypoechoic, solid mass 4.5 × 5 × 6 cm in size, with regular and smooth margins. Ultrasound-guided fine needle aspiration of the thyroid gland was performed to prepare Giemsa-stained smears. Histological examinations of thyroid nodule cytology according to the Bethesda System revealed abundant colloid and few epithelial cells. No cysts, neoplasia and inflammation were observed.

Serum concentrations of total triiodothyronine (T3) and total thyroxine (T4) were measured using radioimmunoassay (Canine total T4 Coat-A-Count, Diagnostic Products Corp., Los Angeles, California, USA; Canine total T3 Coat-A-Count, Diagnostic Products Corp., Los Angeles, California, USA) and serum free T4 concentration was measured using equilibrium dialysis (Nichols Institute Diagnostics, San Clemente, CA) validated for use with equine sera (Sojka et al., 1993; Messer et al., 1995). Sensitivities of the assays were as follow: 3 nmol/L for total T4, 0.3 nmol/L for total T3 and 1.8 pmol/L for free T4. The intra- and inter-assay coefficients of variability were as follow: 4.3 and 4.9% for total T3, 5.3 and 7.1% for total T4 and 7.5 and 7.8% for free T4, respectively. A single measurement of serum thyroid hormone (TH) concentrations is not always considered a reliable indicator of thyroid function (Breuhaus, 2011). Hence, in the present case measurements were repeated three times at 8-h intervals. In all three samples, serum total and free T4 concentrations were below the normal ranges (Table 1). Thyrotropin-releasing hormone (TRH) stimulation test was performed as described by others (Lothrop and Nolan, 1986; Harris et al., 1992). A baseline blood sample was obtained, then 1 mg of TRH (Ferring Arzneimittel GmbH, Germany) was administered intravenously. The second and third blood samples were obtained 2 and 4 h after TRH administration. Under normal conditions, serum T4 peaks at 4 h and T3 at 2 h after TRH administration and in a normal response both hormones should increase twofold to threefold (Lothrop and Nolan, 1986; Harris et al., 1992). In the present case, low response to TRH administration was observed (Table 1). This test confirms the diagnosis of thyroid dysfunction and eliminates the potential influence of endogenous and exogenous factors (Toribio, 2018), however, it cannot differentiate between primary and secondary thyroid dysfunction. To determine the type of hypothyroidism, thyroid-stimulating hormone concentrations must be measured (Frank et al., 2002), which was not available in our clinical setting.

Both iodine excess and deficiency can induce thyroid dysfunction and interfere with the results of thyroid tests (Toribio, 2018). The iodine concentrations of serum and urine were assayed using the Sandell–Kolthoff reaction (Sandell and Kolthoff, 1937), and were found to be in the normal range (39 and 8 μg L^{-1}, respectively). It should be noted that during an at least 5-month period before the TH tests, the gelding did not receive any medications such as anti-inflammatory agents, glucocorticoids or antibiotics that may interfere with thyroid gland function (Toribio, 2018).

Diagnosis

A presumptive diagnosis of shivering (shivers) was confirmed on the basis of the history, the findings of

Table 1. Thyroid hormone analyses in an 11-year-old gelding

	Initial evaluation			After TRH administration[a]			After treatment[b]	Reference ranges[c]	Mean ± SD[d]
	First	Second	Third	Baseline	2 h	4 h			
Total T3, nmol/L	0.33	0.33	0.31	0.32	0.38	–	1.2	0.39–1.52	0.97 ± 0.41
Total T4, nmol/L	5.7	6.1	5.9	5.8	–	7.3	25.5	14–63	22 ± 5.9
Free T4, pmol/L	6.4	6.8	6.7	6.3	–	8.6	28.3	13–51	25 ± 4.8

[a]Serum total T3 concentrations were measured 2 h after TRH administration and serum total and free T4 were measured 4 h after TRH administration.
[b]Four weeks after initiation of levothyroxine treatment.
[c]These values were obtained from 65 adult clinically healthy horses from West Azerbaijan, Iran, which were reached by the Endocrinology Laboratory of Urmia University.
[d]These values were obtained from 65 adult clinically healthy horses from West Azerbaijan, Iran, which were reached by the Endocrinology Laboratory of Urmia University.

physical examinations and the abnormal gait. The TH assays and the low response to TRH administration indicated that the gelding might have been affected simultaneously by hypothyroidism. Thyroid gland enlargement, the results of ultrasonographic examinations and cytological findings of the gland aspirates were associated with a benign or simple colloid goitre.

Neoplasia, iodine deficiency or excess, thyroiditis, thyroid agenesis, biochemical defects, or the ingestion of goitrogenic compounds that block TH synthesis can cause primary hypothyroidism (Toribio, 2018). Pituitary or hypothalamic dysfunctions cause central hypothyroidism (Toribio, 2018). After all, the cause of hypothyroidism and thyroid gland enlargement remained unknown in the present case.

Treatment

Levothyroxine treatment (Custom Pharmaceuticals Ltd., UK) was initiated at a dosage of 20 μg/kg, PO daily. Four weeks after initiation of the treatment, serum total and free T4 and total T3 concentrations were reassessed and results were within the reference range (Table 1).

Outcome

No change in thyroid gland size was observed in a 12-month follow-up evaluation after treatment, considering that levothyroxine administration lasted for 1 year. Significant improvement was observed in the rigidity of hindquarter muscles as well as in hyperflexion abduction of the hindlimbs during forward and backward walking. The problem of manual lifting of the right hindlimb was not resolved. According to information received from the owner, the gelding achieved improved sports performance after receiving treatment.

DISCUSSION

Shivering, a chronic gradually progressive movement disorder, is often characterized by muscle tremors, abduction, hypertonic flexion or extension of the pelvic limbs induced by walking backwards and manual lifting of a hindlimb (Firshman et al., 2005; Baird et al., 2006; Mayhew, 2009; Draper et al., 2015b). It can be unilateral or bilateral, consistent or intermittent (Draper et al., 2015b). Shivering is often first noticed by farriers and is especially problematic when it progresses to a total inability to hold up the hind hooves for trimming (Draper et al., 2015b). Shivering–forward hyperflexion (–FHF) is a condition defined by hyperflexion with abduction of the hindlimbs for the first few strides and during backward walking, as well as abnormal hyperflexion with manual lifting of the limb, and difficult or impossible manual lifting of the hindlimbs (Draper et al., 2015a). The gait abnormalities observed in the studied gelding were consistent with shivering–FHF.

Stringhalt is the most important differential diagnosis for shivering–FHF (Draper et al., 2015a); however, fibrotic myopathy, upward fixation of the patella and equine motor neuron disease are also among the differential diagnoses (Baird et al., 2006). In horses with stringhalt compared to shivering–FHF horses, the distinguishing features within forward walking were shorter stride times, as well as abrupt and rapid hyperflexion earlier in the swing phase (Draper et al., 2015a). In contrast to shivering, acquired bilateral stringhalt is often acute in onset (Draper et al., 2015b). Furthermore, a shivering–FHF horse shows marked intermittent abduction and hyperflexion during forward walking, while in stringhalt a consistent hyperflexion and lack of abduction can be observed, together with a sharp pull of limb toward the abdomen (Draper et al., 2015a). In shivers, the limb is held in a spastic state for a few moments instead of being immediately returned to the ground as in stringhalt (Baird et al., 2006). Another prominent feature differentiating shivering–FHF from stringhalt is the persistence of stringhalt at a trot, whereas shivering does not affect normal gait in trot (Dyson and Ross, 2011). The important finding in shivering is the reluctance to allow manual lifting of the hindlimbs for trimming and shoeing, which is usually not found in stringhalt (Draper et al., 2015a, 2015b). In fibrotic myopathy, before the foot contacts the ground, it is pulled in a caudal direction. It limits the cranial phase of the stride, for the limb pulls it caudally before it can reach a full-length stride (Sullins, 2011a). In upward patella fixation, the affected hindlimb is unable to flex, therefore leading to a posture in which the horse extends the affected limb in a caudally abducted position with the flexed fetlock, highlighting the signs in backward movement or movement in a tight circular direction, while in the case of medial patellar ligament release a quick upward jerk of the hindlimb is usually observed (Sullins, 2011b). Moreover, horses with both fibrotic myopathy and upward patellar fixation have a normal manual lifting of the hindlimbs. Equine motor neuron disease progresses slowly and is characterised by weakness, weight loss, muscle fasciculations, a short-stride gait and symmetrical neurogenic muscle atrophy, and the affected animals often show serum vitamin E concentrations (<1.0–2.0 μg/dL) lower than the normal range (Constable et al., 2017). Serological evaluations of the present case indicated normal concentration of serum vitamin E. Other diseases that can affect the gait include botulism, equine protozoal myeloencephalitis (EPM) and equine herpesvirus type 1 (Goehring, 2011). These diseases were ruled out in the present case on the basis of the findings.

A muscular or nervous system disorder, genetic and infectious factors, osteoarthritis and trauma have previously been postulated to be the cause of equine shivering (Valentine et al., 1999; Davies, 2000; Firshman et al., 2005; Baird et al., 2006; de Lahunta and Glass, 2009; Sullins, 2011c). A recent extensive neuropathological study suggests that shivering is associated with cerebellar Purkinje cell axonal degeneration (Valberg et al., 2015). A more recent study revealed that shivering is characterised by enhanced simultaneous recruitment of the flexor and extensor muscles and a loss of ability to modulate motor unit recruitment in the hindlimbs, which is associated with selective Purkinje cell

distal axonal degeneration; however, a full explanation of the role of Purkinje cell degeneration and shivering is still lacking (Aman et al., 2018). Although equine shivering seems to be a neuromuscular disorder, the precise aetiology and the details of pathogenesis remain obscure and no effective treatment has been reported so far.

A number of management and pharmaceutical interventions including increased exercise/turnout, diet changes, acupuncture, chiropractic, herbs, flunixin meglumine, phenylbutazone, tranquilisers, muscle relaxants and phenytoin have been attempted, but outcomes have been unsuccessful (Firshman et al., 2005; Baird et al., 2006; Draper et al., 2015b). Based on the TH assays and the result of the TRH stimulation test, we concluded that it would be reasonable to evaluate the response to levothyroxine therapy. No other physical, biochemical, histopathological, radiographic and ultrasonographic abnormalities were found. Therefore, to avoid interaction between levothyroxine and other therapeutic regimens on the alteration of clinical signs, no other medications or management interventions were used.

The coincidence of hypothyroidism and clinical signs of shivering were the most prominent features of the case presented here. There is no evidence that hypothyroidism is common in horses, although it is frequently diagnosed based on low TH concentrations (Toribio, 2018). Many conditions, including obesity, insulin resistance, metabolic syndrome, laminitis, anhidrosis, rhabdomyolysis, agalactia, infertility, alopecia and hypothermia have been attributed to low TH concentrations in horses and donkeys (Toribio, 2018). Neuromuscular abnormalities have been considered as well-established problems in hypothyroidism of humans and dogs, and the administration of THs resolved some of these problems (Jaggy et al., 1994; Duyff et al., 2000).

The lack of adequate levels of THs in critical periods of development leads to histological, biochemical and behavioural abnormalities in the central nervous system (CNS; König and Neto, 2002). Postnatal TH replacement therapy has to be initiated shortly after birth to be efficient on the normal development of the brain (Wiersinga, 2001). Moreover, thyroid dysfunction in adult humans is associated with both neurologic and psychiatric abnormalities including dementia, depression, myxoedema coma, dysfunction of the cerebellum and cranial nerves, the signs of which are usually reversible by TH replacement therapy (Mandel et al., 1993; Fukui et al., 2001; Selim and Drachman, 2001; Smith et al., 2002). In human medicine, acquired cerebellar dysfunction has been described with hypothyroidism. The pathogenesis of cerebellar dysfunction in patients with decreased thyroid function is uncertain; however, restoring a euthyroid state with L-thyroxine has reversed the cerebellar symptoms in most patients (Barnard et al., 1971; Hammar and Regli, 1975; Erkulvrawatr, 1977; Selim and Drachman, 2001). CNS neuroprotection by THs has been demonstrated by others in rats and mice (Rami and Krieglstein, 1992; Crupi et al., 2013).

THs are also required for the development and regeneration of peripheral nerves (Barakat-Walter, 1999). Exogenous administration of TH clearly accelerates and improves peripheral nerve regeneration and functional recovery in adult rats (Mohammadi et al., 2013; Barakat-Walter and Krafsik, 2018). Dogs with hypothyroidism were reported to suffer from peripheral neuropathy, lower motor neuron disease, peripheral vestibular syndrome, facial paralysis, laryngeal paralysis, megaoesophagus, myasthenia gravis and gait abnormalities, and treatment with T4 supplementation was successful in most cases (Kern and Erb, 1987; Bichsel et al., 1988; Jaggy et al., 1994; Panciera, 1994; Dewey et al., 1995; Cizinauskas et al., 2000; Higgins et al., 2006). Humans with hypothyroidism show neurologic complications including polyneuropathy (Nemni et al., 1987; Beghi et al., 1989). A case of hypothyroidism as well as peripheral neuropathy has been reported in a 6-year-old gelding with keratoconjunctivitis sicca, and it showed signs of improvement with levothyroxine administration (Schwarz et al., 2008).

It has been concluded that neuromuscular disorders such as myopathy, functional muscle disorder and sensorimotor axonal neuropathy occur in most patients with hypothyroidism (Duyff et al., 2000). Neuromuscular complaints have been resolved during thyroid replacement therapy in most human patients within an average time of about 7 months (Duyff et al., 2000). The skeletal muscle is a major target of TH signalling (Salvatore et al., 2014). The delayed contraction and relaxation of the deep tendon reflex is a classical observation in hypothyroid individuals, whereas the opposite changes are observed in patients with thyrotoxicosis (Braverman and Cooper, 2012), which illustrates the integrated effect of THs on various properties of the skeletal muscle, including the contraction–relaxation cycle (Salvatore et al., 2014). In addition to the direct transcriptional regulation of a number of genes, TH signalling bears secondary effects. Due to the action of muscle regulatory factors, like MYOD1 and myogenin, adaptive effects are related to changes in energy metabolism and modulation of Ca^{2+}-dependent signalling by the changes in intracellular Ca^{2+} handling during contractile activity (Salvatore et al., 2014).

Neuromuscular disorders are among the most probable causes of shivering that are frequently associated with hypothyroidism. Therefore, we proposed a probable association between hypothyroidism and the occurrence of shivering in the present case. Administration of levothyroxine attenuated the clinical signs of shivering, hence, it might provide some clues on the role of THs as a contributing factor to the pathogenesis and the initiation of shivering or, alternatively, to the progression of clinical signs of gait abnormality in horses initially affected with shivering. In the studied gelding there was no pre-purchase history regarding previous diseases, therefore, it was difficult to establish a reasonable cause and effect association between shivering and hypothyroidism. Alternatively, the concurrence of hypothyroidism and clinical signs of shivering might have been an incidental finding.

Our findings in the present gelding were consistent with a patient suffering from simultaneous hypothyroidism and shivering. Although we did not establish a clear relationship between hypothyroidism and shivers, the administration of

levothyroxine was associated with an improvement in the clinical signs of shivering. Therefore, it seems that the evaluation of thyroid gland function should be considered in order to reveal the possible role of TH status in the aetiopathogenesis of shivering in horses.

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