Thyroid Hormone Levels in Foals with Congenital Musculoskeletal Lesions

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ABSTRACT

Fourteen foals with congenital or neonatal musculoskeletal abnormalities are described. Ten of the fourteen foals had abnormally low total serum T_3 and/or T_4 concentrations suggesting hypothyroidism. Response to thyroid-stimulating hormone was determined in two foals and found to be poor. Seven of the foals were necropsied and six of these had histological evidence of thyroid hyperplasia. These findings suggest hypothyroidism as a cause of congenital musculoskeletal lesions.

Key words: Hypothyroid, goiter, musculoskeletal lesions, thyroxine, triidothyronine, equine.

RÉSUMÉ

La concentration d'hormone thyroïdienne, chez des poulains qui présentaient des lésions musculo-squelettiques congénitales

Cet article décrit les anormalités musculo-squelettiques, congénitales ou néonatales, dont souffraient 14 poulains. Dix d'entre eux affichaient une concentration sanguine de T_3 et/ou de T_4 anormalement basse et suggestive d'un hypothyroïdisme. Les auteurs déterminèrent la réaction à l'injection de thyrotrophine, chez deux de ces poulains, et ils constatèrent qu'elle était très faible. L'histopathologie de la thyroïde de six des sept poulains dont ils effectuèrent la nécropsie révéla des lésions d'hyperplasie. Les constations précitées suggéraient l'hypothyroïdisme comme cause des lésions musculo-squelettiques congénitales.

Mots clés : hypothyroïdisme, goitre, lésions musculo-squelettiques, thyroxine, triiodothyroxine, équins.

INTRODUCTION

The thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4), play an important role in energy metabolism, neuromuscular maturation, the action of adrenaline or noradrenaline and muscular and skeletal growth (1). When increased thyroid stimulating hormone (TSH) from the pituitary gland is produced in response to continuous low T_3 or T_4 concentrations hypertrophy and hyperplasia of follicular epithelial cells and increased vascularity of the thyroid results, leading to hyperplastic goiter.

A variety of musculoskeletal lesions in foals have been described and are known to be congenital in nature although the etiology is undetermined (2-6). Ruptured common digital extensors, forelimb contracture, mandibular prognathism, and immature carpal and tarsal bones are associated with hyperplastic goiter in neonatal foals (7,8), but reports of thyroid hormone levels in affected foals are rare. This report describes thyroid hormone levels in fourteen foals that had congenital musculoskeletal lesions. Six cases out of seven which were examined microscopically showed hyperplasia of thyroid follicular epithelial cells

MATERIALS AND METHODS

Fourteen foals admitted to the Western College of Veterinary Medicine between 1981 and 1983 with congenital or neonatal musculoskeletal abnormalities were included in this study. Serum samples were assayed for total serum T_3 (Tri-Tab RIA, Nuclear-Medical Laboratories, Irving, Texas 75061) and total serum T_4 (Tetra-Tab RIA, Nuclear-Medical Laboratories, Irving, Texas 75061) by radioimmunoassay. In selected cases the affected limbs were radiographed. Seven severely affected foals were euthanized with an intravenous barbiturate solution and a complete necropsy performed. Selected tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at six microns and stained with hematoxylin and eosin. Response to intramuscular administration of 15 I.U. of thyroid stimulating hormone (Thytropar, USV Canada Inc., Mississauga, Ontario L4Y 1R9) was measured in two foals by assaying thyroid hormone levels before administration and at various intervals postadministration.

History and Clinical Findings

The age at necropsy or clinical examination, breed, sex, lesions, T_3 and T_4 values are presented in Table I. Typically, foals were weak at birth and required assistance to suckle. Those with forelimb contracture were unable to stand without assistance. In all cases the musculoskeletal lesions were detected at or shortly after birth. The abnormalities included mandibular prognathism, ruptured common digital extensor tendons, angular limb deformities, forelimb contracture, and skeletal hypoplasia, manifested as poorly ossified or malformed carpal or tarsal bones.

The dams of affected foals were clinically normal. Review of the dams' diet during pregnancy revealed no obvious deficiencies, and iodized salt blocks were available in many instances. Other dams and foals on the same

TABLE I
HISTORICAL DATA, LESIONS AND THYROID HORMONE LEVELS OF FOURTEEN FOALS

Foal #	Breed	Sex	Age	Thyroid	Musculoskeletal Abnormality[a]	T_3 (nmol/L)	T_4 (nmol/L)	Normal Values (1) T_3 (nmol/L)	Normal Values (1) T_4 (nmol/L)
1.	App	M	1 da	Goiter	F,R,M	2.2 (L)[c]	136.4 (L)		
2.	Qtr	F	1 da	Goiter	A,F,R,M,S	2.5 (L)	95.2 (L)	11.4-19.0	279-464.3
3.	Arb	M	3 da	N.E.[b]	M	9.0 (L)	101.7 (L)		
4.	Qtr	M	4 da	N.E.	A,F,S	1.6 (L)	25.7 (L)	10.8-18.0	270-450
5.	Qtr	M	7 da	Goiter	F,R,M	3.3 (L)	117.0 (N)[d]		
6.	Qtr	?	7 da	N.E.	F,M	7.1 (N)	120.0 (N)		
7.	Qtr	M	7 da	N.E.	A	7.6 (N)	294.0 (N)	7.3-12.1	71.9-119.8
8.	Qtr	M	10 da	N.E.	R	8.2 (N)	140.0 (N)		
9.	App	F	10 da	Goiter	A	1.8 (L)	217.5 (N)		
10.	TB	F	21 da	N.E.	R	1.4 (L)	18.0 (L)		
11.	Stbd	F	1 mo	Goiter	A,F,R,S	1.1 (L)	3.9 (L)	2.3- 3.7	24.8- 41.4
12.	Qtr	F	35 da	Goiter	A,S	4.1 (N)	52.8 (N)		
13.	TB	M	3 mo	N.E.	S	0.7 (L)	12.0 (L)		
14.	Qtr/X	M	5 mo	N.E.	A,S	N.E.	5.1 (L)	0.9- 1.5	26.1- 43.5

[a]A = Angular limb deformity, F = Forelimb contracture, R = Ruptured common digital extensor tendon, M = Mandibular prognathism, S = Skeletal hypoplasia
[b]N.E. = Not examined
[c](L) = Low
[d](N) = Normal

premises as these cases were also clinically normal. Known goitrogenic plants were not found in the diet and the animals had not received any medication.

Pathological Findings

Angular limb deformities were present as lateral or medial deviations originating at the carpus (six cases) or tarsus (two cases). Usually, the deformities were due to hypoplasia of the carpal or tarsal bones. These were poorly or incompletely ossified, with thickened layers of articular cartilage and small ossified centers. The affected carpal bones were misshapen and the affected central and third tarsal bones were collapsed. In one case asymmetric development of the distal radial epiphysis was present.

Forelimb contracture was invariably a congenital lesion (seven cases). The forelimbs were in fixed flexion at the carpus and the fetlock and could not be manually straightened. Concurrent rupture of the common digital extensor tendon was often present (five cases). The ruptured tendons were within a fluctuant swelling on the distal craniolateral aspect of the carpus formed by the dilated tendon sheath. Rupture invariably occurred at the musculotendinous junction, leaving the distal portion folded and necrotic within the tendon sheath. The microscopic lesions of the ruptured tendons were as described in a previous report (8).

Mandibular prognathism often accompanied forelimb contracture and ruptured common digital extensor tendons (five cases). The mandible extended beyond the maxilla by one to three centimeters. This lesion was invariably congenital.

Thyroid glands of necropsied foals were normal in size and shape. Subjectively, the thyroids often appeared paler and felt firmer than normal when cut in cross-section. Six of the seven foals had histological evidence of hyperplasia. Thyroid follicles were small, crowded, irregularly shaped, and contained very little colloid. The follicular epithelial cells were tall columnar, crowded and occasionally pseudostratified.

Thyroxine and Triiodothyronine Levels

Total serum T_3 and total serum T_4 concentrations and their interpreta-

TABLE II
T_3 AND T_4 LEVELS (nmol/L) OF TWO FOALS AFTER ADMINISTRATION OF TSH

Foal #	Parameter	Baseline	Hours After TSH 1	24	48	72	96
3	T_3	9.0	9.2	11.0	11.0	10.8	—
	T_4	101.7	101.7	74.6	68.2	68.2	—
12	T_3	4.1	4.9	4.0	3.0	3.4	3.2
	T_4	52.8	60.0	61.8	30.9	39.9	47.6

tion are listed in Table I. Ten of the fourteen cases had serum T_3 and/or T_4 concentrations that were judged to be abnormally low. In two of these cases T_3 and T_4 concentrations were within normal limits. The results of a TSH response test administered to two foals are listed in Table II. In both cases the response to TSH administration was poor.

DISCUSSION

Thyroid disease in the horse has many manifestations, including myopathy, decreased endurance, dullness, lethargy, rough hair coat, retarded growth, myxedema and reduced cold tolerance (9-12). Congenital or neonatal hypothyroidism has also been described, either as a sequel to grossly excessive iodine intake or as a disease of unknown cause, although often suspected to be dietary (13-17). Classically, affected foals are born dead or weak, with contracted tendons, poor muscle development, defective skeletal development, hirsutism and goiter. A syndrome of ruptured common digital extensor tendons, mandibular prognathism, forelimb contracture, angular limb deformities and immature carpal and tarsal bones has been described (9). These lesions are associated with severe hyperplasia but without gross enlargement of the thyroid gland, emphasizing the need for microscopic evaluation in suspected cases. Furthermore, thyroidectomy of neonatal foals causes severely retarded development of carpal and tarsal bones (18).

Thyroid hormone levels of adult horses of various breeds and sexes have been reported (19-24) and the total and free serum T_3 and T_4 concentrations of normal foals of various ages are established. These levels are remarkably high at birth and decrease rapidly during the first few months of life (1). The neonatal foal has, in fact, thyroid hormone concentrations higher than any studied species in any physiological state. These findings have made interpretation of foal serum hormone levels possible, but despite an increasing awareness of equine neonatal hypothyroidism, reports of serum T_3 and T_4 levels in affected foals are rare (25-27).

Radioimmunoassay techniques for thyroid hormones have largely replaced outmoded methods such as protein-bound iodine determinations. Since results from different laboratories are variable, reference values should be established for each laboratory or at least determined to fall in the range of published normals. During this study clinically healthy foals and adult horses of various ages from the same geographic area were assayed and thyroid hormone values found to fall within the range of previously published data (1) which is listed as the normal values in Table I. Samples from healthy foals on the same premises would have been preferable as controls but were not available.

In this study, cases were selected by the presence of congenital or neonatal muscoloskeletal lesions (Table I). Evaluation of hormone levels revealed ten of the fourteen cases to have abnormally low T_3 and/or T_4 total serum concentrations as judged by comparison to previously published data (1) and to normal foals and horses. Precise knowledge of the foal's age was necessary to allow this comparison due to the rapid postnatal fall in hormone concentrations. Although total serum T_3 and T_4 concentrations are less reliable than free serum concentrations for direct estimation of tissue hormone status (28,29), in most cases the hormone concentrations of these foals were extremely low, lending confidence to their interpretation. Thus, the findings of low thyroid hormone concentrations in these foals with multiple congenital lesions offers strong circumstantial evidence of hypothyroidism. Further, six of these ten foals with subnormal T_3 and/or T_4 concentrations were necropsied, revealing severe thyroid hyperplasia in five. This lesion is an indication of chronic thyroid stimulation by thyroid stimulating hormone (TSH) in response to low thyroid hormone concentrations. Finally, a TSH-response test administered to two foals revealed poor response with minimal or no increase in postinjection T_3 and T_4 concentrations, even though one of the foals had resting hormone concentrations within the normal range. This emphasizes the value of the TSH-response test and illustrates the pitfalls of interpreting single hormone concentrations alone. The expected response in normal foals is a two to fourfold increase in T_4 concentration by 24 hours after intramuscular or subcutaneous injection of 15 I.U. of TSH (11,17,26). Triiodothyronine concentrations rise quickly to peak at three hours, and return to near baseline levels by 24 hours (30). A test protocol using intravenous TSH and shorter sampling intervals has been reported recently (31).

Two of the ten foals had low T_3 but normal T_4 concentrations. Both foals had severe hyperplastic goiter at necropsy. This may emphasize the importance of T_3 as the biologically active form of the hormone, whereas T_4 may have very limited biological activity (1,28). Also, some studies on the importance of T_3 and T_4 in feedback inhibition of TSH secretion have suggested that T_3 is the more important suppressor of TSH secretion, although T_4 definitely plays a role as well (32). However, since drugs and nonthyroidal illnesses may cause a decrease in T_3 concentrations, (the euthyroid sick syndrome in humans) measurement of T_3 alone is of questionable value (28). In such cases peripheral conversion of T_4 to T_3 may be inhibited, perhaps related to relative or absolute malnutrition (33). Weight loss or malnutrition has been associated with low serum T_3 concentrations (34,35).

Four foals had normal T_3 and T_4 serum concentrations despite the presence of lesions previously associated with hyperplastic goiter. This may be because during the development of most tissues there is a period during which deprivation of thyroid hormones leads to developmental defects which may first appear weeks or months later, by which time thyroid hormone levels may have returned to normal (29). Thus, the developmental lesions of hypothyroidism are often observed during periods when thyroid hormone concentrations are normal. One of the four foals was euthanized and necropsied, revealing typical thyroid hyperplasia. The presence of hyperplastic goiter in conjunction with normal hormone concentrations may be explained in a similar manner. A decrease in circulating hormone levels causes TSH secretion from the pituitary and resultant stimulation of the thyroid epithelial cells. If this TSH

stimulus remains over a period of time, microscopic thyroid hyperplasia occurs. Thus histopathological changes and goiter occur in chronic hypothyroidism and since they regress slowly they will often remain when developmental lesions become detectable, even though T_4 has returned to normal (29).

The findings in this study support the association of hypothyroidism and congenital musculoskeletal lesions that have been described for many years (2,3,5,6,9,26,36,37), although similar lesions may have other causes (7). These lesions include angular limb deformities forelimb contracture, ruptured common digital extensor tendons, mandibular prognathism and skeletal hypoplasia, alone or in combinaton. Their presence should alert the clinician and pathologist to the possibility of hypothyroidism.

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