Thyroid dysfunction and iodine deficiency in a miniature jenny associated with neonatal congenital hypothyroidism dysmaturity syndrome

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Abstract

A 7-year-old miniature donkey jenny with a history of stillborn foals in 2012 and 2013 delivered a miniature jack foal with congenital hypothyroidism dysmaturity syndrome in 2014. Thyroid dysfunction in the jenny was suspected, therefore, a thyrotropin releasing hormone stimulation test and mineral panel assessment were performed, which revealed an inadequate tetraiodothyronine response (10 nmol/l; reference range: 19.8 - 48.3 nmol/l) with low serum iodine (0.009 ppm; reference range: 0.02 - 0.049 ppm) and hair selenium concentration (0.42 ppm; reference range: 1.0 - 3.0 ppm). These findings were compatible with primary hypothyroidism due to iodine deficiency. The jenny was grazed on a pasture containing mustard plants *(*flixweed*: Descurainia sophia;* stinkweed*: Thlaspi arvense;* and wild mustard*: Brassica keber*[1]*),* which contain glucosinolates; their major metabolites can interfere with iodine uptake or organification, causing thyroid dysfunction. The jenny's hypothyroidism and iodine deficiency were identified as the underlying cause of congenital hypothyroidism dysmaturity syndrome in the miniature jack foal.

Background

Congenital hypothyroidism dysmaturity syndrome (CHDS) in foals was first described in Western Canada in 1980.[2] Affected foals had multiple musculoskeletal abnormalities, a grossly normal or slightly visibly enlarged thyroid gland and histologic evidence of thyroid hyperplasia, small follicles and minimal colloid.[2] The syndrome includes: prolonged gestation, hypothermia, severe musculoskeletal abnormalities (mandibular prognathism, contracted tendons, rupture of the common digital extensor tendons, and carpal and tarsal bone dysgenesis) and functional and histologic thyroid abnormalities (including hyperplasia).[3] Severe cases of CHDS are usually euthanized due to an inability to stand at birth, sepsis and developmental orthopedic conditions, e.g. tarsal crush syndrome.[4] Risk factors for CHDS in equids include inadequate mineral intake, exposure to nitrates and consumption of wild mustard plants such as flixweed *(Descurainia Sophia),* stinkweed *(Thlaspi arvense),* wild mustard *(Brassica keber)* or more commercial types of mustard plants known as *Brassica juncea (*Brown and Oriental mustard*)* or *Sinapis Alba* (Yellow mustard*),* the most common mustard plants in Western Canada.[1,5,6] However, exact etiopathogenesis of CHDS remains unknown, hampering management to prevent the condition.

Thyroid dysfunction was reported in donkeys including a report describing 10 adult donkeys with hypothermia.[7] Seven of these 10 were euthanized due to poor prognosis; 4 of 5 had histologic thyroid abnormalities similar to thyroid abnormalities of foals with CHDS.[7] However, none of the donkeys underwent thyroid function testing through assessment of triiodothyronine (T_3) and tetraiodothyronine (T_4) concentrations or thyrotropin releasing hormone (TRH) stimulation tests.[7] Serum thyroid hormone concentrations were higher in donkeys than horses.[8,9]

Case presentation

A 7-year-old miniature donkey jenny with a history of stillborn foals in 2012 and 2013 of unknown cause was maintained on a pasture containing mustard plants from spring through fall. She was fed grass hay and oats in winter and had access to blue (cobalt iodized: iodine 100 ppm and cobalt 120 ppm) and brown (trace minerals: zinc 4000 ppm, iron 1600 ppm, manganese 1200 ppm, copper 350 ppm, iodine 100 ppm and cobalt 50 ppm) salt blocks. She was bred on pasture and was considered a few weeks overdue for foaling according to the owner's observations. She foaled on December 9, 2014 with no complications. The jack foal was examined by a veterinarian shortly after birth and a moderate bilateral

carpal contracture diagnosed. The foal was able to stand and nurse within a normal time frame. In addition, due to apparent hypothermia, the foal was placed under heat lamps for a few hours after birth.

Two weeks after birth, flexural limb deformities of the forelimbs were evaluated and a persistent bilateral contracture and carpal valgus diagnosed (Figure 1). Both front legs were splinted and it was recommended that carpal and tarsal radiographs be done to evaluate the angular limb deformity.

At 1 month of age, the foal was presented for physical examination and carpal and tarsal radiographic evaluation. On presentation, the foal was hypothermic and noted to have moderate bilateral carpal contracture with no rupture of the common digital extensor tendons, bilateral carpal valgus deformity and mild tendon laxity of both hindlimbs (Figure 2). A dorso-palmar image of the left carpus and latero-medial image of the left tarsus (Figure 3) were obtained. Major findings were: moderate carpal valgus deformity of the left carpus with approximately 25° degree of angulation (mild: 5 - 10°; moderate: 15 - 25° and severe: >25°) with concurrent grade II/IV incomplete ossification of the left carpal and distal tarsal bones. There was evidence of compression and/or crushing of carpal and tarsal bones due to inadequate load distribution across tarsal and carpal joints.

A complete blood count and chemistry panel were done; the most remarkable findings were: neutrophilia with 10.98 x 10^9/l (reference values: 2.50 - 6.90 x 10^9/l), elevated aspartate aminotransferase (AST) at 866 u/l (reference values: 0 - 228 u/l) and increased gamma-glutamyl transpeptidase (GGT) at 101 u/l (reference values: 0 - 71 u/l). Six weeks later, the foal developed severe respiratory signs compatible with pneumonia and was euthanized.

Due to the miniature jenny's reproductive history of 2 previously stillborn foals and clinical signs of her most recent foal compatible with CHDS, a series of tests were performed to characterize her thyroid function and to determine if dietary risk factors for CHDS were present (i.e. low trace mineral status, exposure to nitrates or glucosinolates [GSL]).

A TRH stimulation test[10] was performed on the jenny 1.5 months after foaling; serum T_3 and T_4 concentrations were determined (Siemens, Immulite assay, Endocrine Laboratory, Prairie Diagnostic Services, Saskatoon, SK, Canada) before and after 0.5 mg TRH (Sigma Chemical Corp., St. Louis, MO) was given IV. Serum samples were submitted for evaluation of vitamin E, trace minerals[11] (Toxicology Laboratory, Prairie Diagnostic Services), and serum iodine (Animal Health Laboratory, Guelph, ON, Canada). A mane hair sample was submitted for selenium concentration (Colorado State University Veterinary Diagnostic Laboratory, Fort Collins, CO).

Serum cobalt (0.928 ppm) and selenium (0.108 ppm) concentrations were within normal limits (Table). Hair selenium (0.42 ppm) and serum iodine (0.009 ppm) concentrations were deficient. Serum T_3 concentrations were 1.83 and 4.05 nmol/l before and after TRH treatment, respectively. Serum T_4 concentrations were 10 nmol/l both before and after TRH treatment.

Outcome

The miniature jenny was moved to another pasture containing no mustard plants and the owner provided additional mineral supplementation. She was bred in 2015 and foaled a normal foal the following year.

Discussion

In primary hypothyroidism, the thyroid is incapable of responding to stimulation of TSH or TSH with elevated concentrations of TSH. In secondary hypothyroidism, secretion of TRH or TSH is inadequate and is characterized by lower TSH concentrations. Ingestion of goitrogenic plants and deficiency of iodine or its excess are the main causes of primary hypothyroidism.[10,12] Although primary hypothyroidism in adult horses is rare, in foals it occurs in a specific geographic region in western Canada and recognized as congenital hypothyroidism dysmaturity syndrome (CHDS).[2,3] It is characterized by thyroid hyperplasia and severe musculoskeletal abnormalities, mandibular prognathism, moderate to severe angular and flexural limb deformities and incomplete ossification of carpal/tarsal bones.[2,3] Normally, tarsal and carpal bones ossify in the last 2 to 3 months of pregnancy and the process of endochondral ossification starts centrally within the tarsal/carpal bone and continues to the periphery.[13]

There is a grading system, based on radiographic evidence of ossification: grade I: no evidence of ossification of majority of cuboidal bones of the carpus and tarsus; grade II: all cuboidal bones have some evidence of ossification with rounded shape, however, the proximal physis of the third metacarpus/metatarsus is open; grade III: all cuboidal bones are ossified with rounded edges and small in size with increased joint space, but the proximal metacarpal/metatarsal physis is closed and grade IV refers to all cuboidal bones ossified with a cuboidal shape and wider joint spaces.[13] In this case, incomplete ossification of the carpal cuboidal bones (grade II/IV) and rounded edges of the incompletely ossified distal tarsal bones were evident (Figure 2). Unrestricted exercise with angular limb deformities and/or incomplete cuboidal ossification increased probabilities of compression of tarsal and carpal bones, a possibility in this case. Compression and/or crushing of the carpal and tarsal bones in this case were attributed to inadequate distribution of weight across tarsal and carpal joints.

Increased AST without an elevation in creatinine kinase may suggest hepatocellular leakage, whereas GGT in association with elevated AST may be linked to inflammation or hyperplasia of biliary ducts. Perhaps hepatobiliary damage and GSL increased these enzymes, although we do not have clear evidence to support this finding. Regardless, prolonged gestation, hypothermia, contracted flexor tendons, angular limb deformity, and carpal and tarsal osseous dysgenesis meet the case definition for CHDS.

A main risk factor for CHDS is ingestion of endocrine disrupters during pregnancy, e.g. GSL, which are common in the *Brassicae* (mustard) family. Their major metabolites, e.g. isothiocyanates, thiocyanates and oxazolidinethione, can interfere with the uptake and or organification of iodine and subsequently interfere with synthesis of thyroid hormones.[14] Therefore, even if iodine intake is adequate, chronic GSL intake may still produce iodine deficiency or exacerbate an existing iodine deficiency.[14] Higher intake of GSL cause functional iodine deficiency, increase TSH concentrations and the thyroid gland fails to respond to exogenous TSH or TRH.[14]

Donkeys are reported to have higher basal serum concentrations of T_3 (equine reference value: 1.13 ± 0.1 nmol/l) and T_4 (equine reference value: 36.7 ± 2.8 nmol/l) compared to horses.[8] Thus, reference ranges for horses should not be directly applied to donkeys. Postpartum and lactation status can influence circulating thyroid hormones. Higher basal serum T_3 and T_4 concentrations were reported in lactating mares during the first month postpartum compared to nonlactating mares, suggesting higher metabolic rate due to increased energy consumption.[15] In addition, serum and milk TSH concentrations significantly increase after foaling, decrease over time and reach nadir concentrations at ~ 60 days postpartum in mares,[16] which coincides with increased thyroid hormone secretion.[15] Likewise, serum and milk leptin concentrations increased after foaling and declined at 60 days post-partum.[15] In rodents, leptin directly stimulated thyroid hormone synthesis and enhance iodine transfer through the milk during early lactation.[17]

Failure of T_4 to increase following TRH injection was compatible with thyroid dysfunction. Lower concentrations of selenium and cobalt suggested inadequate dietary mineral intake. The owner reported the presence of mustard plants in the field where the jenny grazed and that she had been observed consuming them, consistent with lower basal T_4. Mean serum iodine concentrations were lower in this miniature jenny (0.009 ppm) compared to the reported mean level of 0.214 ppm.[9] Selenium is also involved in thyroid function, as it is necessary for formation of important selenoproteins such as glutathione peroxidase and tissue deiodinases,[18] which regulate conversion of T_4 into the more metabolically active thyroid hormone, T_3 in tissues unable to capture circulating T_3. Thus, severe selenium deficiency can decrease T_3 availability to peripheral tissues, despite a normal hypothalamic-pituitary-thyroid axis.[19]

Normal function of the maternal hypothalamic-pituitary-thyroid axis and adequate concentrations of trace minerals (e.g. iodine and selenium) during pregnancy are essential for normal fetal development, especially growth and maturation of the musculoskeletal system and brain. In humans, effects of severe thyroid hormone deficiency in newborns, secondary to an inadequate supply of iodine during pregnancy, can be irreversible and include: cognitive and motor defects, hearing and speech defects and growth retardation (termed neurological cretinism).[20] Furthermore, depending on the mammalian species and type of placentation, placental transfer of maternal thyroid hormones has an important role in concentrations of

T_3 and T_4 in fetal circulation in early pregnancy. In the second trimester, development of the fetal thyroid gland is complete, which coincides with functional development of the fetal hypothalamo-pituitary-thyroid axis; at this time, the fetus is capable of secreting thyroid hormones into fetal circulation. In addition, placental iodide transfer from maternal to fetal circulation is of great importance for thyroid hormone synthesis; therefore, normal production of thyroid hormones by the fetal thyroid depends on maternal iodine uptake and transport through the placenta.[21] Hence, iodine deficiency caused by inadequate dietary intake or environmental endocrine disruptors (GSL compounds) affecting the thyroid gland and iodine uptake can lead to maternal thyroid dysfunction affecting fetal growth and maturation. We concluded the underlying cause of the CHDS in the jenny's foal was iodine deficiency; consumption of mustard plants likely affected the jenny's ability to store iodine, synthesize thyroid hormone and supply adequate amounts to her fetus.

Learning points

- Primary hypothyroidism is present in some adult donkeys.
- Iodine deficiency can be present in jennies.
- Equid dams delivering CHDS foals should be evaluated to determine if maternal iodine and selenium deficiencies are present.
- GSL present in the diet can disrupt thyroid function.
- Changing mineral supplementation practices and removing or minimizing exposure to endocrine disruptors, e.g. GSL, may improve reproductive performance.

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Figure 1. 23 day old miniature jack foal with bilateral carpal contracture.

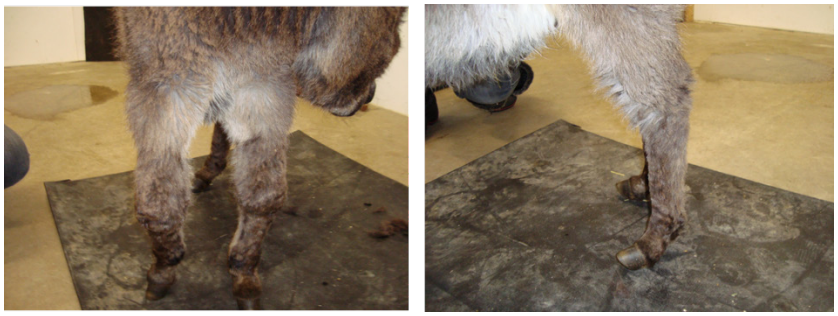

Figure 2. Miniature jack foal at 1 month of age. Note bilateral carpal contracture and angular limb deformity in the image on left and bilateral tendon laxity and hyperextension of the hind digits in the image on right.

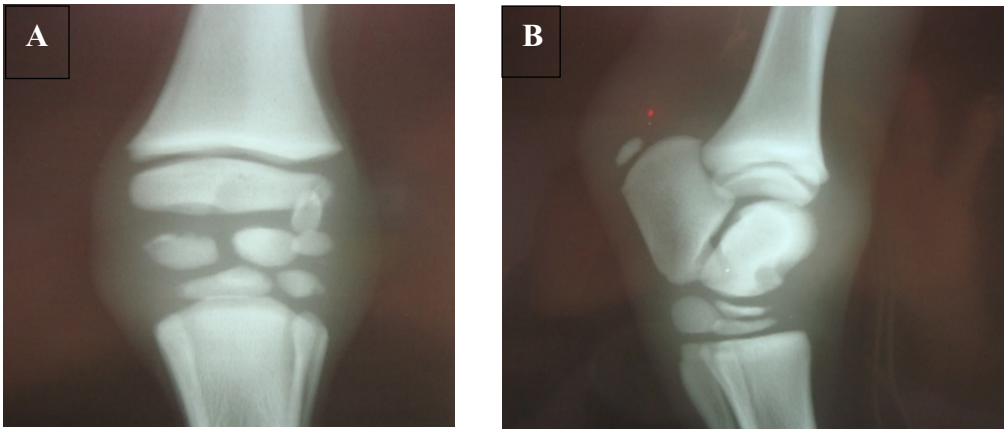

Figure 3. Dorsopalmar view of the left carpus (A) and lateral view of the tarsus (B) of miniature jack foal at 1 month of age. Note incomplete ossification of the carpal cuboidal bones (grade II/IV) and rounded edges of the incompletely ossified distal tarsal bone.

Table. Concentrations of trace minerals, vitamin E and basal thyroid hormones in serum, and selenium in hair of miniature donkey jenny.

Trace minerals	Result	Units	Reference range
Magnesium	22.6	ppm	18 – 35
Manganese	0.006	ppm	0.006 – 0.07
Iron	1.98	ppm	0.084 – 2.57
Cobalt	0.928	ppm	0.90 – 15.0
Copper	1.25	ppm	0.5 – 2.0
Zinc	0.723	ppm	0.47 – 1.70
Selenium	0.236	ppm	0.14 – 0.25
Molybdenum	0.010	ppm	< 0.1
Iodine	0.009	ppm	0.02 – 0.049
Selenium (Hair)	0.42	ppm	1.0 – 3.0 (> 7.0 toxic)
Vitamin E	2.90	ppm	>2 (>4 high)
Thyroid hormones			
Triiodothyronine (T_3)	1.83	nmol/L	1.13 ± 0. 1 (0.76 – 2.0)
Tetraiodothyronine (T_4)	10	nmol/L	36.7 ± 2.8 (19.8 – 48.3)