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Thyroid hormone concentrations in foals affected by perinatal asphyxia syndrome

Alessandro Pirrone [a,*], Sara Panzani [b], Nadia Govoni [a], Carolina Castagnetti [a], Maria Cristina Veronesi [b]

[a] Department of Veterinary Medical Sciences, Università di Bologna, Bologna, Italy
[b] Department of Health, Animal Science and Food Safety, Faculty of Veterinary Medicine, Università degli Studi di Milano, Milan, Italy

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ABSTRACT

The hypothalamus-pituitary-thyroid axis has specific functions, mostly related to metabolic activities, cell differentiation, and development. To the authors' knowledge, there are no studies about thyroid hormone (TH) concentrations in foals affected by perinatal asphyxia syndrome (PAS). Hence, the aims of the study are (1) to evaluate plasma TH concentrations (T_3 and T_4) in healthy foals during the first 7 days of life; (2) to evaluate plasma TH concentration (T_3 and T_4) in critically ill foals affected by PAS during the first 7 days of hospitalization; and (3) to compare TH concentrations between surviving and nonsurviving critically ill foals. Forty-five Standardbred foals were enrolled in this prospective observational study: 21 healthy foals (group 1) and 24 foals affected by PAS (group 2). Jugular blood samples were collected within 10 minutes from birth/admission and every 24 hours for 7 days (t0–t7). TH concentrations were analyzed by RIA. In both groups, T_3 concentration was significantly lower at t4, t5, t6, and t7 compared with t1 ($P < 0.05$), and T_4 concentration was significantly higher at birth than at all other time points ($P < 0.01$). No differences were found in TH concentrations at admission between surviving ($n = 20$) and nonsurviving ($n = 4$) foals. Statistical comparison between healthy and PAS foals divided into age groups showed significantly lower TH concentrations at t0 in PAS foals <12 hours old at admission ($P < 0.01$). In conclusion, PAS may cause lower T_3 and T_4 concentrations in affected foals than in age-matched healthy foals, as reported for other systemic illnesses, such as sepsis and prematurity. TH concentrations showed no prognostic value, which maybe due to the small number of nonsurviving foals in this study. Further studies are needed to find out if thyroid replacement therapy could be useful in the treatment of critically ill foals affected by PAS.

1. Introduction

The hypothalamus-pituitary-thyroid (HPT) axis has specific functions, mostly related to metabolic activities, cell differentiation, and development [1]. In addition to its effects on energy metabolism, thyroid hormones (THs) are essential for both prenatal and postnatal developmental events including organ formation and skeletal maturation [2].

In healthy full-term human neonates at birth, Glinoer et al. [3] reported normal free T_4 and low free T_3 concentrations compared with adults; thyroid-stimulating hormone (TSH) consistently increased during the first 24 hours of life, and an abrupt rise of T_3 and T_4 concentrations was observed. Kratzsch and Pulzer [4] reported that T_4 feedback inhibition caused a TSH decrease from Day 3 or 4 of age.

In newborn foals, THs are essential for normal organ development and growth, and, as it might be expected, deficiencies result in more significant clinical problems in foals than in adults [5]. In horses, serum TH

* Corresponding author. Tel.: +390512097587; fax: +390512097568.
E-mail address: alessandro.pirrone2@unibo.it (A. Pirrone).

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concentrations are much higher in neonates than adults, slowly decreasing to adult concentrations over the first weeks of life [6–8].

Premature human babies have an immature HPT axis, and they show lower T_4 levels than full-term neonates; T_4 concentration is correlated with gestational age and birth weight [9]. Septicemia is also indicated as a cause of low TH concentrations in newborn babies [10]. Low TH levels in human babies are also correlated with respiratory distress syndrome [11] and asphyxia [12]. Perinatal asphyxia triggers several systemic alterations, including a rapid increase in the concentration of some hormones [13,14], but few studies have been conducted on the effect of perinatal asphyxia on TH concentrations [12,15]. The more recent study found significantly lower levels of TSH, T_4, and T_3 in asphyxiated human newborns compared with controls, suggesting a central hypothyroidism secondary to asphyxia [15].

Low TH levels have been measured also in sick foals with noncritical conditions [16–19]. Irvine [20] suggested that the decrease in metabolism reported in sick foals, which results in inadequate thermogenesis and lethargy, may be due to a circulating TH deficiency; furthermore, the severity of the symptoms was related to the severity of hormone deficiency.

Dysfunction of the thyroid gland has been reported in foals born from mares grazing endophyte-infected fescue [19] and in foals with congenital hypothyroidism/goiter [17,21]. In a recent study, a lower concentration of TH was found in sick foals affected by varying pathologies compared with healthy foals [22].

Information about the HPT axis and TH concentrations in critically ill foals is lacking. Total T_4, total T_3, free T_4, and free T_3 levels were lower in septic foals when compared with sick nonseptic foals and healthy foals, and these concentrations were even lower in nonsurviving septic foals [23]. Similar results were reported in premature foals, which had low TH levels and an exaggerated TSH response to TRH [8,24].

To our knowledge, there are no studies about TH concentrations in foals affected by perinatal asphyxia syndrome (PAS). This syndrome is a relatively common neonatal disorder that can result from any event that impairs oxygen delivery to cells occurring prepartum, intrapartum, or during the early neonatal period. Asphyxia triggers varying degrees of multisystemic effects, with renal, gastrointestinal, cardiopulmonary, endocrine, and neurologic symptoms [25]. Despite the clinical relevance of this syndrome, most information regarding the pathophysiology of this disease is directed at infants, and equine-specific information is exceedingly sparse [26].

Hence, the aims of the study are (1) to evaluate plasma TH concentrations (T_3 and T_4) in healthy foals during the first 7 days of life; (2) to evaluate plasma TH concentrations (T_3 and T_4) in critically ill foals affected by PAS during the first 7 days of hospitalization; and (3) to compare TH concentrations between surviving and nonsurviving critically ill foals. We hypothesize that TH concentrations will be lower in PAS foals than in age-matched healthy foals and that survivors will show higher TH concentrations than nonsurvivors.

2. Materials and methods

2.1. Animals

Forty-five Standardbred foals, born during the 2010 and 2011 breeding seasons, were enrolled in this prospective observational study: 21 healthy foals (group 1) and 24 foals affected by PAS (group 2).

Foals included in group 1 were born on a Standardbred breeding farm in Northern Italy. The foals were classified as healthy when they had an Apgar score $\geq$9 [27], a normal clinical evaluation during the period of study, including a complete blood count and serum biochemistry at birth and an IgG serum concentration $\geq$800 mg/dL at 18 to 24 hours of life.

In clinically healthy foals, jugular venous samples for TH measurements were obtained within 10 minutes of birth (t0) and every 24 hours until 7 days of life (t1–t7). Blood was collected into heparinized plastic vials (S-Monovette; Sarstedt), and the sample was delivered to the laboratory within 30 minutes of collection. After centrifugation at 2200 $\times$ g for 10 minutes, all samples were stored at -20 °C and analyzed within 2 months after collection.

Foals included in group 2 were referred to the neonatal intensive care unit after birth. The inclusion criterion for group 2 was the diagnosis of PAS requiring level 2 or 3 of intensive care on the basis of the classification proposed by Koterba [28]. Level 2 care is provided to neonates that are quite severely affected; foals may be unable to stand or unable to nurse from the mare and need round-the-clock care; this level of care usually involves separation of the foal from the dam. Level 3 care is intended for extremely compromised foals that usually have multisystem dysfunction, need round-the-clock care, and must be assisted by specialists.

Foals were classified as affected by PAS on the basis of history and clinical signs, especially those of neurologic dysfunction [29] and exclusion of other neurologic diseases such as meningitis or trauma. Typical historical events included dystocia, red bag, or avillous placenta, and common clinical signs included loss or absence of the suck reflex, inappropriate teat-seeking behavior, dysphagia, seizures, hyperreactivity, and weakness associated with an elevated serum creatinine concentration at less than 24 hours of age [30]. Foals affected by PAS and other pathologies (i.e., sepsis, prematurity, neonatal isoerythrolysis) were excluded from the study. All foals of group 2 received a complete and standardized clinical evaluation at admission. Venous jugular blood was also collected for hematobiochemical evaluation and for blood culture. Serum IgG concentration was measured when the foals were at least 18 hours of age (SNAP Foal, IDEXX, Milano, Italy).

In group 2, plasma TH concentrations were measured at admission (t0) and every 24 hours during the first 7 days of hospitalization (t1–t7). Blood was collected into heparinized plastic vials (S-Monovette; Sarstedt), and the sample was delivered to the laboratory within 30 minutes of collection. After centrifugation at 2200 $\times$ g for 10 minutes, all samples were stored at -20 °C and analyzed within 2 months after collection.