FACULTY OF VETERINARY MEDICINE
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Causes and treatment of Neonatal Maladjustment Syndrome and review of the Madigan Foal Squeeze Procedure

Word count: 13.429

Eline Zonneveld
Student number: 01404479

Supervisor: Prof. Dr. Catherine Delesalle
Co-supervisor: Drs. Berit Boshuizen

A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of Master of Veterinary Medicine

Academic year: 2019 - 2020

GHENT UNIVERSITY

Preface

As long as I can remember I've had the dream to become a veterinarian and with finishing this thesis I'm one step closer to that dream. I would never have accomplished writing this thesis without some very important people in my life. First I would like to thank my parents, who have supported me, not only financial, but also in stimulating me to always reach a step further than I thought I could. I would like to thank my brother, he had to endure me being stressed about writing this thesis for more than a year, something that must not be taken too lightly. I never could have started this thesis without the support of Prof. Dr. Catherine Delesalle and would like to thank her for introducing me to her research team, giving me the chance to investigate this subject. Drs. Berit Boshuizen gave me so much of her scarce time and was always available to answer my questions and make improvements to my work. I would not have been able to write this thesis without her guidance. I would like to thank Prof. Dr. John Madigan for providing me with information and illustrations which added great value to my thesis. I would like to thank my fellow students, Sjoerd Vissers and Ir. Monica Verschuur, who have read this thesis many times, taking out mistakes and giving me ideas about how to write certain sentences, always encouraging me to go on. At last I want to thank everyone else involved in the process of writing this thesis. In the past two years, I have learned how to read scientific papers, how to conduct my own research and how to write about a subject that can be discussed endlessly.

Table of Contents

List of abbreviations

ACTH = Adrenocorticotropic hormone
ATP = Adenosine triphosphate
BW = Body weight
CPAP = Continuous positive airway pressure
CR = Capillary refill
CRI = Constant rate infusion
DMSO = Dimethyl sulfoxide
eCG = Equine chorionic gonadotropin
FPT = Failure of passive transfer
GABA = γ-amino-butyric-acid
HBOT = Hyperbaric oxygen therapy
HIE = Hypoxic-ischemic encephalopathy
HPA axis = Hypothalamic-pituitary-adrenal axis
IgG = Immunoglobulin G
IM = Intramuscular
IV = Intravenous
MFS = Madigan foal squeeze
NMDA = N-methyl-D-aspartate
NMS = Neonatal maladjustment syndrome
NSAID = Non-steroidal anti-inflammatory drug
PAS = Perinatal asphyxia syndrome
PGD2 = Prostaglandin D2
PO = Per oral
Q 12h = Every 12 hours
Q 24h = Every 24 hours
SIRS = Systemic inflammatory response syndrome

Abstract

Neonatal maladjustment syndrome (NMS), Perinatal Asphyxia Syndrome (PAS) or Hypoxic-Ischemic Encephalopathy (HIE) describe an ill-defined syndrome in neonatal foals. Hypoxia is thought to be the major causal factor of this syndrome, leading to a multi-organ ischemic failure and brain damage. Yet, 70-80% of the uncomplicated cases survive and this perspective leads to another pathological pathway, a post-natal persistence of inhibited state of the fetal cerebrocortical activity, due to a disturbed withdrawal of inhibitory neuroactive factors, such as adenosine, allopregnanolone, pregnananolone, prostraglandin D2. NMS foals can exhibit a wide range of symptoms, making not only diagnosing difficult, but providing the right treatments too. Choice of therapy depends on the clinical signs the foal displays. Most applied means of medical support consist of tube feeding, antimicrobials, plasma transfusion, intranasal oxygen therapy and fluid administration. To support this review with the latest data, a selection of veterinarians throughout Europe have been invited to take part in a survey. In this survey, they are asked about what medical support they offered NMS foals, as well as the average survival rate in these foals and the use of a thoracic squeeze technique. This so called Madigan Foal Squeeze technique shows promising results in curing some NMS foals suffering from persistent post-natal inhibition. PAS in infants is similar to the syndrome in equine neonates and used therapies in human medicine, such as therapeutical hypothermia and hyperbaric oxygen therapy can have potential value in treating NMS foals, but more research about their clinical relevance has to be done.

Samenvatting

Neonataal Maladjustment Syndroom (NMS), Perinataal Asphyxia Syndroom (PAS) of Hypoxische Ischemische Encefalopathie (HIE) zijn termen die worden gebruikt voor een moeilijk te omschrijven syndroom dat voorkomt bij neonatale veulens. Hypoxie wordt gezien als een van de belangrijkste factoren in de ontwikkeling van NMS, verantwoordelijk voor ischemische schade aan verschillende organen, inclusief de hersenen. Toch overleeft 70-80% van de ongecompliceerde gevallen en dit perspectief leidt naar een andere causale factor, een persisterende post-natale geinhibeerde status van de foetale cerebrocorticale activiteit, door een verstoorde afname van inhiberende neuroactieve factoren, zoals adenosine, allopregnanolone, pregnanolone en prostaglandine D2. NMS veulens kunnen een breed scala aan symptomen vertonen, wat niet alleen het maken van een diagnose bemoeilijkt, maar ook het verschaffen van de juiste behandelingen. Behandeling is afhankelijk van de klinische symptomen die het veulen vertoont. De meest gebruikte medische ondersteuningen zijn sonde voeding, antibiotica, plasma transfusie, intranasale zuurstof therapie en vocht toediening. Om dit overzicht te ondersteuenen met de nieuwste cijfers, zijn een selectie van dierenartsen verspreid in Europa uitgenodigd om deel te nemen aan een enquête. In deze enquête werd hen gevraagd welke medische ondersteuning zij het vaakst bieden aan NMS veulens, als ook de gemiddelde overlevingskans van deze veulens en over het gebruik van een ‘squeeze’ techniek. Deze techniek wordt de Madigan Foal Squeeze techniek genoemd en laat veel belovende resultaten zien in de genezening van NMS veulens die lijden aan de persisterende post-natale inhibitie. PAS bij kinderen komt overeen met het syndroom in veulens waardoor behandelingen gebruikt in humane geneeskunde een potentiële waarde kunnen hebben in het behandelen van NMS veulens, maar onderzoek naar de klinische relevantie moet nog worden gedaan.

1. Introduction

Being able to stand and walk shortly after birth is a lifesaving development in new born foals. Foals that don't gain this ability or experience delay in their development are at risk of not surviving their first days. The first description of foals with altered behavior was done by Reynolds in 1930. Over the years, the syndrome these foals were suffering from became known as Neonatal Maladjustment Syndrome.

Neonatal Maladjustment Syndrome (NMS), also called Hypoxic Ischemic Encephalopathy (HIE), Perinatal Asphyxia Syndrome (PAS), Barkers or Dummy foal syndrome, is a non-infectious syndrome (Munroe and Weese, 2011) with an incidence estimated at 1-2% (Gold, 2015). Foals affected by NMS are often unable to stand, drink or breathe on their own and suffer from malnutrition and risk of infection in their first days. Around 70-80% of the less severe cases survive (Bernard et al., 1995; Vaala, 1999; Vaala, 2002) after receiving a combination of supportive and medical care, whereas for the complicated cases a survival rate of less than 50% is described (Hess-Dudan and Rossdale, 1996). For human neonates suffering from PAS, a mortality rate of 20% is reported (Antonucci et al., 2014), but numbers vary between different rapports. In human infants, 25% of the survivors of PAS show some form of neurological impairment varying from decreased learning capacity to behavioral problems (Vannucci, 1990; Antonucci et al., 2014).

One of the most important factors in the development of NMS is hypoxia. This hypoxia can occur prepartum, during the partus or postpartum and can be caused by different factors (maternal, placental, fetal, dystocia and more). The effect of this hypoxia is complex and involves multiple organ systems. Due to the lack of oxygen, the sympathetic adrenergic nervous system is activated and the little oxygen that is present is redirected to the central organs (i.e., brain, heart and adrenal glands) (Vaala, 1999). This causes a more severe lack of oxygen in the other organ systems, which can lead to (multiple) organ failure. If this redirection is insufficient, brain injury may occur, causing neurological symptoms. Another period of cell damage occurs during the reperfusion of oxygen deprived tissues, as oxygen free radicals are released, followed by an inflammatory reaction (McSloy, 2008).

Until recently, hypoxia had been presumed to be the main cause of NMS. However, Aleman et al. (2017) have detected the presence of neuroactive steroids that may cause the alteration in behavior of the affected foals. They are conducting research with the hypothesis that a NMS foal is troubled in the transition from intrauterine inactivity to extrauterine consciousness, with physical compression during normal birth playing a role in the activation. Intrauterine inactivity is thought to be induced by a combination of several factors, some of which are inhibitory neurosteroids, such as adenosine, allopregnanolone, pregnanolone and prostaglandin D2. Combined with warmth, buoyancy and cushioned tactile stimulation this can cause a state of *in utero* somnolence (Aleman et al., 2017). In some foals, these neuroinhibitory effects persist after birth and are believed to be, at least partially, responsible for the altered consciousness of the NMS foal (Aleman et al., 2013).

Apart from the aforementioned hypoxemia and postnatal persistence of an inhibited fetal state of cerebrocortical function, there are other factors associated with developing NMS as well. These include meningitis, central nervous system hemorrhage or edema, congenital lesions, endotoxins, sepsis, *in utero* infections and metabolic insults (Diesch and Mellor, 2013) with a wide variety of clinical signs.

Foals presented with NMS are typically divided into two groups: (1) normal, healthy-born foals that develop symptoms between 6-24 hours after birth. These foals are born full-term and have a normal suckingreflex; and (2), foals that show clinical signs directly at birth, with changed reflexes and aberrant

mentation (Munroe and Weese, 2011). Clinical signs of NMS include: no affinity for the mare, inappropriate or absent nursing behavior, hypothermia, aimless wandering, stargazing and a stuporous to comatose state. Seizures are often reported and can be partial, with facials spasms, or more extensive, with convulsions, blindness and circling. As a result of redirecting the blood flow to the central organs, the gastrointestinal and urinary tract may show signs of hypoxic damage (Vaala, 1999). As foals do not receive any antibodies through the placenta, they are immunologically naïve at the moment of birth and need to ingest colostrum (Naylor, 1979). The uptake of antibodies from colostrum is at its peak during the first six hours after birth (Kalinbacak et al., 2005). Foals with NMS often cannot or do not drink enough if any colostrum, causing a deficit in circulating antibodies, leaving the foals susceptible to infections.

With a lack of pathognomonic tests, a diagnosis can be made based on the clinical signs, a possible history of problems during the pregnancy or birth and exclusion of differential diagnoses. Some possible differential diagnoses include: sepsis, bacterial meningitis, hypoglycemia, brain or spinal trauma, Equine herpes virus 1 or white muscle disease (nutritional myodegeneration) (Drummond, 1988; Galvin and Collins, 2004; Gold, 2017).

Management of foals suffering from NMS consists of a wide range of supportive treatment and medical care like antioxidant therapy, seizure control, respiratory and cardiovascular support, bottle or tube feeding or parenteral nutrition and more. As stated before, these foals are likely to suffer from failure of passive transfer (FPT) which leads to immunodeficiency and may require plasma transfusion to raise the antibody levels.

Ongoing studies about the use of a novel physical compression procedure show promising results in reducing the recovery time in some NMS foals (Aleman et al., 2017). For 20 minutes, sustained pressure is applied to the chest of the foal using a rope, imitating stage II of parturition, which is the expulsion of the foal. In healthy neonatal foals this sustained pressure can induce a state of somnolence, leading to a decrease in respiratory rate, heart rate, and rectal temperature, as well as an increase in dehydroepiandrosterone sulfate, androstenedione and adrenocorticotropic hormone (ACTH) plasma concentrations (Toth et al., 2012). This may be the same response a foal experiences during birth (Toth et al., 2012) and squeezing NMS foals appears to lead to a faster recovery rate (Aleman et al., 2017).

An extensive amount of scientific information is available on the causes and treatment of NMS in foals and the goal of this thesis is to write a state-of-the-art review. This article will include a flowchart with an overview of the first steps in treating NMS foals. This can either be used as an educational tool or in clinical environments as a reference To support this article with the latest numbers of prevalence of NMS in Europe, veterinarians from equine clinics located in Europe will be invited to participate in an electronic survey (**Appendix I and II**). The novel physical compression, or Madigan Foal Squeeze procedure, will be included in this survey. The participants will be asked about usage of this novel physical compression procedure and their success rates. Not much scientific research has been performed on the Madigan foal squeeze making it hard to review the effectiveness of this method. More scientific research on this topic is required.

2. The normal partus and development of the neonatal foal

Mares have a very broad range in gestation length, ranging from 320 to 380 days, with an average of 335 to 342 days (Satué et al., 2011). A longer gestation length can be the consequence of an arrested development during early months of gestation or can be caused by poor uterine quality (Brinsco et al., 2011). A gestation of 300-320 days is considered short and carry the risk of delivering a premature foal or a foal that is nonviable without care (Satué et al., 2011). Many factors influence the length of gestation and these can be divided into maternal, fetal and environmental factors (Meliani et al., 2011). Described maternal factors include breed, age and parity. Colt foals are carried for a longer time than fillies (Davies Morel et al., 2002) and the weight and breed of the foal also influences the gestation length. Nutrition, month of conception and the exposure of the mare to light (photoperiod) are environmental factors that influence the gestation length (Meliani et al., 2011).

In the last month of gestation, the pregnant mare can show various signs of readiness for foaling, such as development of the lower part of the udder, followed by the base, vulvar laxity and edema, relaxation of the sacrosciatic ligaments around the tailhead and filling of the teats (Brinsko et al., 2011b). Closer to parturition, an accumulation of wax can be seen at the teat, the teats start to point outwards and there is a change in the color, mineral composition and pH of the milk (Brinsko et al., 2011b). Signs of readiness for foaling vary enormously between mares, making an accurate prediction of parturition very difficult.

Progesterone is required in establishing and maintaining pregnancy in all mammals, as it inhibits myometrium activity and promotes contraction of the cervix, keeping it tightly closed (Chwalisz and Garfield, 2006). In the first 120 days of gestation, progesterone is produced by maternal tissue, the corpus luteum. Around day 38 of gestation the endometrial cups appear, they are of fetal origin and produce equine chorionic gonadotropin (eCG) (Brinsko et al., 2011a). The exact role of eCG is not clearly known but it plays an important role in sustaining the primary corpus luteum. Together with FSH, originating from the maternal pituitary, eCG stimulates the development of secondary corpora lutea, contributing to the progesterone production (Boeta and Zarco, 2012; Antczak et al., 2013). Regression of the endometrial cups is complete around day 130 of gestation, causing a withdrawal of circulating eCG and a fetoplacental unit starts to produce 5a-pregnanes to maintain the pregnancy (Boeta and Zarco, 2012; Antczak et al., 2013). Progesterone production also stimulates allopregnanolone (5a-pregnane-2a-ol-20-one) production in fetal tissues which has an important role in suppression of the fetal consciousness *in utero* (Diesch and Mellor, 2013; Hirst et al., 2014).
The onset of labor is a result of combined maternal and fetal endocrine activity, with prostaglandin playing a central role. With the increased activity of the fetal hypothalamic-pituitary-adrenal axis (HPA) in the last 24-48 hours before parturition, fetal cortisol concentrations rise, stimulating prostaglandin synthase and prostaglandin E2 production by the placenta and myometrium contractions start (Ousey and Fowden, 2012). A quick maturation of the fetal tissues take place under the influence of the increased HPA axis activity, as well as the onset of colostrum and milk production (Diesch and Mellor, 2013). The endocrinology of pregnancy in the horse is complex and can be read in detail elsewhere (Fowden et al., 2008; Ousey and Fowden, 2012; Tennent-Brown et al., 2015).

Parturition is divided into three stages: preparation, expulsion of the foal and expulsion of the placenta. The first stage of parturition lasts between 30 minutes and 4 hours during which cervical dilatation and reposition of the foal occure, as well as uterine contractions increasing in intensity and frequency. The second stage, the expulsion of the foal, is a shorter process and should last 5 to 20

minutes. During this stage, the chorioallantois ruptures and with a combination of abdominal contraction and release of oxytocin the foal is delivered. The three stages of parturition are described in detail by Brinsko et al. (2011b). A huge transition has taken place for the neonate, from intrauterine protection and dependency to a relatively independent state and a need of rapid onset of development. The first 4 days have been stated as most critical for the neonatal foal, this is a period in which it needs to establish somatovisceral homeostasis (Brinsko et al., 2011c). Development of thermoregulation, the onset of breathing, stabilization of an adequate pulmonary gas exchange and being able to find a new source of nutrients are examples of necessary developments the newborn foal must go through in order to maximize survival chances. A normal respiratory and cardiac rhythm should be established within 1 minute and the foal should be able to stand 1 to 2 hours after partus (Knottenbelt et al., 2004; Brinsko et al., 2011c). Without help, the foal must be able to nurse within 1 to 3 hours (Brinsko et al., 2011c). The most important vital signs for the neonate foal are stated in Table 1.

Table 1. *An overview of vital signs in the neonatal foal*
Knottenbelt et al., 2004; Brinsko et al., 2011c

Normal respiratory and cardiac rhythm	<1 minute after birth
Being able to stand	1-2 hours after birth
Being able to nurse	1-3 hours after birth
Rectal temperature	37.5-38.9°C
CRT	1-2 seconds
Heart rate	40-80 beats/minute immediately after birth
Respiratory rate	75 breaths/minute at birth 35-50 breaths/minute at 1 hour of age

Essential for the immune status of the foal is the uptake of colostrum. Since the equine epitheliochorial pattern of placentation prevents transfer of immunoglubulins *in utero, the* foal is hypogammaglobulinemic and thus immunocompromised at birth (Naylor, 1979). Transfer of immunoglobulin G (IgG) from mare to foal must occur via colostrum uptake, as specialized enterocytes lining the gastrointestinal tract of the neonate foal, which are able to take up immunoglobulins from the lumen via pinocytosis (cell drinking) and transfer them into the bloodstream (Sprayberry, 2003). Foal serum IgG concentration reaches its maximum level approximately 12 hours after birth, with a maximal absorption during the first 6 hours (Burns, 2007; Hofsaess, 2001). After 6-8 hours, the efficacy of the specialized enterocytes begins to decline and are replaced by normal enterocytes after the first day of life (Sprayberry, 2013). This means that after 6-9 hours, sera of healthy foals should contain >8 g/L IgG and those with serum IgG lower than 8 g/L suffer from a partial or total failure of passive transfer (Hofsaess, 2001). To prevent FPT, the foal should absorb at least 1-1,5 litre of colostrum with a IgG concentration of 60 g/L or more (Chavatte and Cash, 1998).

3. Pathogenesis of Neonatal Maladjustment Syndrome

Over the years, various pathological pathways have been described, ranging from hypoxia to postnatal persistence of fetal inhibition as well as other factors such as meningitis, central nervous system hemorrhage or edema, congenital lesions, the presence of endotoxins, sepsis, *in utero* infections and metabolic insults with a wide variety of clinical signs (Diesch and Mellor, 2013). Hypoxia can occur prepartum, during the partus or postpartum and can be of different origins (i.e. maternal, placental, fetal, dystocia and more). Effects of this hypoxia work multisystemic on the gastrointestinal, renal, cardiopulmonary, endocrine and neurological systems (Vaala, 1999). A second period of cell damage occurs during the reperfusion of oxygen deprived tissues, as the formed oxygen free radicals induce inflammatory reactions in the reperfused tissues. A relatively newer theory describes the post-natal persistence of fetal inhibition, with a delayed clearance or increased production of the inhibitory neuroactive factors adenosine, allopregnanolone, pregnanolone and prostaglandin D2 (Aleman et al., 2013). These factors, combined with warmth, buoyancy and cushioned tactile stimulation maintain a physiological intrauterine state of unconsciousness (Aleman et al., 2013). An increased level of inhibition is reached during labor, by compression of the thorax in the birth canal (Aleman et al., 2017). It is suggested that this compression during birth primes the brain to facilitate the onset of arousal with release of stimulating factors such as 17β-estradiol and noradrenaline (Diesch and Mellor, 2013). A combination of withdrawal of inhibitory facters and the increase of 17β-estradiol and noradrenaline as well as new sensory inputs such as cold, the experience of sight and contact with the mare promote the onset of awareness (Diesch and Mellor, 2013).

These different pathways of the development of NMS are not strictly separated, as oxygen status influences the production of neurosteroids (Mellor, 2005). An increase in allopregnanolone production is seen in fetal sheep brains after occlusion of the umbilical cord (Nguyen et al., 2004), as well as a rise in plasma adenosine concentrations during periods of hypoxia (Mellor, 2005).

3.1 Hypoxia

Hypoxic ischemic injury to the brain of the neonatal foal is thought to be one of the major factors in developing NMS. Hypoxemia (too little oxygen in the blood), hypoxia (inadequate supply of oxygen on tissue level) and ischemia (decreased tissue perfusion) are to be distinguished from each other. In case of ischemia, a shift from aerobic to anaerobic metabolism occurs with the production of lactate and oxygen free radicals, shifting intracellular balances to an acidosis and increasing the risk of reperfusion injury (Vaala, 1999).

Hypoxia can occur during the different stages of labor and can be of maternal, placental or fetal origin. Factors that may cause hypoxia in the fetus and neonatal foal are listed in **Table 2**, this list is not limited and combinations of factors are possible. Most of the listed factors alter the uteroplacental perfusion causing interference in the fetal blood and oxygen supply or disrupt normal cardiovascular function of the neonatal foal. Alteration of the uteroplacental perfusion can be seen in the presence of (severe) maternal illness, anemia, hypoproteinemia and endotoxemia (Vaala, 1999). Age and parity related degenerative changes to the endometrium affect fetal and placental development, containing excess fibrous tissue and lymph-filled cysts (Wilsher and Allen, 2012). Competition for the limited space in de uterus between two fetuses in twin pregnancy usually results in one twin overgrowing the other, starving the disadvantaged twin. This leads to its death which can provoke placental separation and abortion of both fetuses (Wilsher and Allen, 2012). Inducing parturition with a range of drugs such as oxytocin or prostaglandins accelerates the normal parturition procedure and can result in dystocia or the delivery of a premature foal when mare and fetus are not ready for birth (Ousey, 2002). If stage II of parturition is prolonged to more than 40 minutes, a significant reduce in vitality of the foal is reported (McCue and Ferris, 2012). Malpresentation is one of the causes of dystocia and in case of a posterior presentation of the foal in the birth canal, umbilical cord compression can occur (Higgins and Snyder, 2005).

Table 2. Factors that may cause hypoxia in the fetus and neonatal foal.
(Vaala, 1999; Galvin and Collins, 2004; McSloy, 2008)

In utero	**Intra-partum**	**Post-partum**
Placental insufficiency (twinning, small placenta, advanced maternal age)	Dystocia (cord compression and thoracic trauma)	Neonatal cardiopulmonary disease
Placentitis (bacterial, fungal or endophyte)	Cesarean section (maternal hypotension and hypocarbia)	Prematurity
Maternal illness	Premature placental separation (Red bag delivery)	Dysmaturity
Post-term pregnancies	Meconium aspiration	Sepsis
Chronic uteroplacental separation	Induced parturition	

In case of mild hypoxemia, a redistribution of the cardiac output takes place after activation of the sympathetic adrenergic nervous system (Vaala, 1994). During this period, the blood flow to central organs, such as the heart, brain and adrenal glands, is increased, an attempt to provide these organs with enough oxygen to maintain their normal function and to prevent cell damage (McSloy, 2008). The

first damage is to be expected in the organs are deprived of their part of cardiac output to protect the central organs, such as the gastrointestinal tract and kidneys (Vaala, 1994).
When redistribution proves to be insufficient, cerebral brain injury is induced via different pathways (**Fig. 1**). First, neurons switch to anaerobic metabolism due to mitochondrial damage, with lactate accumulation causing a decreased intracellular pH which inhibits adenosine triphosphate (ATP) production (Cowled and Fitridge, 2011). ATP reduction leads to Na^+-K^+-ATPase failure with influx of Na^+ and Ca^{2+}, causing loss of cell integrity, water influx and cell swelling, edema and brain necrosis (Vaala, 1999; Gold, 2015; Toribio, 2019). Due to the ATP reduction, the release of glutamate, a physiological excitatory neurotransmitter, is increased and the uptake reduced, resulting in high extracellular concentrations of glutamate, now acting as a neurotoxin and leading to excitotoxicity (Vaala, 1999; Toribio, 2019). Activation of the NMDA-receptors (N-methyl-D-aspartate) will result in Ca^{2+} influx, activating lytic enzymes, such as proteases, phospholipases, phosphatases, lipases, nucleases and neuronal nitric oxide synthases, leading to the production of free radicals and delayed neuronal death (Vaala, 1999; Galvin and Collins, 2004; Morales et al., 2011; Toribio, 2019).
A second wave of cell death occurs during the reperfusion phase of ischemic tissues. During the period of ischemia, hypoxanthine is formed out of the degradation of ATP and can be degraded to uric acid and superoxide anion (McCord and Roy, 1982). Under the influence of restored oxygen, transformation to hydrogen peroxide and a hydroxyl radical takes places (McCord and Roy, 1982; Cowled and Fitridge, 2011; Toribio, 2019). Together with nitric oxide and peroxynitrite, these reactive oxygen species play a major part in cell damage during reperfusion phase, causing lipid peroxidation of cellular membranes (Cowled and Fitridge, 2011). This alters cell function and induces the production of prostaglandins, thromboxanes and leukotrienes out of arachidonic acid derived from membrane damage and contribute to ischemia by inducing vasoconstriction (Cowled and Fitridge, 2011).

Systemic Inflammatory Response Syndrome (SIRS) is associated with a widespread malignant and multifactorial proinflammatory response, which can lead to a systemic immune response, shock and death (Furr, 2003). A proinflammatory response is needed to eradicate infection, but when the hosts' immune response is not adequate in eliminating the infection, systemic inflammation can induce more tissue damage than the original pathogen (Wong and Wilkins, 2015). Not only can infections induce a systemic inflammatory response, but tissue injury, necrotic cells and ischemia-reperfusion injury are thought to be initiating factors as well (Wong and Wilkins, 2015). When SIRS is initiated after infection, the syndrome is labeled as sepsis (Furr, 2003). Multiple lists of criteria are available in veterinary medicine and the following criteria could be used in diagnosing SIRS in equine neonates, displaying two or more criteria (Corley et al., 2010): body temperature >39.2°C (hyperthermia) or <37.2°C (hypothermia), heart rate > 120 beats/minute (tachycardia), respiratory rate > 30 breaths/minute (tachypnoea), white blood cell count > 12.5 x 10^9/l or >10% immature neutrophils and evidence of sepsis, cerebral ischemia or hypoxia, or trauma.
Microglia are the dominant immune cells of the central nervous system (CNS), perform phagocytic activities and play a role not only in tissue repair and amplification of inflammatory effects, but also in neuronal degeneration (Davalos et al., 2005). During a period of ischemia, microglia are activated, exhibiting a wide array of functions, such as phagocytic, inflammatory and anti-inflammatory cytokine production, antigen presention and the release of matrix metalloproteinases (Davalos et al., 2015). The released matrix metalloproteinases damage the blood-brain barrier, causing an infiltration of leukocytes and increasing susceptibility of the CNS to damage (Liu and McCullough, 2013). Progression of SIRS can lead to Multiorgan Dysfunction Syndrome, the impairment of more than one major organ system, and ultimately death (Furr, 2003).

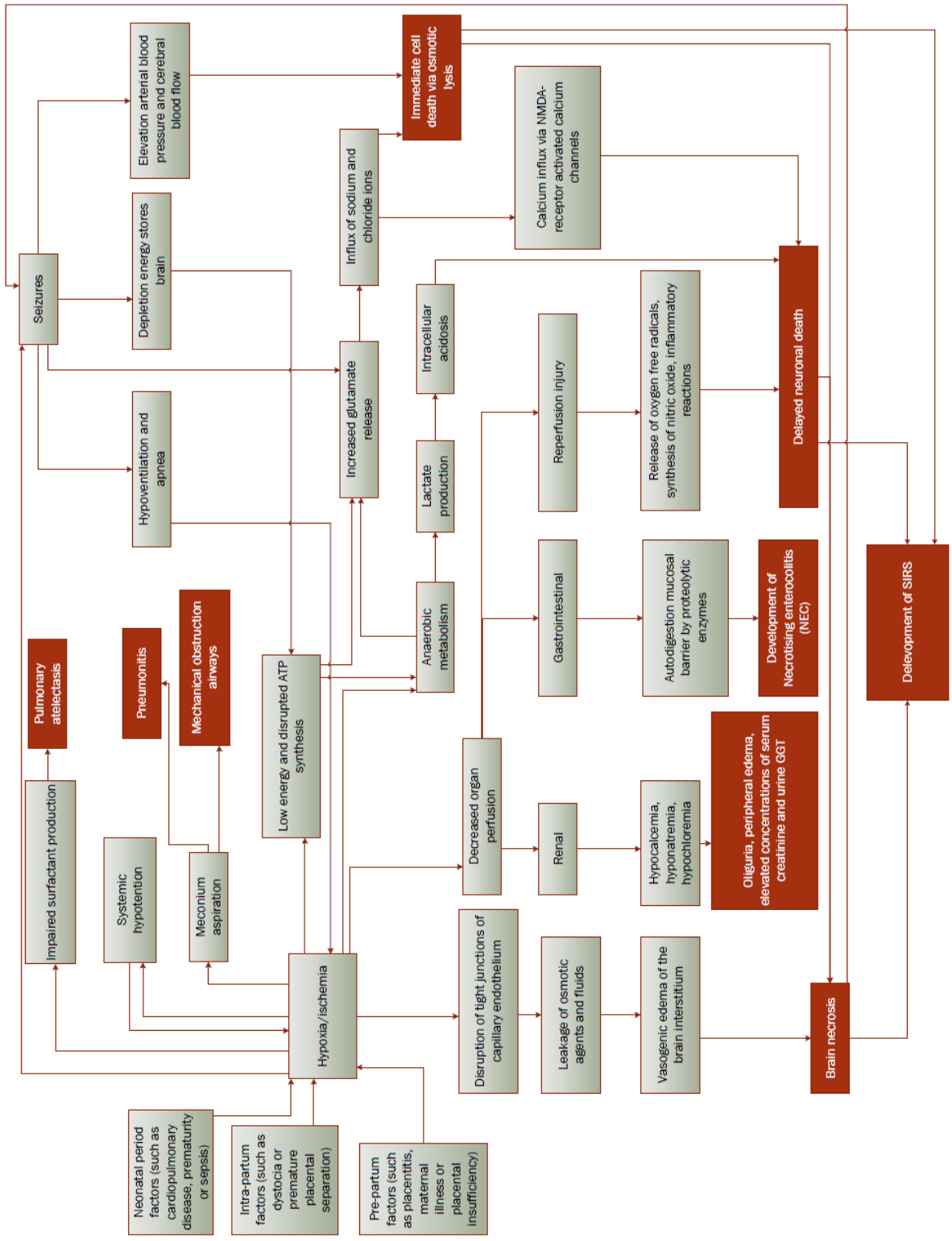

Fig. 1. *Pathways of hypoxia leading to cerebral brain injury.*

3.2 Post-natal persistence of inhibited fetal state

Neuroinhibitory effects of adenosine, progesterone metabolites allopregnanolone and pregnanolone, prostaglandin D2 and a placental neuroinhibitory peptide, combined with other factors such as warmth, cushioned tactile stimulation and buoyancy, keep the late-term fetus in an unconscious state during development of the brain while simultaneously protecting the uterus from damage caused by motility of the fetus' long limbs (Mellor et al., 2005). After birth, a transition takes place in the neonatal foal, going from intrauterine dependency of the placenta and uterus to autonomous activity extrauterine (Aleman et al., 2017). Post-natal persistence of this unconscious sleep-like state has been suggested to be linked to some mild NMS cases, as a cause to the delayed onset of consciousness (Aleman et al., 2013).

Adenosine, also called sleep inducing agent, is produced by all tissues but the placenta, the fetal liver contributing most to its circulating concentration (Mellor et al., 2005). Acting via A_1 receptors, adenosine reduces excitability and promotes sleep when present in high circulating and tissue concentrations (Mellor et al., 2005). The biological half-life of adenosine is short and a rapid response is possible. Plasma concentrations increase during periods of hypoxia and contributes to minimizing neuronal damage through the suppression of the cerebral metabolism (Mellor and Diesch, 2007) Loss of placenta at birth and increasing oxygen plasma concentration due to the onset of breathing of the newborn foal leads to a decreasing adenosine concentration and thus to a decrease in the adenosine inhibition of cerebral cortical function (Diesch and Mellor, 2013).

Allopregnanolone (5α-pregnane-3α-ol-20-one) and pregnanolone (5β-pregnane-3α-ol-20-one) are neuroactive metabolites of progesterone, produced by the fetal CNS and the placenta from cholesterol or progesterone (Hirst et al., 2008). These metabolites act on γ-amino-butyric-acid ($GABA_A$) receptors, increasing the inhibitory effects of the GABA pathways on the CNS, inducing sedative or hypnotic and anesthetic effects (Mellor et al., 2005). Experiments showed that infusion of allopregnanolone in healthy foals induced a NMS-like state with obtundation, lack of affinity for the mare and a decreased response to external stimuli (Madigan et al., 2012). In healthy foals, pregnanolone concentration decreases in the first 48 hours of life, whereas in NMS foals increased concentrations are registered (Aleman et al., 2013). At birth, with the loss of the placenta, a significant source of allopregnanolone and pregnanolone is removed, leading to a further decline in neuroinhibitory effects.

Another sleep-inducing factor is prostaglandin D2 (PGD2), which has many functions, such as promoting sleep, acting as an anti-coagulant and vasodilator, regulating pain sensation and regulating body temperature (Urade and Hayaishi, 2000; Saito et al., 2002). PGD2 is produced in the fetal brain by the enzyme lipocalin-type prostaglandin synthase from prostaglandin H2 (Urade and Hayaishi, 2000). PGD2 circulates in the cerebrospinal fluid and study shows that infusion of PGD2 into the subarachnoid space promotes sleep (Hayaishi, 2002) and that this sleep is electro physically and behaviorally indistinguishable from physiological sleep (Urade and Hayaishi, 2011). PGD2 binds with Prostaglandin D_1 receptors, mainly located in the forebrain (Hayaishi, 2002; Urade and Hayaishi 2011) and stimulates paracrine activation and adenosine release (Mellor, 2005).

Contributing to this sleep-like state is an inhibitory peptide, produced by the placenta, causing suppression of fetal activation and respiration (Mellor et al., 2005). A study reports that *in utero* fetal breathing inhibition is induced by administration of a placental extract after umbilical cord occlusion in fetal sheep (Alvaro et al., 1993). Not much is known about this peptide but the same study shows that the peptide weighs probably between 3.5 and 10 kD and originates in the placenta (Alvaro et al., 1993).

A withdrawal of inhibition occurs during birth with loss of placental supply of adenosine, allopregnanolone, pregnanolone and some precursors, and placental inhibitory peptide, while the

onset of breathing and thus increased oxygenation decreases adenosine concentrations in the brain (Diesch and Mellor, 2013). The transition to extrauterine life is further supported by activators, such as 17β-estradiol, noradrenaline and sensory impulses (Diesch and Mellor, 2013). 17β-estradiol is a steroid hormone with neuronal excitatory actions, and a study by Mellor and Gregory (2003) showed behavioral arousal and awareness in newborn lambs after injecting 17β-estradiol. In one study, 17β-estradiol promoted arousal in inactive lambs after delivery by caesarian section, this may suggest a therapeutic possibility (Mellor et al., 1972). Noradrenalin, or norepinephrine, is a neurotransmitter originating from neurons in the locus coeruleus and has a key role in brain activity and arousal (Sara, 2009; Diesch and Mellor, 2013). Strong tactile stimulation (such as passing through the birth canal) and umbilical cord severance have activating effects on the locus coeruleus, increasing noradrenalin production and contributing to the onset of arousal (Mellor and Diesch, 2006). A combination of a decrease in inhibitory and an increase in excitatory neuroactive factors result in a successful transition from intrauterine to extrauterine life.

4. Symptoms

Foals with NMS can display a wide range of symptoms that vary in severity according the degree of impairment. Clinical symptoms can be mild to severe, ranging from a loss of affinity for the mare, loss of suckle reflex, aimless wandering with circling into one direction combined with central blindness and head tilt, stargazing, seizures and symptoms of multiple organ failure (Vaala, 1994, McSloy, 2008). Poor health of the mare during pregnancy, abnormal placentation, multiple organ dysfunction, comorbidity, FPT and seizures are factors associated with nonsurvival of NMS foals in a retrospective study (Gold et al., 2015). Hess-Dudan and Rossdale (1996) divided NMS foals into 2 different categories based on events during the pregnancy or parturition and on the presence of clinical signs of NMS directly postpartum. Category 1 describes a normal pregnancy and birth, the foal's behavior immediately after birth is normal but clinical signs of NMS develop within 6-24 hours after birth. Category 2 describes abnormalities during pregnancy or partus and abnormal behavior of the neonate foal immediately after birth. The prognosis for category 2 foals is significantly poorer, as these foals often suffer damage to multiple organ systems (Hess-Dudan and Rossdale, 1996).

Disruption of astrocyte function and neuronal cell viability due to a period of cerebral ischemia causes impairment of protective and physiological functions, such as free radical scavenging, glutamate uptake, synaptic activity, water balance and other metabolic and nutritional activities (Morresey, 2009; Toribio, 2019). If the period of ischemia is short, tissue damage may be reversible (Vaala, 1994). Neurologic disease or metabolic derangements such as metabolic acidosis, hypoglycemia, hypocalcemia, hyponatremia, hypochloremia and iatrogenic water overload affecting the electrolytes can induce seizures (Hess-Dudan and Rossdale, 1996). Seizure episodes in NMS foals can range from subtle signs to overt seizure activity and diagnosing them can be challenging in the subtle cases (Hess-Dudan and Rossdale. 1996). Three phases can be recognized in a seizure episode starting with a pre-ictal period (Morresey, 2009). In this first stage the foal may show signs of depression, stargazing or inappropriate behavior. The second stage may not be noticeable in the more subtle cases and consists of the typical seizure activities, such as tonic-clonic convulsions, altered consciousness, opisthotonus and circling (McSloy, 2008 and Morresey, 2009). This ictal period is followed by the post-ictal phase, involving possible depression and blindness (Morresey, 2009). It can be difficult to distinguish a seizure episode from a foal that is unable to use its legs in the right order to turn onto its brisket, making convulsion-like movements (Hess-Dudan and Rossdale, 1996). Common signs of a seizure episode in foals are facial spasms and grimacing, eye blinking, pedaling movements, abnormal breathing patterns with tachypnea and apnea and rigid movements of a limb or all limbs that cannot be suppressed by restraint (Hess-Dudan and Rossdale, 1996; McSloy, 2008; Vaala, 1999). Medical suppression of these seizures is important, because they can result in additional brain injury through hypoventilation or apnea leading to additional hypoxemia, increased arterial blood pressure and cerebral blood flow, additional release of glutamate and other excitatory amino acids and exhaustion of energy stores in the brain (Vaala, 1999).

Kidneys are very susceptible to hypoxia and the shift of cardiac output to central organs decreases the glomerular filtration rate, inducing tubular necrosis and renal failure (Vaala, 1994). Indications of renal ischemia can be oliguria (<1 ml urine/kg BW/h), elevated concentrations of serum creatinine and urine GGT and peripheral edema (Vaala, 1999; Galvin and Collins, 2004). Intestinal ischemia is another manifestation of the redirected cardiac output. Auto digestion of the mucosa and bacterial invasion of the gut wall can lead to necrotizing enterocolitis, and ileus, gastric reflux, colic, abdominal distension and diarrhea can be seen in the affected foal (Vaala, 1994).Icterus can be seen in foals suffering from NMS, as a result of hepatocellular necrosis and biliary stasis after a hypoxic event, responsible for increased hepatocellular and biliary enzymes (Vaala, 1999). Failure of passive transfer of colostral

immunoglobulin occurs when the newborn foal has an inadequate uptake of colostrum. Foals depend on this colostrum containing IgG, as the equine epitheliochorial pattern of placentation prevents transfer of immunoglobulins *in utero* from mare to fetus, leaving foals agammaglobulinemic at birth (Naylor, 1979; Sprayberry, 2013; Ayala and Oliver-Espinosa, 2016). Factors associated with FPT are: an inadequate or no uptake of colostrum, prepartum loss of colostrum by the dam, season of foaling (more foals with FPT in January, February and March), low foal exam score (small, skeletal abnormalities, decreased vigor) and dystocia (Clabough et al., 1991). Foals suffering from FPT are predisposed of developing illness in the first three months of life and have a higher chance of needing medical therapy than healthy foals, as FPT can lead to infections and death (McGuire et al., 1975; McGuire et al., 1977; Clabough et al., 1991). Monitoring colostral specific gravity pre-suckling and immune status of the foal can give indications about the risk of developing FPT (Tyler-McGowan et al., 1997). IgG concentration in colostrum can be measured in field by refractometry or colostrometry (Venner et al., 2008). The immune status of the neonatal foal can be checked via serum total globulin concentration and a field test, the SNAP Foal Ig test, is available (Pusterla et al., 2002).

FPT, as well as other factors such as dystocia, placentitis, infection of the umbilical cord rest and unsanitary environments can be predisposing for infection and sepsis, a major cause of morbidity and mortality in the neonatal foal (McGuire et al., 1977; Paradis, 1994; Sanchez, 2005). Clinical signs of early stages of sepsis can be: hyperemic mucous membranes, tachycardia and petechiae due to capillary leak (Sanchez, 2005). Septic shock can occur in the more advanced stages of sepsis and can present itself in various ways, as depression, recumbency, hypovolemia (cold extremities, thread pulse and a long capillary refill time) or hypoglycemia (Sanchez, 2005). Development of septicemia in combination with NMS is associated with poor prognosis (Vaala, 1994) as well as foals with concurrent disease, were recumbent or required vasopressors or inotropes (Lyle-Dugas).

5. Diagnosis

Diagnosing NMS can be challenging, as there are no pathognomonic clinical signs, but by ruling out differential diagnoses, combined with a possible history of hypoxia prepartum, intrapartum or postpartum and presence of neurologic impairment and other related clinical signs, an assumption can be made. Laboratory findings are not pathognomonic but the following findings are associated with NMS: azotemia, hypochloremia, melena, reflux, hypoxemia, hypercapnia, respiratory acidosis, elevated serum concentrations of creatinine-kinase (a muscle enzyme) and myocardial enzymes, hyperbilirubinemia and elevated liver enzymes (Vaala, 2009). Differential diagnoses that have to be taken into account include sepsis, epilepsy, hypoglycemia, prematurity or dysmaturity, metabolic disorders, infectious diseases (bacterial or viral meningitis), liver disease and hepatoencephalopathy, head trauma or congenital abnormalities, keeping in mind that one diagnosis does not rule out the other (Vaala, 2009; Tennent-Brown et al., 2015). A complete blood count, serum biochemistry, arterial blood gas analysis, blood culture, urinalysis and evaluation of circulating IgG levels can help identify other disorders involved (Vaala, 2009).

Measurement of biomarkers is a potential diagnostic tool for foals suffering from NMS and several studies investigate biomarkers present in foals and human infants (Bennet et al., 2010; Ringger et al., 2011; Graham et al., 2018). Ubiquitin C-terminal hydrolase 1 and phosphorylated axonal forms of neurofilament H are found to be significant higher in foals with clinical signs of NMS than in healthy foals (Ringger et al., 2011). Another study reveals that these biomarkers were increased after brain injury (Lee et al., 2018). This suggests that the biomarkers can be used to indicate brain injury and more research should be done about the implications of this in diagnosing and assessing the NMS foal. Septic meningitis can display similar neurologic symptoms, including stupor and seizures and can be differentiated from NMS by elevated leukocyte count and total protein concentration via cerebrospinal fluid analysis (Vaala, 1994).

Increased progesterone and pregnenolone concentrations were found in ill, neonatal foals and remained increased over a period of 48 hours in foals diagnosed with NMS, whereas a decrease was noticed in other sick (not NMS) foals (Aleman et al., 2013). This suggests that serial pregnenolone and progesterone analysis could be useful in diagnosing the NMS foal. A study about plasma adrenomedullin concentration in neonatal foals shows promising results, finding a 6-fold increase in critically ill foals, compared with a healthy control group (Toth et al., 2014). More studies are necessary to evaluate prognostic value (Toth et al., 2014).

Other diagnostic tools used in human medicine to diagnose HIE and assess brain damage in infants, include cranial ultrasound, electroencephalography, computed tomography and magnetic resonance imaging (Bano et al., 2017). These methods are not always available to practitioners and have not yet been determined in foals, making more research necessary to use these methods on regular basis.

In human medicine, an Apgar (appearance, pulse, grimace, activity and respiration) scoring system is used to evaluate the severity of asphyxia in infants and a modified Apgar score has been developed for neonatal foals (**Table 3**). Depending on the score, the foals are placed in three groups: the normal foal (7-8 points), the foal that requires intervention with mild to moderate asphyxia (4-6 points) and a life threatening sick foal with severe asphyxia (0-3 points) (Vaala, 1994). This scoring system could be used as guide in making a quick assessment of the patient.

Table 3. Modified Apgar Scoring System for assessment of the neonatal foal

After: Martens, R.J., 1982. Pediatrics. Mansmann, R.A., McAllister, E.S., Pratt, P.W., Equine medicine and surgery, Third edition. American Veterinary Publications, Santa Barbara, CA, USA.

Observations	Assigned values		
	0	1	2
Heart and pulse rate	Undetectable	<60 beats/min	>60 beats/min
Respiration rate and pattern	Undetectable	Slow, irregular	60 breaths/min, regular
Muscle tone	Lateral recumbency, limp	Lateral recumbency, evidence of some muscle tone	Able to maintain sternal recumbency
Nasal Stimulation	Unresponsive	Grimace with mild rejection	Cough or sneeze

6. Treatment

Referral of NMS foals to a hospital is often necessary, as treatment of NMS exists of supportive therapy and aims to maintain oxygen status, seizure control, glucose levels, thermoregulation, reducing inflammation, and more. The foals often require a multidisciplinary approach as multiple organ systems can be affected. The owner should be notified about the potential high costs of the treatments, which can easily run over $2,000.00 for a hospitalization lasting 4-10 days (Bernard et al., 1995; Sualez et al., 2007). Bottle feeding, plasma administration, intravenous fluids, antimicrobials and dextrose are the most administered medical treatments, in less than 50% of the cases treatments such as dimethyl sulfoxide (DMSO), vitamin E, intranasal oxygen, diazepam, corticosteroids, mannitol, allopurinol and other therapies are used (Aleman et al., 2017). Choice of therapy depends on the clinical presentation of the foal, laboratory findings and owner compliance.

6.1 Gastrointestinal support

A frequent complication after an ischemic insult is ileus, resulting from autolysis of the mucosal gut wall (Vaala, 1999). As ileus can result in bowel distention and colic, it can be necessary to administer nasogastric decompression, enemas, metoclopramide (0.25-0.5 mg/kg BW/h infusion q 6-8 h) and erythromycin (1-2 mg/kg BW PO q 6 h) to stimulate gastric flow or cisapride (10 mg PO q 6-8h) and erythromycin to increase intestinal motility (Vaala, 1999). Enteral nutrition is thought to be more beneficial in supporting the gut, improving gut barrier function and bowel movement, but is contra-indicated when intestinal disease is present (Carr, 2018). The passage of manure, a normal amount of borborygmi and the absence of dilated small intestines on abdominal ultrasound can be signs of (restored) gut function and indicates that enteral feeding can be administered (Vaala, 1999; Carr, 2018). Sick foals require less milk than healthy foals, 5-10% BW/day compared with 15-30% BW/day respectively (Carr, 2018). When initiating enteral feeding and starting with 1-2% BW/day, a gradual increase in volume is crucial and gut function should be monitored frequently, until an uptake of 50-100 kcal/kg BW/day is reached (Carr, 2018). When the foal is not able to stand and nurse, a nasogastric tube can be placed to decrease the risk of aspiration pneumonia (Carr, 2018). Parenteral feeding via IV catheter can be administered when enteral feeding is insufficient or can be used as a primary source of nutrition in case of severe gastrointestinal dysfunction (Vaala, 1999; Galvin and Collins, 2004). Complications associated with parenteral nutrition are catheter-related thrombophlebitis, hypertriglyceridemia, hyperglycemia, hypokalemia and loss of the beneficial effects of enteral feeding on the gut, all contributing to reduced survival rates (Vaala, 1999; Galvin and Collins, 2004; Myers et al., 2009; Carr, 2018). Enteral feeding should be chosen over parenteral feeding when possible, but the parenteral route can be used to fill the gap that occurs in the not yet recovered foal. Gastric ulceration is commonly reported in ill neonatal foals as intestinal ischemia can damage mucosal integrity and administration of omeprazole paste (4 mg/kg BW PO q 24h) can have protective effects, increasing intragastric pH (Vaala, 1999; Sanchez et al., 2004).

6.2 Respiratory support

Hypoxemia and hypoxia can be addressed in several ways, including pharmacological respiratory stimulators, intranasal oxygen insufflation, continuous positive airway pressure (CPAP) and mechanical or manual ventilation. Mechanical ventilation delivers positive pressure breath via endotracheal tube with a given tidal volume (volume of air inhaled in the lung with every breath) and changes de patients

natural negative pressure ventilation to a positive one, increasing the intrathoracic pressure with impact on the cardiopulmonary system and often promotes lung pathology (Pham et al., 2017). CPAP can be used when the patient is able to breathe on its own, the machine delivering air on a constant pressure level to keep the airways open, without causing increased intrathoracic pressure and its side effects (Diblasi, 2009). The physiological PaO_2 in neonate foals is around 90 mmHg and the $PaCO_2$ under 50 mmHg (Bazzano et al., 2014). In case of mild to moderate hypoxemia, improvement of the oxygen status can sometimes be achieved by placing the foal in sternal recumbency or to a standing position first, possibly supplemented with humidified intranasal oxygen (10L/minute) (McSloy, 2008; Vaala, 1999). When this seems insufficient and the foal suffers severe hypoxemia (PaO_2 < 40 mmHg, $PaCO_2$ > 70 mmHg), acidemia or respiratory muscle fatigue, mechanical ventilation or CPAP is indicated (Vaala, 1999; Axon et al., 2015a). Details about ventilation support can be read elsewhere (Palmer, 2005). Mechanical ventilation is very expensive and labor-intensive (Calvin and Collins, 2004), a cheaper and less labor-intensive alternative is pharmacological stimulation of the central respiratory centrum. Caffeine (initial dose of 7,5-12 mg/kg BW followed by maintenance rate of 2,5-5 mg/kg BW PO q25h), an adenosine A1 and A2 receptor antagonist, can be used to stimulate the central respiratory centrum in case of apnea (Axon et al., 2015a; Bairam, et al., 2015). In a retrospective study, doxapram was found to be more effective than caffeine in rapidly correcting hypercapnia (Giguère et al., 2008). Doxapram (constant rate infusion (CRI) of 0.02-0.05 mg/kg BW/h IV), a pyrrolidinone derivate, is known to cause cardiac and respiratory stimulation in horses and can be used as treatment for respiratory acidosis secondary to neonatal encephalopathy (Giguère et al., 2007; Papich, 2016).

6.3 Anticonvulsive therapy

Seizure control is crucial in preventing further brain damage as well as external trauma. The oxygen demand in brain and muscles increases during seizures, aggravating the hypoxic status (Galvin and Collins, 2004). To stop seizures immediately, diazepam (0.1- 0.2 mg/kg BW IV) or midazolam (0.1 mg/kg BW IV) can be used, as these drugs have a rapid, but short-term action (Galvin and Collins, 2004; McSloy, 2008; Vaala, 1999). In case of severe or repetitive (more than two) seizures diazepam can be followed by phenobarbital (2-3 mg/kg BW IV q 12h) administration (Galvin and Collins, 2004; McSloy, 2008; Vaala, 1999). The foal should be monitored closely: phenobarbital has a half-life of more than 200 hours and side effects that can be noticed include hypothermia, respiratory depression and hypoperfusion (Vaala, 1999; Axon and Wilkins, 2015a). Sudden stop of administration of phenobarbital can lead to a relapse of seizures, therefore gradually decreasing the dosage over the course of 24 to 48 hours is advised (McSloy, 2008). Alternatively, a CRI of 50 mg midazolam in 90 ml of 0,9% saline can be administered (2-6 ml/h per 50 kg BW) to limit seizure activity long-term (Wilkins, 2005). The short half-life and the potential of flumazenil (0.01 mg/kg BW IV over 15 seconds) to antagonize the effects make midazolam a more preferred choice of treatment when regular evaluation of the foal's neurologic condition is required (Axon and Wilkins, 2015a). Azepromazine can lower the seizure threshold and increased the risk of seizures, and should not be used in foals suspected of NMS (Vaala, 1999). Xylazine is also contraindicated, as it reduces cerebral blood flow (Axon and Wilkins, 2015a). To minimize self-trauma, soft beds, padded stalls and wrappings or helmets can be used. Other drugs than diazepam and phenobarbital can be useful in reducing seizures, such as DMSO, mannitol, glucose, IV fluids, vitamin E, vitamin C, allopurinol, magnesium sulfate and thiamine (Galvin and Collins, 2004; Axon and Wilkins, 2015a). DMSO (0.5-1 g/kg BW IV q 24h) acts as a free radical scavenger and can contribute to decreasing the brain swelling and inflammation when administered in a 20% solution (Galvin and Collins, 2004; Vaala, 1999). Mannitol (0.25-2.0 g/kg BW IV) in a 20% solution can be administered when cerebral or interstitial edema is present and it can be used for its free radical

scavenging properties as well (McSloy, 2008; Vaala, 1999). Caution is advised when administrating glucose to foals in the early post-hypoxic period as hyperglycemia can exacerbate hypoxic injury to the brain (Vaala, 1999). It is recommended preventing either hyper- and hypoglycemia and maintaining glucose within a range of 80-110 mg/dl (Galvin and Collins, 2004). Vitamin C (50-100 mg/kg BW IV) and vitamin E (500-4000 units/foal PO) are used for their antioxidant properties in the aqueous and lipid environment respectively, but more research about the efficacy in foals is needed (Axon and Wilkins, 2015a). Allopurinol is used in frequently in human neonatology, as it has an antioxidant effect as xanthine oxidase inhibitor (Galvin and Collins, 2004; Axon and Wilkins, 2015a). Magnesium sulfate infusion (50 mg/kg BW/h for the first hour, 25 mg/kg BW/h after the first hour as CRI), a NMDA receptor antagonist, is thought to reduce seizures through blocking influx of excess calcium that can cause neuronal cell death (Galvin and Collins, 2004; Axon and Wilkins, 2015). Studies about the use of magnesium sulfate infusion in newborn babies show signs that this may have beneficial effects treating perinatal asphyxia (Gathwala, 2010; Hossain et al., 2013). Thiamine can be administered for its assumed neuroprotective function, as it helps to sustain aerobic brain metabolism, but no scientific research is done yet on its clinical actions in foals with NMS (Vaala, 2009).

6.4 Fluid therapy

Conservative fluid therapy can be administered to stimulate cerebral perfusion and maintain physiological fluid volume (McSloy, 2008). The dehydration status can be estimated via prolonged capillary refill (CR), tacky or dry mucous membranes and presence of a skin tent (Hollis and Corley, 2007). Mild (5%) dehydration shows signs of a normal CR (<2 seconds), slightly tacky mucous membranes and a skin tent that lasts for 1-3 seconds, whereas moderate (5-10%) dehydration shows a CR of 2-3 seconds, tacky mucous membranes and a skin tent that disappears after 3-5 seconds. In case of severe (>10%) dehydration, the CR is >4 seconds, the mucous membranes are dry and the skin tent persists for 5 seconds or more (Hollis and Corley, 2007). When correction of dehydration is necessary, a summation of maintenance requirements, ongoing losses and dehydration status multiplied by the BW of the foal equals the volume of fluids required (Hollis and Corley, 2007). Aim to correct the dehydration over a period of 24 hours and if administered, parenteral nutrition must be taken into account in calculating total maintenance fluid volume (Galvin and Collins, 2004; Hollis and Corley, 2007). General maintenance requirement lies about 5-7 ml/kg BW/h of a polyionic isotonic fluid, administered intravenously, but close monitoring is necessary and the fluid balance (the difference between fluids taken in and urine output) should be small (Vaala, 1999; Galvin and Collins, 2004; Hines, 2014). A normal urine output of the foal is around 150 ml/kg BW/day and specific gravity should be less than 1.010 (Hines, 2014). An indwelling urinary catheter should be inserted to monitor urine output and to prevent urine scalding in the recumbent foal (Corley, 2002). The above mentioned parameters should be monitored closely to prevent overhydrating, as it can have adverse effects on the recovery by worsening cerebral edema (Galvin and Collins, 2004; Hines, 2014; Divers, 2015) In case of overhydration, furosemide (0,25-1 mg/kg BW IV) can be used to increase urine flow rate (Hollis and Corley, 2007).

In case of hypoglycemia, 20 ml of 50 percent glucose can be added to a balanced electrolyte solution, as the use of five percent glucose is not recommended in combination with hypovolemia, as it will decrease plasma sodium concentration (Hollis and Corley, 2007).

Plasma is rich in fibronectin, complement, coagulation factors, albumin and immunoglobulin G and thus can be administered to treat sepsis or in case of failure of passive transfer (Hollis and Corley, 2007). The ideal source of plasma is commercially available hyper immune plasma, but when unavailable, the dam or another donor can be used (Hollis and Corley, 2007). The amount of plasma

needed can be estimated, as 10 g of IgG administered, can give a rise of 1 to 2 g IgG/liter in the foal (Stoneham, 1997).
Administration of whole blood is often done in case of neonatal isoerythrolysis and is not discussed here.

6.5 Thermoregulation

Accidental hypothermia in neonates can be life-threatening, however therapeutic hypothermia is used in newborn infants and it is believed that this cooling results in long-term neuroprotection (Jacobs et al., 2013; Cornette, 2012). As preferably only the brain is cooled, cerebral metabolism is slowed down, leading to a decrease in excitatory neurotransmitter accumulation and free radical release (Thoresen et al., 1997). In addition the release of proinflammatory cytokines and apoptotic processes are suppressed (Globus et al., 1995; Cornette, 2012). Arrhythmia and thrombocytopenia are reported possible side effects occurring after therapeutic hypothermia in human infants, but where not found clinically important (Shah, 2010). To the author's knowledge, no studies on therapeutic hypothermia in foals have been done yet and it could be valuable to first learn to recognize the foal that would benefit from therapeutic hypothermia before applying this technique in clinical environment.
Accidental hypothermia, on the contrary, can predispose to death of the newborn. A rectal temperature less than 37°C is suggestive for hypothermia in the neonatal foal and can be the result of different factors (Ousey et al., 1997). Hypoxemia during birth can result in metabolic acidosis, leading to a depressed heat production capacity (Eales and Small, 1985). In addition, sick foals can have a lower metabolic rate (about 25%) than healthy foals due to inactivity (recumbent, sedated or asleep), affecting their thermoneutral zone and demanding higher air temperature to prevent heat loss (Ousey et al., 1997). Severe hypoglycemia can lead to additional hypothermia, as a compensatory mechanism to decrease energy demand (Tran et al., 2012). To reduce heat loss, the sick foal should be placed in a warmed environment, according to the foals need. Its coat needs to be dried immediately and blankets under and over the foal can reduce additional heat loss (Ousey et al., 1997).

6.6 Glucocorticoids

The use of glucocorticoids in perinatal asphyxia is controversial, as it is known to promote both neuroprotective and neurotoxic effects. Some studies show an increased cerebral hypoperfusion after the use of glucocorticoids, exacerbating neuronal injury, while other studies describe the anti-inflammatory, neuroprotective functions of glucocorticoids (Vannucci and Perlman, 1997; Lear et al., 2014, Harding et al. 2016). In another study, adverse effects on brain development were noted after administration of dexamethasone in neonatal rats, due to a decrease in glutamate transporter-1 and subsequently a decrease in glutamate reuptake (Chang et al., 2013). These effects were reduced when β-lactam antibiotic ceftriaxone was administered before dexamethasone, as ceftriaxone is known to increase glutamate transporter-1 expression (Chang et al., 2013).
To reduce intracranial pressure, mannitol has found to be more effective than dexamethasone, as the latter has a greater disadvantageous effect on blood pressure and is detrimental for cerebral perfusion pressure (Levene and Evans, 1985). A study conducted by Hart and others (2011) found that a low-dose of hydrocortisone showed to dampen the proinflammatory effect to endotoxin, with no adverse effects of on the innate immune response of neonatal foals. In equine internal medicine, dexamethasone (0.1-0.25 mg/kg BW IV every 6-24h) is commonly used in acute CNS trauma, for its free radical scavenging properties and can lead to a decrease in catecholamines and glutamate concentrations and apoptosis-related cell death (Reed, 2010). After dexamethasone administration,

the horse needs to be monitored for the possible development of laminitis or *Aspergillus spp.* pneumonia and after clinical improvement of the patient, dexamethasone can be exchanged for prednisolone (0.5-1 mg/kg BW PO) to reduce the chance of laminitis (Reed, 2010). To the authors' opinion, corticosteroids have to be used with care in foals diagnosed with NMS and more studies are needed to determine the effects on the neonatal brain.

6.7 Antimicrobials

In case of sepsis, a broad-spectrum, bactericidal and intravenously administered drug is advised, to contain the rapidly progressive infection (Furr, 2003; Magdesian, 2017). An empirical choice of antimicrobials must be made to start the initial treatment and can be adjusted after acquiring culture results. A combination of aminoglycoside and beta-lactam or third-generation cephalosporin is considered first-line therapy for septic neonatal foals (Magdesian, 2017). IV administration is often required, as gut and muscle perfusion can be suboptimal, decreasing the bioavailability (Magdesian, 2017). The site of infection determines the choice of antimicrobial, as the blood-brain barrier hinder the penetration of several antimicrobials, such as aminoglycosides, into the cerebrospinal fluid, having little effect in treating CNS infections (Furr, 2003). Antimicrobials that are known to penetrate the CSF are some third and fourth generation cephalosporines, imipenem, chloramphenicol, fluoroquinolones, rifampin and metronidazole, and are listed in **Table 4**. Fluoroquinolones should be handled with care in neonatal foals, as it can be associated with cartilage toxicity (Magdesian, 2017).

***Table 4**. Antimicrobials with penetration to the CSF (Furr, 2003; Mitchell et al., 2007; Magdesian, 2017)*

Drug	Dosage
Ceftazidime	20-50 mg/kg IV q 6h
Cefotaxime	40-50 mg/kg BW IV
Ceftriaxone	40 mg/kg BW IV q 6h
Cefepime	11 mg/kg BW IV q 8h
Imipenem (extralabel)	5-10 mg/kg BW IM q 12h or 10-20 mg/kg BW IV q 6h
Chloramphenicol (extralabel)	15-25 mg/kg BW PO q 6h
Fluoroquinolones	5 mg/kg BW IV q 24h or 7.5 mg/kg BW PO q 24h
Metronidazole (extralabel)	15-25 mg/kg BW PO q 6h Or 10 mg/kg PO, IV q 8-12
Minocycline	4 mg/kg BW PO q 12h
Doxycycline	10 mg/kg BW PO q 12h
Rifampin (extralabel)	5-10 mg/kg BW PO q 12h

Other antimicrobials that can be used in septic foals are stated in **Table 5**. When using aminoglycosides, close monitoring of the foal is warranted as it can have toxic effects on the tubular epithelial cells of the kidney (Riviere and Spoo, 2001). To optimize efficacy and reduce toxicity, therapeutic drug monitoring and urinalysis are recommended (Furr, 2013).

***Table 5**. List of antimicrobials used in septic neonatal foals other than listed in **Table 4** (Corley and Hollis, 2010).*

Penicillins	Penicillin potassium or sodium	22,000-44,000 IU/kg BW IV, q 6h
	Ampicillin	22-30 mg/kg BW IV, PO q 6-8h
	Amoxicillin	13-30 mg/kg BW PO q 8h
	Ticarcillin-clavulanic acid	50 mg/kg IV q 6h
First generation cephalosporins	Cefazolin	15-22 mg/kg BW IV q 6-8h
	Cephalothin	10-20 mg/kg BW IV q 6h
	Cephalexin	25 mg/kg BW PO q 6h Or 30 mg/kg BW PO q 8h
	Cefadroxil	20-40 mg/kg BW PO q 8-12h
Second generation cephalosporins	Cefuroxime Na	16-33 mg/kg BW IV q 8h
	Cefoxitin	20 mg/kg BW IV q 6h
Third generation cephalosporins	Cefoperazone	30 mg/kg BW IV q 8h
	Cefotaxime	40 mg/kg BW loading dose, then 6.7 mg/kg BW/h IV CRI
	Ceftizoxime	20-50 mg/kg IV q 6h
	Cefpodocime proxetil	10 mg/kg BW PO q 6-8-12h
	Ceftiofur	5-10 mg/kg BW IV, SC, IM q 6-12h or 5 mg/kg IV loading dose, then 0.42 mg/kg/h CRI
Fourth generation cephalosporins	Cefquinome	1 mg/kg BW IM or IV q 12h
Aminoglycosides	Amikacin	25 mg/kg BW IV q 24h
	Gentamicin	8-16 mg/kg BW IV q 24h
Sulfonamides	Trimethoprim-sulfonamide	25-30 mg/kg BW PO q 12h

Potentiated sulfonamides, such as trimethoprim-sulfadiazine, can be used after the initial treatment of the septic foals with beta-lactams and aminoglycoside or cephalosporins. As potentiated sulfonamides do not target all gram-negative bacteria and have little effect on anaerobe microbes, they can be used orally and are simpler to administer after the foal left the hospital (Magdesian, 2017). When using oxytetracycline or tetracycline, the foal needs to be monitored closely as these antimicrobials can cause nephrotoxicity, whereas doxycycline and minocycline are less nephrotoxic and can be used in patients with renal failure (Magdesian, 2017). The specificities of each antimicrobial in neonatal foals can be consulted elsewhere (Furr and Mogg, 2003; Corley and Hollis, 2010; Magdesian, 2017)

6.8 Other

In human medicine, other drugs or methods of treatment are described and the significance for neonatal foals is still to be determined. One of them is melatonin, a free radical scavenger and antioxidant, with promising results of neuroprotection in some studies (Carloni et al., 2007; Fu et al., 2011). Administration of melatonin in fetal sheep after umbilical cord occlusion show an attenuation of cell death and reduced inflammation in the fetal brain, suggesting the protective features of melatonin (Welin et al., 2007).

Several studies suggest that deferoxamine can have a protective role against delayed neurotoxicity by preventing lipid peroxidation and depletion of antioxidants in neonatal rat models (Papazisis et al., 2008; Kletkiewicz et al., 2016).

In human medicine, studies about postnatal magnesium sulfate infusion show promising results in improving neurologic outcomes and its use is also reported in equine neonates (Bhat et al., 2009; Gathwala, 2010; McSloy, 2010). Administered via CRI, it decreases calcium influx in cells by blocking calcium channels as a NMDA-receptor antagonist (Gathwala, 2010; McSloy, 2010). Magnesium therapy is started with a loading dose of 50 mg/kg BW/h over an hour and followed by a maintenance dose of 25 mg/kg BW/h for 24 hours (McSloy, 2010).

A new study shows that vitamin B12, or cyanocobalamin, has free radical scavenging properties that could be beneficial in reducing ischemic damage to tubulus cells of the kidneys, increasing cell survival during reperfusion (Li et al., 2020). Further observation has to be done to indicate clinical importance of vitamin B12 in equine neonates diagnosed with NMS.

In hyperbaric oxygen therapy (HBOT), a patient has to breathe 100% oxygen inside a pressurized chamber, experiencing the influences of both mechanical effects of pressure and increased oxygenation (Slovis, 2008). Some studies show promising results of HBOT in rat models with acute inflammatory response after traumatic brain injury (Vlodavsky et al., 2006). The research showed a decrease in secondary cell death and reactive neuroinflammation after HBOT. In two newborn infants, a decrease in total creatine phosphokinase was noted, indicating a reduction in the systemic inflammatory process (Orozco-Gutierrez et al., 2010). Therapeutic effects of HBOT can consist of: reversion of hypoxia, alteration of ischemic effect, influencing vascular reactivity, reducing edema, modulating nitric oxide production, modifying growth factors and cytokine effect, promoting cellular proliferation, modulate immune system response, enhance oxygen radical scavengers and more (Slovis, 2008). Hagyard Equine Medical Institute has used a hyperbaric oxygen chamber for several years in treating different kind of disorders, such as thermal burns, ileus, CNS edema, peripheral neuropathies, ischemic injuries and perinatal asphyxia (Slovis, 2008). Several other equine clinics offer HBOT and more scientific data and controlled studies are needed to validate this treatment for foals with NMS.

7. Madigan Foal Squeeze procedure

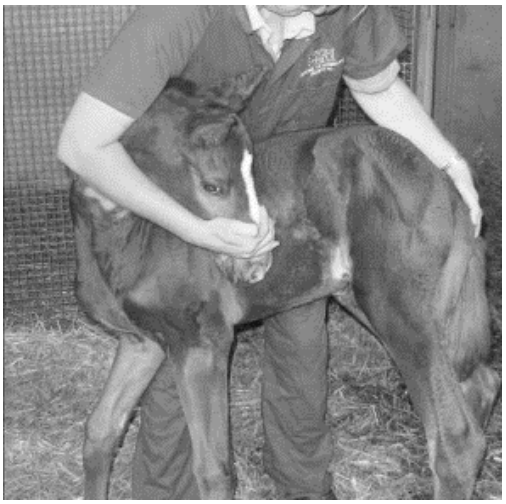

***Fig. 2**. Folding of the foal to make it lie down. From: Equine Emergency and Critical Care Medicine*

Congruent with the recent findings of increased inhibitory neurosteroids in some NMS foals, a new way to treat the syndrome has come to light. Foals are very sensitive to restraint and 'folding' the foal with its head to the withers (**Fig. 2**) will cause the foal to lie down (Axon and Wilkins, 2011). Squeeze-induced somnolence is a commonly used restraining technique in foals. Restraining the foal with a rope induces a sleep-like state with inhibition of voluntary activity, a decrease in heart and respiratory rate and rectal temperature (Toth et al., 2012). During this restraint, healthy foals remained in the sleep-like state until pressure was released and exhibited electroencephalographic patterns consistent with slow wave sleep, with an increased tolerance to external stimuli, such as plasma administration (Toth et al., 2012; Pickles et al., 2014). This reaction is described as flopping reaction or reflex relaxation by various authors and it is suggested that this squeezing technique mimics the passing of the foal through the birth canal and activates the HPA (Aleman et al., 2017). After 20 minutes of applied pressure, an increase in androstenedione, dehydroepiandrosterone sulfate and ACTH is seen, but the role of the neuromodulatory effects of these steroid hormones is not yet completely known (Toth et al., 2012). It has been reported that this squeeze aids to the recovery of foals diagnosed with NMS (Aleman et al., 2017).

The squeeze method was applied to several NMS foals anecdotal[1,2,3,4] and in 2017 Drs. Aleman and her study group tried to map out the use of the squeeze on NMS foals and the response of the new treatment. In this survey, 51 veterinarians, veterinary technicians and farm managers participated, mostly located in the United States. The foals were divided into two groups; foals that underwent the squeeze procedure and foals that where not squeezed. A faster recovery was noted in some foals with NMS treated with the squeeze procedure than foals treated only medical (Aleman et al., 2017). More research is needed to determine if the squeeze method can be beneficial to some NMS foals, and which clinical signs indicate use of the squeeze will be successful. In a recent study, two calves, showing signs of NMS after delivery by caesarean section, were subjected to the sqeeze technique (Stilwell et al., 2020). After removal of the rope the calves woke up immediately and unlike before the squeeze, exhibited an increased affinity for the dam and tried to drink (Stilwell et al., 2020).

[1] https://www.thatsfarming.com/news/the-madigan-squeeze-saved-this-calfs-life Last consulted 14-4-2020

[2] https://thehorseaholic.com/madigan-squeeze-saves-dummy-foal/ Last consulted 14-4-2020

[3] https://www.newcastleequinecentre.net.au/dummy-foal-nursing-after-squeeze-procedure/ Last consulted 14-4-2020

[4] https://www.dehoefslag.nl/laatste-nieuws/tineke-haan-het-veulen-had-geen-oog-voor-de-merrie.html?fbclid=IwAR0h_qZjnleR9VIGRNoYFCsmCQ7X6Cj7AWifvZp30u6b-M1xC7D6XC8Snz0 Last consulted 14-4-2020

On the website of the University of California, campus Davis[5], a written instruction is published on how to use the Madigan Foal Squeeze method (MFS). The instructions explain how to prepare the rope used for the squeeze and the advice is given to use this technique on foals with NMS symptoms under 24 hours of age, followed by a detailed description of the rope placement on the foal. The rope is placed across the neck at the withers, between the front legs and back to the withers through a fixed loop. Then, 2 half-hitches are placed behind the elbow and 6 inches to the back and start to apply pressure while standing behind the foal. When the foal lies down, the same pressure must be applied for 20 minutes. After 20 minutes, the pressure is released and the rope removed. The foal is now free to choose whether to stand up or sleep some more and it should not be forced. In **Appendix III**, images illustrating the rope technique can be consulted and detailed instructions can be read on the website of the University of California[5].

[5] https://compneuro.vetmed.ucdavis.edu/sites/g/files/dgvnsk5376/files/inline-files/mfsm_instructions_0.pdf Last consulted 14-4-2020

8. The questionnaire

Veterinarians throughout Europe were invited to participate in an electronic survey. The invitation was sent via e-mail to veterinarians with an online website that could be found via Google.com. The invitation was sent to both small practices and bigger clinics, as well as to university hospitals. The intention of the survey was to collect data about the prevalence of NMS in Europe and the preferred medical treatment choices. Additionally, some questions about the Madigan Foal squeeze were included to collect data about the use and experience of this novel technique. Each participant received an e-mail (**Appendix I**), asking the participants to follow a link to the questionnaire available on Survey Monkey from 05-05-2019 until 13-09-2019. A selection of 84 veterinarians from different countries throughout Europe were asked to participate in the study. Veterinarians from Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Norway, Poland, the United Kingdom, Slovenia, Spain, Sweden and Switzerland were invited to participate.
Before starting the survey, the participants were informed about the nature of the survey, the length and the anonymity of the participants.
All questions, except for the comment box, were multiple choice, with a variable number of answers per question. In the first question, the participants are asked about the amount of neonatal foals admitted to their care in 2018, with no criteria to the reason why they were admitted. Then, the participants were asked if they had access to a neonatal intensive care unit. Question three sought information about the percentage of foals diagnosed with NMS regarding all neonatal foals admitted to the participants care, to illustrate the prevalence of NMS in Europe. Treatment of NMS is discussed in question four and five. Question 4 was a list of frequently used medical therapies and the participants were asked to choose one or more of the following answers: placement on bed, use of a sternal pillow, thermoregulation, bottle feeding, tube feeding, parenteral nutrition, intranasal oxygen, antimicrobials, intravenous fluid therapy by means of boluses, fluid therapy constant rate infusion, ACTH administration, DMSO administration, NSAID administration, corticosteroid administration, mannitol administration, vitamin E administration, plasma transfusion, gastroprotectants, anticonvulsant therapy or Madigan Foal Squeeze. The last answer option consisted of a text box where the participants could fill in another than above named therapy. The fifth question focused on where the NMS diagnosed foals were treated and possible answers were; only in the clinic, some at home but mostly in the clinic, most at home some in the clinic and only at home. This was asked to try to determine the differences in treating NMS diagnosed foals at home or in clinic environment. Question six to nine attended to the Madigan foal squeeze technique. The participants are asked how frequently they have been using the squeeze, if they applied it with or without other treatment methods and what their average recovery rate of NMS diagnosed foals was, with or without the application of the MFS. The questions can be found in **Appendix II**. The responses were registered via Survey Monkey and the data was copied to Microsoft Excel 2013.

Results

During the period the link to the questionnaire was available, 14 veterinarians responded to the invitation. The 14 respondents were located in Belgium (2), England (1), Estland (1), Finland (1), France (1), Germany (2), Ireland (1), Romania (1), The Netherlands (2), Sweden (1) and Switzerland (1). More than 800 neonatal foals were admitted to the care of the participants in 2018 and around 120 foals (N = 120/800, 15%) were diagnosed with NMS (**Fig. 3**). Seventy-one percent of the participants had access to a neonatal intensive care and most veterinarians treated the foals exclusively in a clinic (86%). One veterinarian treated the foals only at home and one did both but mostly in a clinic. Each veterinarian used a wide range of medical treatments, including tube feeding (100%), antimicrobials (93%), plasma transfusion (93%), intranasal oxygen (86%), fluid therapy constant rate infusion (86%), gastroprotectants (79%), anticonvulsant therapy (79%), intravenous fluid therapy by means of boluses (71%), placement on bed (71%), parenteral nutrition (57%), use of sternal pillow (57%), corticosteroids (43%), vitamin E (43%), thermoregulation (36%), NSAIDs (29%), mannitol (29%), bottle feeding (21%), allopurinol (7%), DMSO (7%), ACTH (7%) (**Fig. 4**). 30% had not used the Madigan Foal Squeeze procedure before, 55% applied MFS 1-10 times and 15% applied the squeeze procedure more than 10 times. Of the participants that performed the squeeze, 90% did this only in combination with other treatments and one participant combined the MFS in half of the cases with other treatments. An average recovery rate of 75% was stated by 9 participants, while some experienced a lower recovery rate or no recovery at all (**Fig. 5**). The average recovery rate was 55% with no difference between the foals treated with MFS or without MFS, except for 2 participants. One of them stated no recovery while using the MFS and a recovery of 75% without MFS. The other participant experienced a recovery rate of 50% with MFS and 25% without MFS. One of the participants who treated the foals only at home reported a recovery rate of 50% in NMS foals treated without MFS. More data needs to be collected to analyze the recovery rate of NMS foals treated outside clinic environments.

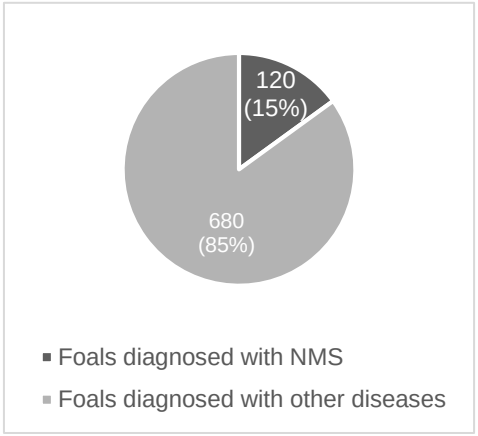

***Fig. 3**. Foals admitted to the veterinary care of the participants*

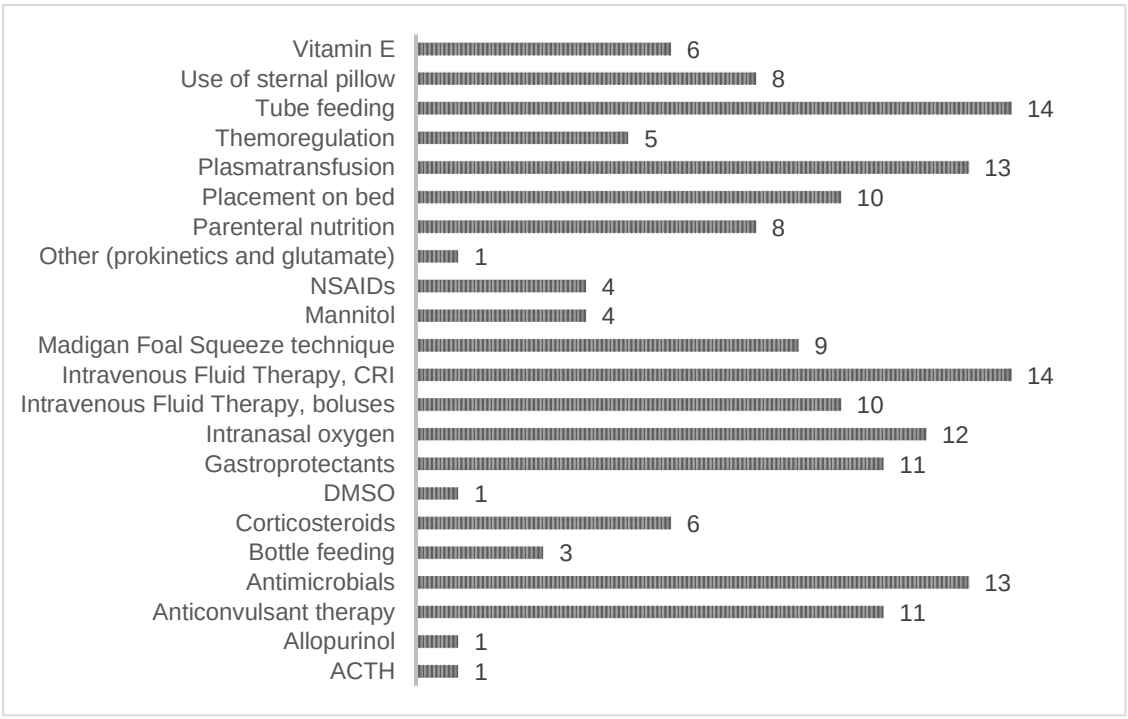

Fig. 4*. Frequently used medical support in foals diagnosed with NMS, ordered alphabetically*

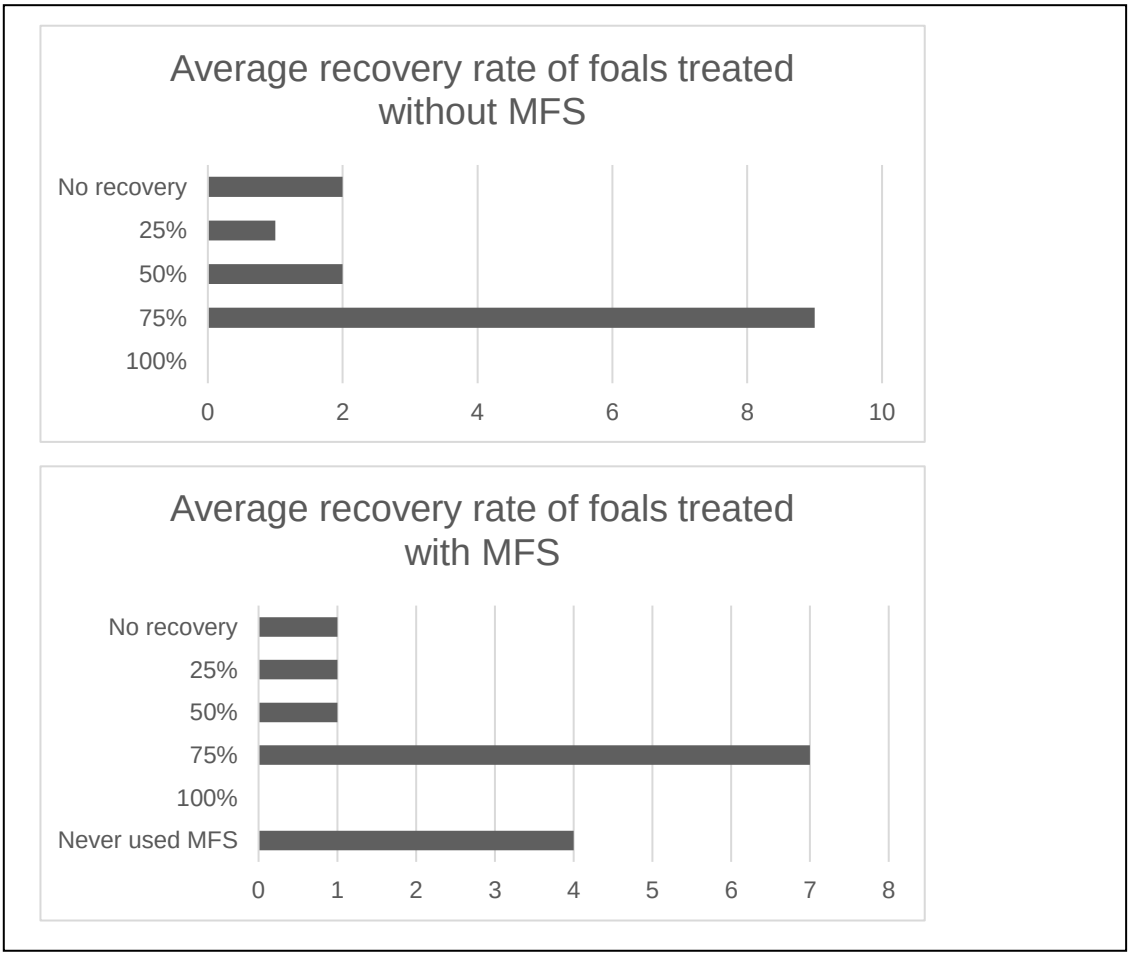

Fig. 5*. The average recovery rate per participant*

9. Flow Chart

The arrival of a foal with NMS symptoms can be chaotic and the following flowchart (**Fig. 6**) can be used as a guide in clinic environments. The target audience is the veterinary medicine student in the last part of his or her training, as the step from student to independent veterinarian can be big challenge. They can consult this flowchart to minimalize the chance of missing an important step in supporting the foal. This flowchart is not limited and personal preferences could be different than the presented ways of treatment. Please note that if the foal shows signs of other diseases, this chart will not serve you well.

The first step is to recognize the symptoms displayed by a foal with NMS, i.e. indifference to environment and the dam, absence of a sucking reflex, aimless wandering or lateral recumbency.

1. A clinical examination with recording of the physical parameters is essential to evaluate the foals' health status. An assessment of heart rate, respiratory rate, rectal temperature, auscultation of chest and abdomen, dehydration status, presence of sucking reflex, state of consciousness and basic haematology should be performed and trauma or other differential diagnoses should be excluded.
2. Oxygen therapy should be started when the foal has an abnormal breathing pattern or if hypoxia is suspected, starting with administration of humidified oxygen via nasal insufflation and placement of the foal in sternal recumbency. In case of low PaO2, mechanical ventilation or CPAP should be considered.
3. To suppress seizures or seizure-like activities, first choice of medical treatment is diazepam or midazolam. In case of severe, repetitive or persistent seizures, phenobarbital could be administered. Preferably the foal should be kept in a quiet environment after the initial assessment to lower the in pact of external stimuli.
4. Frequent monitoring of serum glucose concentration is necessary to adjust proper glucose administration. When normal gut sounds are present, bottle feeding or feeding via nasogastric tube is preferred. In case of gastrointestinal malfunction, parenteral nutrition can be used. Be careful with using a 5% glucose solution when hypovolemia is present, as glucose can decrease plasma sodium concentrations, exacerbating hypovolemia.
5. The foal should receive intravenous fluids according to dehydration status and maintenance requirements. A urinary catheter should be inserted and connected to a closed urine collection system, to be able to measure urine output and prevent urine scalding in the recumbent foal.
6. Additional medical support can be administered, such as antimicrobials, DMSO, allopurinol, magnesium sulphate, thiamine, omeprazole, vitamin E or plasma.

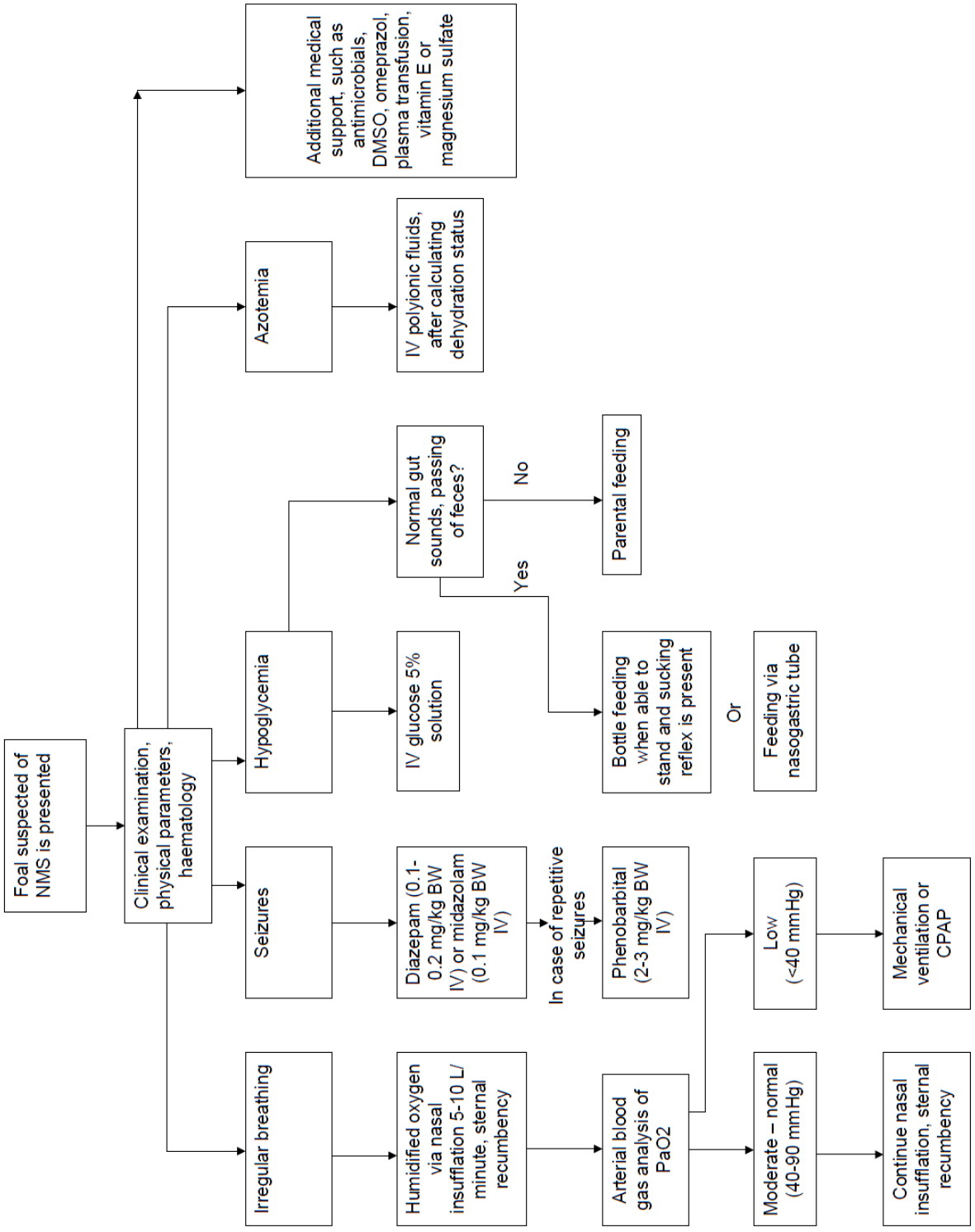

Fig. 6. Flowchart for management of the NMS foal

10. Discussion

This small study shows that NMS is a common disease in neonatal foals in Europe, with approximately 15% (N = 120/800) of sick neonatal foals suffering from this syndrome. A preference under veterinarians exists to treat the affected foals in a clinical environment (N = 12.75/14, 91%), rather than treating the foals in the field (N = 1.25/14, 8.9%). The overall recovery rate was 50%, lower than the recovery rate of 70-85% elsewhere reported (Vaala, 2002; Aleman et al., 2017) and no difference was noticed in recovery rate between foals treated with or without MFS.

Limitations of this study include the small amount of respondents, the equal randomized presentation of the respondents and the difficulties of standardized diagnosing and performance of the squeeze. Although the survey invited both veterinarians with and without hospitalization access, it is possible that more respondents with access to an equine clinic have responded. This could influence the outcome, as clinics usually treat the more severe sick foals, but have better access to treatments. No description of required symptoms and clinical findings were included in the survey, this may have caused inclusion of foals not suffering from NMS. As for the squeeze method, no guidelines for applying the rope technique were included, and the possibility exists that the technique was not performed correctly by the respondents. The results of this survey need to be interpreted with care, keeping the limitations in mind.

Sharing experiences in treating NMS can have several advantages, as much is still unclear about this syndrome and the ideal way to treat it. The affected foals can display an amazing range of clinical signs and treatment has to be modified on each foal individually. Treatment of NMS foals is mostly supportive and a wide range of medical products are available. Nursing care of NMS foals can be expensive and time-consuming, and treatment often requires hospitalization. When hospitalization is not possible, or the owner's financial means are not sufficient, the foal suffers great disadvantage. While treatment of NMS is mostly supportive, anecdotal evidence of positive effects of a squeeze method on some NMS foals brings a new opportunity in treating the affected foals, hasting the recovery and reducing hospitalization time. With this method, it may even be possible to treat some foals diagnosed with NMS in the field, reducing hospitalization-related stress and expenses. In a previous study, promising results show signs of a quicker recovery in NMS foals which received the squeeze procedure, decreasing the time to full recovery (Aleman et al., 2017). In the present study, recovery time was not included in the survey. Several explanations can lead to the lower recovery rate found in this study. An unequal randomized presentation of the respondents could have influenced the outcome, as 10 out of 14 respondents state to have access to a neonatal care unit, and thus may be treating the more severe cases, with a higher mortality rate. On the other hand, contributing to the lower recovery rate could be the respondents stating to treat some NMS foals in the field, which makes providing intensive care nearly impossible.
In the survey Aleman and her team conducted, the major part of the respondents were from the United States and geographic location linked differences in medical preferences and customs could lead to a difference. The small sample size could also influence the recovery rate as 2 out of 14 stated to experience no recovery at all, and studies with a larger sample size and better standardization are necessary to confirm the data.

According to the survey, most preferred medical treatment consists of tube feeding, plasma transfusion, intravenous fluids and antimicrobials. Similar results were obtained in the previous surbey and this emphasizes the need of supportive treatment in management of the NMS foal.

Recognizing the NMS foal is a challenge to many veterinarians, as the displayed symptoms can range from a reduced sucking reflex to lateral recumbency or impetuous seizures. A point of interest in diagnosing hypoxic brain injury is the use of biomarkers in plasma, such as ubiquitin C—terminal hydrolase and phosphorylated axonal forms of neurofilament (Ringger et al., 2011). The biomarkers could have clinical importance in diagnosing the NMS foal and even though no correlation between ubiquitin C—terminal hydrolase levels and outcome were present in a study in foals with HIE (Lee et al., 2018), further studies are necessary to determine importance in foals with brain injury.

Being able to identify NMS foals that could be responsive to the thoracic squeeze method would be a big step in the management of NMS foals, as it could prevent referral to clinic, reduce costs and improve welfare of foal and dam. It is proposed that pressure of the birth canal during parturition might play a role in the onset of extra uterine neuroactivation (Aleman et al., 2017) and discovery of factors that could counteract on this activation could lead to a better understanding of managing these foals. It is suggested that serial pregnanolone and progesterone analysis could be useful in diagnosing the NMS foal, but as most foals with symptoms of NMS require immediate medical attention clinical relevance has yet to be determined.

Important factors in prevention of NMS are health of the mare during pregnancy, guidance through delivery and quick recognition of abnormal development of the neonatal foal. A rapid onset of multi-systemic supportive treatment is recommended to limit the broad range of symptoms. Therapeutic hypothermia is established as standard treatment in human neonates with hypoxic-ischemic encephalopathy, as it decreases mortality and increases long-term neurodevelopmental outcome (Jacobs et al., 2013). This could be a promising therapy in foals after going through a hypoxic event.

This review of NMS in foals is not limited and makes it clear that more research is needed to clarify the pathologic pathways and optimal treatment in this syndrome. NMS is a common disorder in neonatal foals, emphasizing the need of more scientific exploration. Extraction of knowledge from human medicine in developing methods of diagnosis and treatment of infants suffering from PAS could be valuable, but differences in financial means and the availability of medical implements (CT, MRI, intensive care) could cause difficulties. The role of the thoracic squeeze procedure used in treating foals suffering from post-natal persistence of fetal cerebrocortical activity is something that requires further investigation to understand the clinical relevance.

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APPENDIX I

Email accompanying the questionnaire

Dear sir/madam,

My name is Eline Zonneveld, I'm a last year veterinary student from Ghent University, Faculty of Veterinary Medicine, Belgium. I am conducting a survey to collect data about the prevalence and treatment of Neonatal Maladjustment Syndrome and your input would be very much appreciated.

Click the link below to start the survey that will take you approximately 5 minutes.

https://nl.surveymonkey.com/r/NV77WF6

Thank you for your participation!

With kind regards,

Eline Zonneveld
Email: eline.zonneveld@ugent.be
Telephone number: +31616836465

Ghent University
Faculty of Veterinary Medicine
Department of Virology, Parasitology and Immunology
Research Group Comparative Physiology
Prof. Dr. Catherine Delesalle
Drs. Berit Boshuizen

APPENDIX II

The questionnaire

Dear sir/madam,

Thank you for participating in this short questionnaire about Neonatal Maladjustment Syndrome (NMS) in foals. It will take approximately 5 minutes to complete. The answers will be processed completely anonymous and the name of your clinic will not be mentioned in public sources.

Neonatal Maladjustment Syndrome (NMS), also called Hypoxic Ischemic Encephalopathy is a big challenge in the Equine Medicine Field. This questionnaire is to support my veterinary medicine thesis 'Causes and Treatment of Neonatal Maladjustment syndrome and review of the Madigan Foal Squeeze Procedure'.

The Madigan Foal squeeze (a novel physical compression procedure designed to treat NMS in foals) is also included in this questionnaire to examine the use of this technique by veterinarians in Europe.

I thank you in advance for answering these questions.

1. How many neonatal foals were admitted to your care in 2018?
    a. 0-10 foals
    b. 10-50 foals
    c. 50-100 foals
    d. More than 100 foals

2. Does your clinic have a neonatal intensive care unit?
    a. Yes
    b. No

3. How many foals were diagnosed with NMS as percentage of all the neonatal foals admitted to your care?
    a. 0-10%
    b. 10-20%
    c. 20-30%
    d. More than 30%

4. Which treatment options does your clinic use in NMS cases? (Multiple answers possible)
    a. Intravenous fluid therapy, by means of boluses
    b. Fluid therapy, constant rate infusion
    c. Intranasal oxygen
    d. Tube feeding
    e. Bottle feeding
    f. Antimicrobials

g. Parenteral nutrition
h. Plasmatransfusion
i. Placement on bed
j. Use of a sternal pillow
k. Thermoregulation
l. ACTH administration
m. DMSO administration
n. NSAID
o. Corticosteroid administration
p. Mannitol administration
q. Allopurinol administration
r. Vitamin E administration
s. Gastroprotectants
t. Anticonvulsant therapy
u. Madigan Foal Squeeze
v. Other (open answer)

5. Where do you treat NMS foals?
    a. Only in my clinic
    b. Some at home, but mostly in my clinic
    c. Most at home, some in my clinic
    d. Only at home

6. How many times did you use the Madigan Foals Squeeze Procedure (MFS)?
    a. 1 time
    b. 2-10 times
    c. More than 10 times
    d. Never
    e. I have never heard of it

7. How frequently did you use other treatments while using MFS?
    a. MFS was my only treatment
    b. In approximately half of the cases I combined MFS with other treatments
    c. I only used MFS in combination with other treatments
    d. I have never used MFS

8. What was the average recovery of the NMS-foals treated with MFS?
    a. No recovery
    b. 25%
    c. 50%
    d. 75%
    e. 100%
    f. I have never used MFS

9. What was the average recovery of the NMS-foals treated without MFS?
    a. No recovery
    b. 25%
    c. 50%
    d. 75%
    e. 100%

10. This box has room for comments or if you wish to receive the results of this questionnaire in time, please leave an email-address:
    a. Open answer

APPENDIX III

Illustrating photos on applying the Madigan Foal Squeeze technique from the written instructions on the website of University of California, campus Davis[5], with personal permission from prof. Dr. John Madigan.

Step 1: Put the rope over withers and between front legs

Step 2: Run the rope through the loop at end of the rope and snug rope.

Step 3: Begin by making the first half hitch around the chest, just behind elbow.

Step 4: Keep the rope snug (photo of first half hitch in place)

Photos of two half hitches in place

Step 5: Stand behind foal and begin to put tension on rope. The foal will then lie down.

Step 6: When the foal is lying down, keep tension on rope for the next 20 minutes and release.