Neonatal Encephalopathy in Calves Presented to a University Hospital

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Background: While studies have examined bovine dystocia in relation to calf survival, little has been published regarding perinatal morbidity and treatment of newborn calves beyond failure of transfer of passive immunity (FTPI). Neonatal encephalopathy (NE) is a clinical syndrome commonly diagnosed in infants and foals but is poorly described in calves.

Hypothesis/Objectives: To identify risk factors for development of NE in calves and factors predictive of survival.

Animals: Neonatal calves presented to a University hospital over a 10-year period.

Methods: Retrospective cohort study (2005–2015). Medical records of all neonatal calves presented to the hospital were examined, and cases of NE were identified. Data pertaining to demographics, dam parity, labor, treatment, and outcome were collected and analyzed with univariate and multivariate statistics.

Results: Of 200 calves in the final analysis, 58 (29%; 95% CI: 22.8–35.8%) were classified as NE and 142 calves as non-NE. In univariate analysis, factors significantly associated with diagnosis of NE included male sex, presence of dystocia, abnormal position in the birth canal, and prolonged labor. In the multivariate model, only orientation of the calf in the birth canal remained significant (OR 2.14; 95% CI: 1.02–4.49; P = 0.044). Overall survival of calves with NE was good (45/58; 77.6%; 95% CI: 64.7–87.5); dam parity and being a twin was significantly associated with nonsurvival.

Conclusions: Calves born after dystocia, especially if malpresented, should be closely monitored for nursing behavior within the first 24 hours of life. Prognosis for survival is good, but supportive care might be required for several days.

Key words: Bovine; Hypoxic; Ischemic; Weak.

Perinatal calf morbidity and mortality are important for both veterinarians and producers given the investment in both achieving pregnancy and supporting a cow through gestation. Given its importance, identification of risk factors that influence calf survival has long been a topic of study.

Foals that present with central nervous system (CNS) deficits that occur within the first 3 days of birth with no obvious congenital, metabolic, genetic, or traumatic cause are often assumed to have suffered from hypoxic cerebral injury. Diagnostic terminology for these cases varies; the terms dummy foal syndrome, hypoxic-ischemic encephalopathy (HIE), perinatal asphyxia syndrome (PAS), or neonatal maladjustment syndrome (NMS) are often used interchangeably. However, in both human and equine medicine, this is often a diagnosis based on clinical signs and can encompass multiple etiologies. Advanced imaging of the brain to confirm hypoxic-ischemic damage is not routinely performed in veterinary medicine and a definitive antemortem test has not been established. More recently, the term neonatal encephalopathy (NE) has been suggested to describe the clinical syndrome in humans and foals. While clinical descriptions vary, inability to find the udder and nurse were identified as the most common clinical signs in foals diagnosed with NE.

In neonatal calf medicine, the term “dummy” has been used for decades but was typically applied to calves with the nebulous diagnosis of weak calf syndrome (WCS). This syndrome became a “catch-all” diagnosis for stillborn calves or those born small, weak and that failed to thrive, typically dying within days of birth. These calves were not typically described as exhibiting CNS deficits, and several studies reported that genetic, infectious or nutritional etiologies could result in a diagnosis of WCS.

There have been a series of studies documenting respiratory acidosis in neonatal calves both experimentally and in naturally occurring cases of dystocia, and severity of acidosis has been correlated with non-survival and reduced absorption of colostral IgG. While these calves could have experienced a hypoxic

Abbreviations:

FTPI failure of transfer of passive immunity
NE neonatal encephalopathy
C-section cesarean section
CNS central nervous system
HIE hypoxic-ischemic encephalopathy
PAS perinatal asphyxia syndrome
NMS neonatal maladjustment syndrome
WCS weak calf syndrome
NSAID nonsteroidal anti-inflammatory drug
MRI magnetic resonance imaging
EEG electroencephalography

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cerebral injury, there has been little description of the clinical signs, treatment, and survival of such calves in the neonatal period beyond immediate resuscitation and survival. Despite the lack of case definition, many veterinarians have likely recognized NE in calves, especially clinicians who also work with foals. A recent paper found that 155 of 1,065 foals (14.5%) presenting to a referral hospital at less than 14 days of age were diagnosed with NE. The condition was also recognized in 2 of 65 (3.5%) camelid neonates that were presented to a referral hospital at less than 30 days of age. Given that over 33 million calves are born in the United States annually, recognition of NE and identification of risk factors for development of disease and nonsurvival are important. The objective of this retrospective study was to identify risk factors for development of NE in calves and factors that influence survival. Known risk factors in foals include dystocia and C-section; we hypothesized that the same risk factors would be associated with risk of NE in calves.

Materials and Methods

Medical records from the Purdue University Veterinary Teaching Hospital were searched to identify records of all calves born in the hospital or that presented within the first week of life from January 2005–January 2015. As not all calves born in the hospital received an independent medical record, all records of cows that presented for dystocia, elective obstetric boarding, C-section, or other parturition-related presentation were also reviewed. Over 900 records were initially identified; those lacking information specifically related to the calf were excluded along with stillborn or deformed calves requiring immediate euthanasia. The remaining calf and/or cow records (n = 379) were evaluated further and were excluded if the cow/calf was discharged immediately postpartum (prior to nursing) or if there was no specific information on nursing behavior in the medical record.

From the remaining cases (n = 222), a clinical diagnosis of NE was made if the calf did not have a suckle reflex and did not nurse from the dam or a bottle within the first day of life (Day 0). As previous observational studies of bovine parturition have determined that calves may require assistance nursing within the first hours of life, it was classified as a non-NE calf. Calves that were administered Colostrum via orogastric tube immediately after birth for clinician convenience and/or maternal factor (e.g., cow still in surgery) were retained in the non-NE group if subsequent nursing was successful by Day 1.

As Indiana is considered a selenium-deficient region, calves described simply as “weak” without an inability to nurse or diagnosed with nutritional myodegeneration were excluded. While clinical signs may not be observed until 1–2 days after birth in foals, calves that nursed initially and then stopped nursing, for whatever reason, were excluded to avoid confounding the data.

Data collected from each calf record included sex, breed, birthweight, age of dam, parity of dam, length of labor, season of birth, total plasma protein (TPP) concentration within 24 hours of birth, and day of age when the calf first nursed from the dam or a bottle. Estimated length of labor was based on owner-reported information and was classified as <1 hour, 1–6 hours, or >6 hours; no distinction between stage I and stage II labor could be made based on medical records. Season of birth was defined as winter (December–February), spring (March–May), summer (June–August), or autumn (September–November). Total plasma protein was used to assess passive transfer of colostral immunoglobulins as this has been shown to be an appropriate stall-side test and is superior to serum gamma-glutamyltransferase (GGT) in beef calves. Calves with TPP >5.5 mg/dL were considered to have adequate transfer of passive immunity and TPP <5.0 mg/dL was considered FTPI; values between 5.0 and 5.5 mg/dL were considered to have a partial failure of transfer of passive immunity. Clinicopathologic values and necropsy findings were examined when available.

Dichotomous variables included induction of labor, the presence of dystocia, vaginal assistance attempted at the farm prior to arrival at the hospital (either by owner or referring veterinarian), vaginal assistance attempted at the hospital, C-section, and normal orientation of the calf. Dystocia was defined as the necessity of vaginal assistance (manual or with chains) or C-section to extract the calf. No attempt at grading the degree of assistance was made given the lack of information in the medical record. The calf jack was not used in the hospital in any case. The degree of assistance was not mutually exclusive; for example, some cows had attempted vaginal assistance on the farm, in the hospital, and still required a C-section. Cows that presented for elective C-section were also included. Normal calf orientation was defined as cranial presentation in a dorsoventral position with both front legs preceding the head in the birth canal. Caudal presentation was considered abnormal in this study to remain consistent with previous publications describing dystocia in beef cattle. Calves not in normal orientation were defined as malformed.

Different treatments were also recorded as dichotomous variables and included use of antibiotics, thiamine, vitamin E-selenium supplementation, oxygen therapy, caffeine, plasma administration, nonsteroidal anti-inflammatory drugs (NSAIDs), and administration of a commercial colostrum supplement. As the NE calves by definition lacked the ability to nurse, enteral feeding was not considered a treatment variable. The day in which the calf successfully nursed from the dam or from the bottle was recorded. The primary outcome measurements were a diagnosis of NE and survival to discharge. Long-term follow-up was not attempted because of the case population.

Data that were continuous numerical variables were assessed for normality by the Shapiro-Wilk test, and if normally distributed compared by Student’s t-test. Confidence intervals (95%) for frequency counts of categorical variables were determined using a binomial distribution. Categorical data were compared in univariate analysis by the chi-square test of independence, or Fisher’s exact test if expected frequencies for >20% of cells were less than 5. Variables associated with being a NE case in univariate analysis were further evaluated in a multivariate logistic regression model. For all comparisons, statistical significance was set at P < 0.05.

Results

Demographics and Parturition-Related Factors

Results are summarized in Table 1. A total of 200 calves were statistically analyzed, including 58 (29%; 95% CI: 22.8–35.8%) calves with NE and 142 calves classified as non-NE. Not all records had a complete data set; the number of records analyzed for each variable is indicated as needed. Most of the calves, 189/200
(94.5%), were born in the hospital. Mixed-breed beef cattle were the predominant breed identified (47.5%); the remainder of the calves represented 10 breeds: Angus (12%), Shorthorn (12%), Hereford (11.5%), Chianina (5.5%), Holstein (3%), Maine Anjou (3%), Simmental (3%), Charolais (1.5%), Ayrshire (0.5%), and Guernsey (0.5%). If grouped by production type, 192/200 (96%) calves originated from beef production or show farms, and 8/200 (4%) calves were from dairy farms. There was no significant difference in breed between non-NE and NE calves ($P_{=0.69}$). Most births were in the spring (50.5%), followed by winter (39.5%), summer (7.5%), and autumn (2.5%). Season of parturition did not differ between groups ($P_{=0.11}$).

Sex of the calf was not recorded in 8 cases (7 non-NE, 1 NE); of the 192 calves with sex recorded, 135 (70.3%) were male and 57 (29.7%) were female. Male calves were overrepresented in the NE group ($P_{=0.041}$), but birthweight between the groups did not differ ($P_{=0.58}$) (Table 1).

Information on parity was available in 131 cows, and the majority were primiparous dams that ranged from 1 to 4 years of age. The multiparous cows with known parity had undergone 2–9 previous pregnancies. There was no association between diagnosis of NE and age ($P_{=0.59}$) or parity ($P_{=0.55}$) of the dam. In 34 cases, labor was induced; there was no association between induction of labor and diagnosis of NE ($P_{=0.24}$). There were 14 calves that represented 8 sets of twins (6 live pairs, 1 born with a dead twin, 1 presented at 3 days of age). Being a twin was not significantly associated with diagnosis of NE ($P_{=0.12}$).

Length of labor was estimated in 159 cases, 41 of which were diagnosed with NE (9.4%) were born in the hospital during obstetric boarding or after elective C-section due to a maternal factor. Most of the calves (71.7%) were born after 1–6 hours of labor; the remaining calves (18.8%) were born after 6 or more hours of labor. Prolonged labor (>6 hours) was noted in 31.7% of NE calves and 14.4% of the non-NE group. This difference was significant ($P_{=0.037}$).

In total, 145/200 (72.5%) calves were born after dystocia, including 49/58 (84.5%) NE calves and 96/142 (67.6%) non-NE calves. A C-section was performed in 32/58 (59.9%) of NE calves and 85/142 (55.2%) of non-NE calves. There was a significant association between dystocia and diagnosis of NE ($P_{=0.015}$), but no association between delivery by C-section and diagnosis of NE ($P_{=0.54}$).

### Table 1. Univariate analysis (chi-square or Fisher’s exact test, or t-test [wt]) of selected variables between calves diagnosed with neonatal encephalopathy (NE) (n = 58) and calves without NE (n=142) born in the hospital or presented at <1 week of age between 2005 and 2015.

| Variable                     | N   | All Calves n (% of N) | NE Calves n (%) | Non-NE Calves n (%) | $P$-value |
|------------------------------|-----|-----------------------|-----------------|---------------------|----------|
| Demographic data             |     |                       |                 |                     |          |
| Body weight (kg) ($\mu \pm$ SD) | 171 | 45.2 ± 9.6            | 44.4 ± 7.5      | 0.58                |          |
| Sex number (%)               | 192 | 57                    | 135             | 0.041b              |          |
| Male                         | 135 (70.3) | 46 (80.7)            | 89 (65.9)       | 0.041b              |          |
| Female                       | 57 (29.7)  | 11 (19.3)             | 46 (34.1)       | 0.041b              |          |
| Season of birth, number (%)  | 200 |                       |                 | 0.11                |          |
| Winter                       | 79 (39.5)  | 28 (48.3)             | 51 (35.9)       | 0.11                |          |
| Spring                       | 114 (71.7) | 26 (63.4)             | 88 (74.6)       | 0.11                |          |
| Summer                       | 15 (7.5)   | 4 (6.9)               | 11 (7.6)        | 0.11                |          |
| Autumn                       | 5 (2.5)    | 3 (5.2)               | 2 (1.4)         | 0.11                |          |
| Dam parity, number (%)       | 131 | 37                    | 94              | 0.55                |          |
| Primiparous                  | 96 (73.3)  | 26 (70.3)             | 70 (74.5)       | 0.55                |          |
| Multiparous                  | 35 (26.7)  | 11 (29.7)             | 24 (25.5)       | 0.55                |          |
| Parturition-related variables|     |                       |                 |                     |          |
| Labor length, number (%)     | 159 | 41                    | 118             | 0.037b              |          |
| <1 h                         | 15 (9.4)   | 2 (4.9)               | 13 (11.0)       | 0.037b              |          |
| 1–6 h                        | 114 (71.7) | 26 (63.4)             | 88 (74.6)       | 0.037b              |          |
| >6 h                         | 30 (18.9)  | 13 (31.7)             | 17 (14.4)       | 0.037b              |          |
| Induction, number (%)        | 200 | 7 (12.1)              | 27 (19.0)       | 0.24                |          |
| Yes                          | 34 (17.0)  | 7 (12.1)              | 27 (19.0)       | 0.24                |          |
| Dysstocia, number (%)        | 200 | 49                    | 96 (67.6)       | 0.015b              |          |
| Yes                          | 145 (72.5) | 49 (84.5)             | 96 (67.6)       | 0.015b              |          |
| C-Section, number (%)        | 200 | 52 (55.2)             | 85 (59.9)       | 0.54                |          |
| Yes                          | 117 (58.5) | 49 (49.5)             | 135             | 0.54                |          |
| Calf orientation             | 184 | 49                    | 100 (25.9)      | 0.007b              |          |
| Abnormal                     | 58 (31.5)  | 26 (46.9)             | 100 (25.9)      | 0.007b              |          |
| Twin, number (%)             | 200 | 7 (12.1)              | 7 (4.9)         | 0.12                |          |

$^a$Number of calves for which data were available for a given variable.

$^b$Indicates a statistically significant difference between the NE and non-NE groups.
Calf position was recorded for 184 calves, including 49 in the NE group and 135 in the non-NE group. Overall, 58/184 (31.5%) calves were malpresented and 42/58 (72.4%) required a C-section. In the non-NE group, 35/135 (25.9%) calves were malpresented compared to 23/49 (46.9%) of NE calves. Malpresentation was significantly associated with a diagnosis of NE \((P = 0.007)\). Of the NE calves that were malpresented, 9/23 (39%) were in caudal position, 7/23 (30%) were in cranial presentation but with lateral deviation of the head or unilateral shoulder flexion, 5/23 (22%) were breech, 1 (4.3%) was in transverse presentation, and 1 was associated with a uterine torsion (4.3%).

In multivariate analysis of calf gender, labor length, dystocia, and calf position, malpresentation was the only variable that remained significant for development of NE \((OR 2.14; 95\% CI: 1.02–4.49; P = 0.044)\) (Table 2).

### Treatment and Outcome

Overall, 45/58 (77.6%; 95% CI: 64.7–87.5) calves with NE and all non-NE calves survived to discharge from the hospital. Of the surviving NE calves, 33/45 (73.3%) began nursing independently in the hospital before discharge. These calves began nursing on Day 1 \((n = 9)\), Day 2 \((n = 10)\), Day 3 \((n = 12)\), Day 4 \((n = 2)\), and Day 6 \((n = 2)\). There were 11/45 (24.4%) NE calves that were discharged alive before the development of independent nursing due to owner preference; the median age of these calves was 2 days old (range 1–6 days). The remaining calf was discharged but the day of nursing could not be determined from the medical record.

Concurrent diseases were identified in 43/200 calves and fell into 4 basic categories: musculoskeletal disease (primarily flexural limb deformities), diarrhea, pneumonia, or meconium staining. Calves with NE were significantly more likely to have a concurrent disease \((P = 0.001)\) (Table 3). Only 27 calves had bloodwork performed, primarily in NE calves after the onset of disease and in only 3 nonsurviving calves.

There was no effect of season, sex, calf birthweight, labor length, dystocia, and need for C-section on survival of NE calves (Table 4). While there was no significant effect of TPP concentration on survival, only 8 of 13 nonsurvivors had TPP concentrations recorded, 5 of which had TPP concentrations of <5 g/dL. Data on dam parity were available in 37/58 of calves in the NE group, consisting of 29 survivors and 8 nonsurvivors. All 8/8 non-surviving NE calves with information on dam parity were born to primiparous dams. Being born to a primiparous dam and being a twin were significantly associated with nonsurvival of NE calves \((P = 0.044\) and \(P = 0.005\), respectively). There was no difference in survival between calves with NE that presented normally and those that presented abnormally \((P = 0.16)\).

Of the 13 nonsurvivors, 4 died within 4 hours of birth (3 died, 1 euthanized). There were 3 calves that were born in the hospital and subsequently euthanized at 15 hours, 2 days, and 4 days of age due to lack of improvement in ability to nurse. There were 2 calves that presented at 3 days of age and were diagnosed with NE and subsequent FTPI and sepsis; 1 died and 1 was euthanized on the day of presentation. There were 2 calves that were born in the hospital and subsequently died on days 3 and 7, respectively. Both calves were presumed to have died from sepsis secondary to NE, and both had necropsies performed that confirmed sepsicemia. The calf that died at 3 days of age had no histopathologic changes in the CNS. However, the calf that died at 7 days of age had evidence of hemorrhage in the subarachnoid space of the thoracic spinal cord. Histopathology of the brain did not reveal any abnormalities. This calf had begun nursing independently 2 days before death. Of the remaining 2 calves, 1 was euthanized at 2 days of age with no reason recorded and 1 calf died but the age of death or reason was not recorded. Among calves diagnosed with NE, there was no effect of any treatment on survival (Table 5).

### Discussion

This study identified male gender, dystocia, prolonged labor, and calf malpresentation as risk factors for...
development of NE in neonatal calves. While approximately 30% of calves in this study were diagnosed with NE, this should not be over interpreted given the high number of cases that were excluded from analysis because of incomplete medical records or immediate postpartum discharge from the hospital before nursing. After multivariate analysis, calf malpresentation remained a significant risk factor for NE in calves. Abnormal fetal orientation is a risk factor for NE in human infants, with occipital-caudal position (head first, facing forward) 28 or noncephalic presentation 29 associated with NE as compared to normal occipital-cranial position (head first, facing backward). While dystocia is a risk factor for NE in foals, 30 the importance of foal orientation has not been described. Equine dystocia is primarily due to improper orientation of the foal within the birth canal, ranging from 64 to 77% of cases presenting for dystocia, 31–33 while fetal-dam size disparity is rare, at 2–6% of cases. 32,33 However, these studies did not report on perinatal morbidity beyond survival. 31–33 Conversely, in the current study, abnormal presentation comprised 41% of all cases of calves born after dystocia where calf orientation was recorded. This likely correlates with the increased significance of fetal-dam size disparity, which is considered to be the most common reason for dystocia in cattle. 34 With regard to calf size, increased birthweight and male sex have been shown to strongly correlate with incidence of dystocia. 27,34–37 While this finding likely explains the predominance of male calves in the overall study population, it is unclear why male calves had an increased risk of NE compared to female calves when birthweight was not different between sexes or groups.

There have been few studies specifically examining the prevalence of dystocia in beef cattle. One large retrospective study of over 2,000 parturitions in a mixed-breed beef herd found a dystocia prevalence of 17% and 4% in primiparous and multiparous dams, respectively. 27 A more recent paper specifically examined dystocia in 3-year-old primiparous beef dams and found a dystocia occurrence of 14.1%. 38 There are a wide range of reported dystocia rates in dairy cattle

Table 4. Univariate analysis (chi-square or Fisher’s exact test, or t-test [wt]) of selected variables of 58 calves diagnosed with neonatal encephalopathy (NE) that survived (n = 45) or did not survive (n = 13) to discharge from the hospital.

| Variable                        | N   | All NE Calves | Survivors | Nonsurvivors | P-value |
|---------------------------------|-----|---------------|-----------|--------------|---------|
| Demographic data                |     |               | All NE    | Survivors    | Nonsurvivors | P-value |
| Body weight (kg) (μ ± SD)        | 49  | 46.3 ± 9.6    | 40.2 ± 7.8 | 0.081        |
| Sex, number (%)                 | 57  | 44            | 13        | 0.70         |
| Male                            |     | 46 (70.3)     | 36 (78.3) | 10 (21.7)    |
| Female                          |     | 11 (29.7)     | 8 (72.3)  | 3 (27.3)     |
| Season of birth, number (%)     | 58  |               |           | 0.63         |
| Winter                          |     | 28            | 20 (71)   | 8 (35.9)     |
| Spring                          |     | 23            | 18 (40)   | 5 (54.9)     |
| Summer                          |     | 4             | 4 (6.9)   | 0 (0)        |
| Autumn                          |     | 3             | 3 (5.2)   | 0 (0)        |
| Dam parity, number (%)          | 37  |               |           | 0.044       |
| Primiparous                     |     | 26            | 18 (69.2) | 8 (30.8)     |
| Multiparous                     |     | 11            | 11 (100.0)| 0 (0)        |
| Parturition-related variables   |     |               | All NE    | Survivors    | Nonsurvivors | P-value |
| Labor length, number (%)        | 41  |               |           | 0.23         |
| <1 h                            |     | 2 (4.9)       | 2 (100.0) | 0 (0)        |
| 1–6 h                           |     | 26 (63.4)     | 21 (80.8) | 5 (19.2)     |
| >6 h                            |     | 13 (31.7)     | 10 (76.9) | 3 (23.1)     |
| Induction, number (%)           | 58  |               |           | 0.33         |
| Yes                             |     | 7 (12.1)      | 7 (100)   | 0 (0)        |
| Dystocia, number (%)            | 58  |               |           | 0.67         |
| Yes                             |     | 49 (84.5)     | 37 (75.5) | 12 (24.5)    |
| C-Section, number (%)           | 58  |               |           | 0.91         |
| Yes                             |     | 32 (55.2)     | 25 (78.1) | 7 (21.9)     |
| Total plasma protein            | 43  |               |           | 0.005       |
| <5 mg/dL                        |     | 14 (32.6)     | 9 (64.3)  | 5 (35.7)     |
| 5–5.5 mg/dL                     |     | 18 (41.9)     | 16 (88.8) | 2 (11.1)     |
| >5.5 mg/dL                      |     | 11 (26.6)     | 10 (90.9) | 1 (9.1)      |

aNumber of calves for which data were available for a given variable.

bIndicates a statistically significant difference between the NE and non-NE groups.
from large operations, with dystocia rates consistently higher in primiparous dams.34 One study of over 7,000 dairy parturitions found that the parturitions of 18.9% of primiparous and 6.9% of multiparous dams were classified as “severe dystocia.”35 Dystocia in mares is generally considered to be less common, although one study documented dystocia in 10% of births.31 Increased risk of dystocia in primiparous mares has not been described in horses, possibly due to the difference in age at first breeding. In the current study, 88/200 (44%) calves were born to dams that were 1–2 years of age at time of calving and presumably not fully mature in size. In contrast, in the previously mentioned study, the average age of mares giving birth was 10.3 years of age with a range of 3–29 years, likely decreasing the risk of fetal-dam disparity.31

Calves in the NE group were more likely to have been born after reported labor time of >6 hours than calves in the non-NE group. However, the distinction between length of time in stage I and stage II labor could not be determined from the medical records. Due to management practices on beef cattle operations, onset of stage II labor may go unnoticed. While it has been demonstrated in mares that stage II labor lasting >40 minutes is significantly associated with foal nonsurvival,31 there has been no correlation between labor time and diagnosis of NE in foals. In human infants, length of labor is associated with increased incidence of NE.4,39

While antibiotics were commonly used, there was no consistency in other treatment modalities used in this study aside from enteral feeding that was continued for up to 6 days of age. Oxygen therapy, caffeine, and antioxidant therapy (including thiamine) could not be recommendations for foals with NE,4 but were only sporadically administered to calves in the current study. One explanation is that a diagnosis of NE (or synonym) only recently began to be used in the medical records of calves and was correlated with increased use of specific treatments and modalities. For example, caffeine is a respiratory stimulant that decreases neuronal apoptosis after perinatal hypoxia in late gestation bovine fetuses resulted in stillbirth and abnormal mentation in the calves that survived. However, brain histopathology of the nonsurviving bovine fetuses was reported normally, even in the calves that had survived several days and displayed neurologic abnormalities, including inability to nurse.12

Table 5. Univariate analysis (chi-square or Fisher’s exact test) of treatments used in 58 calves diagnosed with neonatal encephalopathy (NE) that survived (n = 45) or did not survive (n = 13) to discharge from the hospital.

| Treatment                      | All NE Calves (n (% of N)) | Survivors (n (%)) | Nonsurvivors (n (%)) | P-value |
|--------------------------------|-----------------------------|-------------------|----------------------|---------|
| Antibiotics                    | 58                          | 43 (76.8)         | 35 (81.4)            | 8 (18.6) | 0.081    |
| Thiamine                       | 57                          | 11 (19.3)         | 7 (63.6)             | 4 (36.4) | 0.22     |
| Oxygen insufflation            | 58                          | 7 (12.1)          | 5 (71.4)             | 2 (28.6) | 0.22     |
| Plasma                         | 57                          | 6 (10.5)          | 5 (83.3)             | 1 (16.7) | 0.99     |
| Nonsteroidal anti-inflammatory drugs | 58                      | 24 (41.4)         | 19 (79.2)            | 5 (20.8) | 0.99     |
| Synthetic colostrum            | 56                          | 42 (75.0)         | 34 (81.0)            | 8 (19.0) | 0.47     |
| Vitamin E and Selenium         | 58                          | 19 (32.8)         | 15 (78.9)            | 4 (21.2) | 0.99     |
| Caffeine                       | 58                          | 7 (12.1)          | 6 (85.7)             | 1 (14.3) | 0.99     |

*Number of calves for which data were available for a given variable.

Overall, survival was 77.6% for calves diagnosed with NE in this study. This is similar to a recent foal retrospective that reported 79.8% survival6 but higher than another that reported a 45.6% survival.43 The only risk factors associated with calf nonsurvival in this study were birth to a primiparous dam or being a twin; however, this is difficult to interpret given the low number of nonsurvivors. Factors related to foal nonsurvival in foals with NE include seizures, FTP1, prematurity, and placental abnormality.43 While FTP1 was detected in calves in the current study, no prematurity, seizures, or placental abnormalities were noted in the medical records.

Multiple antepartum and peripartum factors can lead to perinatal hypoxia in the fetus. These factors likely vary in importance depending on species and case criteria given that the diagnosis of hypoxia is often clinical. Socioeconomic status, family history of neurologic disease, infertility treatment, severe pre-eclampsia, viral illness, or having an abnormal placenta in the absence of intrapartum risk factors accounted for 69% of NE cases in human infants.28,44

Brain MRI examination and post-mortem histopathology revealed that >90% of infants diagnosed with NE had evidence of acute brain injury most consistent with intrapartum trauma rather than developmental or inborn cerebral damage.45 Maternal factors, including dystocia, have been associated with increased risk of NE in foals in one study30 but were not significant in a more recent retrospective.6 In the current study, both antepartum (male gender and calf position) and intrapartum (dystocia and labor length) risk factors were identified. However, only calf position was retained in the final multivariate analysis.

Histopathologic evidence of hypoxic-ischemic cerebral injury has not been demonstrated in a calf diagnosed with NE antemortem and may be absent on post-mortem examination of foals diagnosed antemortem with NE.5,42,43,46 In an experimental model in utero perinatal hypoxia in late gestation bovine fetuses resulted in stillbirth and abnormal mentation in the calves that survived. However, brain histopathology of the nonsurviving calves was reportedly normal, even in the calves that had survived several days and displayed neurologic abnormalities, including inability to nurse.12
Multiple nonhypoxic/ischemic etiologies for NE have been suggested, including persistent elevations of progestagens in neonatal foals diagnosed with NMS. It is not known why these neuromodulatory pregnancies would fail to decrease after birth, but could explain the quick recovery and lack of lasting neurologic effects often observed in foals diagnosed with NE. Given that the clinical signs associated with NE likely represent more than one underlying etiology in foals and antigen, it might be that the calves in this study represent a certain subset of NE akin to the milder syndromes seen in foals. Another contributing factor could be that the median age of presentation for foals diagnosed with NE was 14 hours of age whereas 94.5% of the calves in this study were born in the hospital, allowing for earlier recognition of clinical signs.

A major limitation of this study was inclusion of calves in the NE group based solely on a clinical diagnosis without a reference standard antemortem diagnostic test. In addition, full neurologic examinations and bloodwork (including assessment of acid-base status) were not routinely performed in newborn calves. Furthermore, only 2 of the nonsurvivors had a necropsy performed as owners often decline a post-mortem examination when there is no suspicion of herd health disease. Despite being the preferred way to diagnose antemortem hypoxic cerebral injury, advanced imaging is rarely performed in calves with NE, likely due to financial limitations and availability of equipment. These limitations are likely more pronounced in neonatal calf medicine and therefore unlikely to be a realistic option for most neonatal calves, especially considering that even basic diagnostic tests are often reserved for animals of great individual value.

One goal of this study was to increase knowledge of NE in calves and to improve early diagnosis and management. In human infants with suspected hypoxic cerebral injury, early identification is a crucial component of successful treatment. Infants with evidence of a hypoxic event, need for resuscitation, and acidemia detected on fetal umbilical arterial blood are recommended for electroencephalography (EEG) and brain MRI to confirm hypoxic injury. Given that advanced imaging and EEG are unlikely to become standard practice for diagnosis of NE in calves, recognition of risk factors will remain crucial to early diagnosis. Calves born after dystocia, especially when in abnormal orientation, should be closely monitored for nursing behavior in the immediate postpartum period.

Conclusions

In conclusion, calves born after dystocia, especially those malpresented, should be closely monitored for NE immediately postpartum. If NE is suspected, the prognosis for recovery and survival is good with appropriate medical intervention. In cases of NE, recovery of nursing ability may take up to 6 days.

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