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Occurrence, hematologic and serum biochemical characteristics of neonatal isoerythrolysis in Arabian horses of Iran

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Keywords

neonatal isoerythrolysis, hemolytic anemia, Arabian horses, Khouzestan

Abstract

Neonatal isoerythrolysis is a major cause of anemia in newborn foals. However, there are no documented data regarding the occurrence of neonatal isoerythrolysis in Arabian horses of Iran, which are mostly raised in Khouzestan province. Hence, this study was carried out to investigate the occurrence of neonatal isoerythrolysis in Arabian horses of Khouzestan and assess the hematologic and serum biochemical profile of affected foals. A total of 20 neonatal foals, under one week of age, and their dams were involved in this study. Clinical examinations revealed no abnormality except in one foal with icteric mucous membranes, lethargy, tachycardia, tachypnea, hypothermia and hemoglobinuria which led to death. The diagnosis of neonatal isoerythrolysis was made based on erythrocyte agglutination in cross-match test between the mare serum and foal erythrocytes with the titer of 1:128, while other studied cases were assumed negative according to the test results. In the laboratory assessment, the foal with hemolytic anemia showed a major decline in hematocrit, hemoglobin concentration and erythrocyte count along with considerable leukocytosis and neutrophilia. Serum total and direct bilirubin concentrations in the NI case was about ten times higher than in the rest of the foals. This study revealed that neonatal isoerythrolysis can occur in Arabian foals of Khouzestan and is associated with severe anemia and icterus which may lead to death. These findings can be beneficial in the establishment of preventive measures in Arabian horse breeding industry in the region, as well as improving therapeutic methods.

Abbreviations

NI: neonatal isoerythrolysis
EDTA: ethylenediaminetetraacetic acid
PBS: phosphate buffered saline
RBC: erythrocyte count
HCT: hematocrit
HGB: hemoglobin concentration
MCV: mean copuscular volume
MCHC: mean copuscular hemoglobin concentration
WBC: leukocyte count
AST: aspartate aminotransferase
ALP: alkaline phosphatase
GGT: gamma-glutamyl transferase

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Introduction

Neonatal isoerythrolysis (NI), as an acute hemolytic disease, is considered as one of the most important causes of anemia in neonatal foals. The disease originates from maternal alloantibodies directed against foal erythrocyte surface antigens [1], which are produced following exposure of mare to incompatible blood groups (blood leakage from placenta during pregnancy/parturation or incompatible blood transfusion). Over 30 equine erythrocyte antigens have been identified that produce 8 blood groups, among which, Aa and Qa are responsible for the majority of NI cases [2,3,4]. However, other erythrocyte antigens may also be involved [5].

Maternal antibodies of IgG type cannot transfer transplacentally. However, they will be absorbed intact to the foal blood circulation through colostrum ingestion within the first few hours of birth. If the foal inherits erythrocyte antigens from the sire that the mare does not possess, NI would be possible in which maternal antibodies will bind offspring erythrocytes leading to intravascular and extravascular hemolysis [2].

Neonatal foals are normal at birth, but the symptoms will develop within 12 to 48 hours which may include lethargy, tachypnea, tachycardia, pale mucous membranes, icterus, hemoglobinuria, shock and even death, depending on the intensity of erythrocyte destruction and anemia. In addition, neurological signs, metabolic acidosis, toxic hepatopathy and dysfunction in various organs might be observed as a consequence of hypoxemia and tissue hypoxia. Furthermore, severe rise in non-conjugated bilirubin can result in encephalopathy or kernicterus in the involved newborn foals [3].

The disease should be considered in multiparous mares or mares with the history of previous foals with NI, although it cannot be completely ruled out in the first foaling. NI can be prevented in two stages: 1) Identification of the foals at risk through blood typing of both parent horses or cross match between them before parturition, and 2) Prevention of foals from exposure to the mare antibodies via prohibition of the neonate from nursing by its mother during the first 30 to 48 hours [1]. Identification of erythrocyte-bound antibodies in foal blood is essential for NI diagnosis which is performed by hemolytic or agglutination tests [6,7].

Epidemiologic studies revealed that around 14% of foals illustrate incompatibilities in red blood cell antigens with the dam [8]. However, not all incompatible pregnancies result in alloimmunization and NI [8]. The disease prevalence differs between various horse breeds [4] and has been reported to be approximately 2% in Standardbreds and 1% in Thoroughbreds [9], while its occurance is higher in mule foals due to the presence of specific donkey erythrocyte antigens [10].

There are no documented data regarding the occurrence of NI in Arabian horses of Iran which are mostly raised in Khouzestan province, South-West Iran. Taking into account the importance of horse breeding industry in khouzestan, besides the critical complications of NI in neonatal foals which was occasionally suspected in previous clinical observations in the region, it seemed necessary to perform a study in this field. Hence, this study was carried out to investigate the occurrence, and the associated clinical and laboratory findings of neonatal isoerythrolysis in Arabian horses of Khouzestan.

Results

Clinical signs and characteristics

The studied arabian horses were 11 male and 9 female neonatal foals which ranged in age between 6 hours to 6 days. The dams were between 4 to 16 years old and had 0 to 12 previous deliveries. All foals were properly fed with colostrum in the first day of birth and no abnormal signs were recorded in clinical examinations except in one (Table 1).

The latter mentioned was a 3 day old male foal which was referred to the Veterinary Hospital, Shahid Chamran University of Ahvaz, Iran, with the history of acute lethargy and icterus for the last few hours while it was otherwise born and fed normally in the first 2 days of birth. The mare had one previous normal pregnancy with no NI history in the offspring. The clinical examination revealed severely icteric mucous membranes (Figure 1), hemoglobinuria, hypothermia with increased heart and respiratory rates. Neonatal isoerythrolysis causing hemolytic anemia was suspected according to the intensity of anemia and icterus and absence of prior illness in the foal, the mare's breeding history, and exclusion of differential diagnoses. Additionally, the diagnosis was supported by the incompatibility on cross-matching.

Therapeutic measures including fluid therapy and blood transfusion were considered. However, the foal did not survive for transfusion to be performed.

Cross-match test

A definitive diagnosis of NI was made in one foal based on the erythrocyte agglutination in exposure to maternal serum with the titer of 1:128.

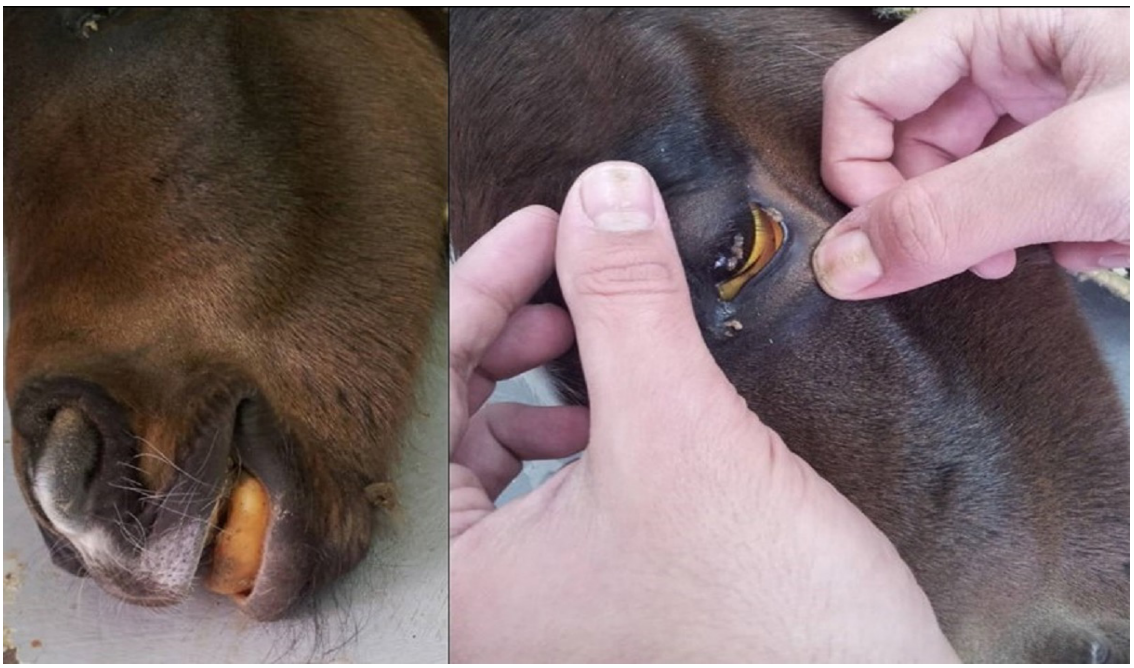

Figure 1.
Icteric mucous membranes of gingiva (left) and conjunctiva (right) in the foal with neonatal isoerythrolysis.

Table 1.
Characteristics of studied foals.

No.	Sex	Foal age	Dam age (years)	Dam Parity (except the present foal)	Agglutination titer
1	Male	3 days	6	1	1:128
2	Female	4 days	8	3	1:4
3	Male	6 days	11	7	1:4
4	Female	6 hours	10	3	1:2
5	Female	1 days	13	7	0
6	Female	3 days	4	0	1:2
7	Male	4 days	4	0	0
8	Male	6 days	5	1	1:8
9	Female	2 days	4	0	1:2
10	Male	4 days	8	5	0
11	Female	3 days	6	2	0
12	Female	3 days	5	0	0
13	Female	3 days	8	4	1:4
14	Male	2 days	5	1	1:2
15	Male	1 days	7	2	0
16	Male	1 days	5	1	1:2
17	Male	2 days	16	12	1:2
18	Male	2 days	7	3	1:8
19	Female	1 days	10	5	1:4
20	Male	16 hours	4	0	0

Titers of 0, 1:2, 1:4 and 1:8 were observed in other cases assessed which were considered negative (Table 1). Based on titration results, foals were devided into five groups to compare hematologic and biochemical data. However, it should be noted that as there was only one NI case found in this study, the data obtained was impossible to be statistically compared to other groups.

Hematologic assessment

The foal with hemolytic anemia showed a major decline in HCT, Hb and RBC, despite no significant difference in erythrocyte parameters in other foals (Table 2). Erythrocyte morphologic changes in the anemic foal included marked anisocytosis, mild polychromasia and echinocytosis, and a low number of metarubricytes.

Leukocyte total and differential counts did not reveal any significant differences between groups (Table 2). However total leukocyte and neutrophil count was considerably higher in the NI foal (titre of 1:128).

Erythrocyte indices and platelet count did not differ between groups including the NI foal.

Biochemical assessment

The lowest amount of serum glucose and protein was observed in NI foal while there was no significant difference in oth-

Table 2.
Hematologic results as mean ± SE in various neonatal foal groups based on erythrocyte agglutination test results.

	Erythrocyte agglutination titer					
	0 (n=7)	**1:2 (n= 6)**	**1:4 (n= 4)**	**1:8 (n= 2)**	**1:128 (n=1)**	***p* value**
WBC ($\times10^3$/uL)	7.08 ± 1.45	4.18 ± 0.75	6.00 ± 1.91	5.65 ± 1.37	14.9	0.264
Lymph ($\times10^3$/uL)	1.81 ± 0.49	0.9 ± 0.13	1.1 ± 0.11	0.9 ± 0.0	1.3	0.173
Mono ($\times10^3$/uL)	0.36 ± 07	0.23 ± 0.04	0.23 ± 0.06	0.25 ± 0.1	0.7	0.234
Neut ($\times10^3$/uL)	4.9 ± 1.04	2.98 ± 0.61	4.66 ± 1.77	4.5 ± 1.27	12.9	0.341
Eos ($\times10^3$/uL)	0.0 ± 0.0	0.04 ± 0.03	0.0 ± 0.0	0.0 ± 0.0	0	0.344
RBC ($\times10^6$/uL)	10.8 ± 0.62	10.9 ± 0.56	10.44 ± 1.07	10.66 ± 1.29	2.33	0.911
HGB (g/dL)	16.41 ± 0.61	14 ± 1.76	14.83 ± 0.85	13.65 ± 2.01	4	0.403
HCT (%)	47.18 ± 2.05	46.01 ± 1.88	46.73 ± 5.23	46.35 ± 7.67	10.8	0.938
MCV (fL)	45.71 ± 1.62	42.36 ± 0.74	44.83 ± 1.6	43.4 ± 1.69	46.4	0.193
MCH (pg)	12.25 ± 0.4	14.36 ± 0.24	14.33 ± 0.89	12.7 ± 0.35	17.1	0.263
MCHC (g/dL)	33.51 ± 0.34	34.01 ± 0.34	32.06 ± 1.68	29.3 ± 0.35	37	0.190
RDW (%)	17.28 ± 0.37	17.46 ± 0.13	16.56 ± 0.26	17.1 ± 0.00	16	0.184
Plt ($\times10^3$/uL)	204.83 ± 15.01	166.83 ± 27.76	139 ± 50.71	184 ± 25.45	112	0.316

There were no significant difference in hematologic parameters between groups ($p \geq 0.05$).

Table 3.
Biochemical results as mean ± SE in various neonatal foal groups based on erythrocyte agglutination test results.

	Erythrocyte agglutination titer					
	0 (n=7)	**1:2 (n= 6)**	**1:4 (n= 4)**	**1:8 (n= 2)**	**1:128 (n=1)**	***p* value**
Urea (mg/dl)	37 ± 7.18	48.83 ± 7.29	35.33 ± 7.53	22.5 ± 2.5	38	0.681
Creatinine (mg/dl)	1.53 ± 0.2	1.64 ± 0.3	1.46 ± 0.23	1.55 ± 0.19	1.2	0.981
Glucose (mg/dl)	112 ± 20.39	129.33 ± 33.69	163.67 ± 25.11	62 ± 19	40	0.162
Protein (g/dl)	5.6 ± 0.43	5.5 ± 0.36	5.26 ± 0.5	6.4 ± 0.3	4.7	0.858
Alb (g/dl)	3.57± 0.15	3.56 ± 0.22	3.53 ± 0.26	4.25 ± 0.15	3.7	0.992
AST (U/l)	115.14 ± 19.55	129.33 ± 27.31	97 ± 8.73	95.00 ± 92.00	304	0.725
ALP (U/l)	4045.7± 665.38	4509.3 ± 756.54	2830.3 ± 1302.8	3982 ± 700.0	2632	0.531
GGT (U/l)	34.00 ± 11.81	35.00 ± 15.00	30.00 ± 9.7	38.50 ± 8.04	55	0.601
Bilirubin total (mg/dl)	2.92 ± 0.28	2.77 ± 0.29	3.19 ± 0.98	2.39 ± 0.38	26.49	0.759
Bilirubin direct (mg/dl)	0.35 ± 0.021	0.35 ± 0.02	0.31 ± 0.04	0.46 ± 0.005	12.55	0.612

There were no significant difference in serum biochemical parameters between groups ($p \geq 0.05$).

er groups (Table 3). Serum total and direct bilirubin levels in the affected foal were more than 10 times the mean values in various groups along with a relative increase in AST and GGT activity (Table 3).

Discussion

This study was performed to investigate the occurrence of neonatal isoerythrolysis in Arabian horses of Khouzestan, South-West Iran. Out of 20 newborn foals studied in the region, one case of acute NI was found. The symptoms were in accordance with the previously reported NI cases in other breeds which most obviously includes icterus, tachycardia and tachypnea and eventually death [2,3,11,12]. Many of the clinical signs observed are a result of the decrease in oxygen-carrying capacity of blood [13].

The dam, gave birth to the NI foal, was 6 years old with one previous foaling. Although it did not seem to be any correlation between parity and the foal hemolytic disease, yet no positive case was found in primiparous mares here. However, NI has already been reported in foals born to primiparous mares with no history of previous blood transfusion [14] which might be attributed to transplacental sensitization of the mare to fetal erythrocytes in early pregnancy.

Neonatal isoerythrolysis was reported in various horse breeds. However, there was no previous documented report of NI in Iran and it was recorded for the first time in Arabian horses of Khouzestan through the present study.

In a 5 year retrospective study of clinical cases of NI in foals, the disease was recorded in American Paints, warmblood cross, Standardbred, Thoroughbreds, and Quarter Horses. There were no affected Arabian horses despite that they accounted for about 10% of total neonatal equid population at the studied hospital [2].

In another study, neonatal isoerythrolysis was reported in a 5-day-old female Standardbred foal with icterus and listlessness which was diagnosed based on agglutination in cross-match between the mare serum and foal erythrocytes. The unusual finding was the marked reticulocytosis displayed with automated and manual methods [15].

In the present investigated Arabian foals, neonatal isoerythrolysis was associated with erythrocyte agglutination with mare serum diluted up to 1:128. There were substantial leukocytosis and neutrophilia along with a major decline in hematocrit, hemoglobin concentration and erythrocyte count with a slight decrease in platelet count in the affected foal compared to healthy newborn animals. It should be noted that in other foals, the agglutination titers of 1:2 to 1:8, which were considered negative, did not accompany any significant change in leukocyte or erythrocyte parameters, as expected.

Anemia as one of the characteristics of the disease is caused by attachment of maternal alloantibodies to neonatal RBCs resulting in primarily hemolysis or hemagglutination followed by extravascular or intravascular hemolysis [1]. Thrombocytopenia, has been reported concurrently with NI, in horse and mule foals [2,16,17] which might be attributable to antiplatelet alloantibodies, coagulopathies due to inflammatory or hypoxic-ischemic injuries, or other causes.

Increased WBC and neutrophil counts was reported previousely by Boyle et al (2005) in some of the foals with NI [2]. This neutrophilia is most possibly due to sympathoadrenal and neurohormonal responses to anemia. However, Wong et al. (2012) observed persistent neutropenia, without any detectable infection, coupled with neonatal isoerythrolysis in a 3-day-old Thoroughbred colt [14]. A positive granulocyte agglutination test with the mare's serum along with flow cytometric analysis led to a clinical diagnosis of alloimmune neonatal neutropenia. The foal was treated successfully with prophylactic antimicrobials combined with recombinant human granulocyte colony-stimulating factor (rhG-CSF).

In biochemical analysis, bilirubin concentration (total and direct) in the NI case was about ten times higher than the rest of the foals. In contrast, serum glucose and protein levels were extremely reduced in the foal with hemolytic anemia when compared to others.

Icterus as a result of increased serum indirect bilirubin, secondary to hemolysis, is one of the key features of neonatal isoerythrolysis. However, direct hyperbilirubinemia has rarely been reported in association with NI [2] which presumably indicates hepatocellular damage due to bilirubin overload in hepatocytes and hemosiderosis in addition to anemic hypoxia in the studied hemolytic foal. Serum AST activity was consistent with these findings [18]. Uncommonly, toxic hepatopathy (from severe hemolysis) or hepatocellular necrosis (from anoxia) may result in an increase in concentrations of liver enzymes, ammonia, and bile acids [13].

A Retrospective case series study of 72 foals with NI by Polkes et al., (2008) revealed that the most common causes of death or euthanasia in these animals were development of liver failure, kernicterus, and complications related to bacterial sepsis [19]. In addition, they found that total bilirubin concentrations more than 27 mg/dL can increase the chances of developing kernicterus up to 17 times in foals with NI. In the same context, kernicterus was diagnosed at necropsy in a 5 day old Thoroughbred foal that died following a clinical history of seizure and severe icterus and laboratory profile of anemia, hyperbilirubinemia and hypoglycemia [20]. Hypoglycemia and hypoproteinemia in the present affected foal may be the result of anorexia as well as hepatopathy which disrupt normal carbohydrate and protein metabolism.

This study described the occurrence of neonatal isoerythrolysis in Arabian horses of Khouzestan, for the first time. The diagnosis was made based on cross-match test between mare and foal, clinical examinations and laboratory analysis. The symptoms of the disease were icterus, hemoglobinuria, tachycardia and tachypnea while severe anemia, leukocytosis and hyperbilirubinemia were the most significant laboratory signs. These findings can be beneficial in the establishment of preventive measures in Arabian horse breeding industry in the region as well as improving therapeutic methods.

Materials and Methods

Animals and sample collection

This study was performed on Arabian horses in Khouzestan province, a subtropical area located in the South-West of Iran. A total of 20 neonatal foals under one week of age and their dams were included in this study from January 2017 through December 2017. All animals were used after institutional approval of the Animal Handling Committee of Shahid Chamran University of Ahvaz. Each foal's signalments including age, sex, colostrum ingestion in the first 24 hour of birth, and the number of previous deliveries (parity) of the dam was recorded. In addition, the foals were clinically examined regarding the condition of mucous membrans, heart and respiratory rates, body temperature and the presence of hemoglobinuria and neurological symptoms.

Blood samples were collected from the jugular vein of foals and mares into tubes with anticoagulant (EDTA) for hematologic and agglutination tests and without anticoagulant for serum seperation and biochemical analysis.

Cross-match test

A cross-match between the mare serum and foal erythrocytes was performed in order to detect the presence of anti-foal erythrocyte antibodies in the mare serum. Briefly, EDTA-anticoagulated foal blood samples were washed 3 times with phosphate buffered saline (PBS) and after the final washing, a 2% suspension of red blood cells in PBS was prepared.

The agglutination test was performed in a 96-well microplate. Fifty µl of the mare serum was added to 50 µl of PBS in the first well of the row, and then increasing dilutions of 1:2 antisera in PBS were prepared through 1:4096. Afterwards, 50 µl of foal washed RBCs suspension was added to each well and incubated at 37°C for 30 min and then for 30 min at room temperature (25°C). The additional 30 min at room temperature was conducted to permit RBCs to settle and agglutination patterns to form.

Wells were recorded as negative if they contained a button of RBCs that would disperse when the microtiter plate was slanted; positive wells exhibited mat formation that did not disperse when slanted, and the titer of positivity was recorded. The test was considered positive if agglutination occurred at 1:16 antibody dilutions.

Hematologic assessment

Hematological parameters including erythrocyte count (RBC), hematocrit (HCT), hemoglobin concentration (HGB), mean copuscular volume (MCV), mean copuscular hemoglobin concentration (MCHC), and leukocyte count (WBC) were determined by the BC-2800 Vet hematology analyzer (Mindray, China). Differential leukocyte counts and erythrocyte morphology were also evaluated in microscopic examination of blood smears.

Biochemical assessment

Serum biochemical parameters including total protein, albumin, glucose, urea, creatinine, total and direct bilirubin concentration and AST, ALP and GGT activities were assessed with a biochemistry autoanalyzer (BT-1500, Biotechnica, Italy) using Parsazmun kits (Iran).

Statistical analysis

ANOVA and Tukey's Post Hoc tests were employed to compare laboratory-obtained values between groups using SPSS software Version 16 (SPSS Inc., Chicago, IL, USA). All values were expressed as mean and standard error (SE) and $p < 0.05$ was considered as statistically significant.

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Author contributions

Conceived and designed the experiments: S.M.J, M.R.J., A.G.M. Performed the experiments: S.M.J., A.G.M., M.M.Z. Wrote the paper: S.M.J.

Conflict of interest

The authors declare that they have no conflicts of interest.

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