Genetic Disorders Affecting Equine Blood Cells and Coagulation Factors: A-State-of-The-Art Review

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Abstract: Genetic diseases that affect blood cells and clotting factors in the horse are uncommon. Unfortunately, the prognosis is reserved, because the treatment in many cases is only symptomatic and when it fails, euthanasia of the patient is the only viable option. The detection of carriers is of pivotal importance in order to prevent the spread of these disorders in the equine population. This manuscript reviews the current state of knowledge of genetic diseases that affect red blood cells, leukocytes, platelets and clotting factors in the horse.

The genetic diseases that affect equine red blood cells are defects in the activity of enzymes and cofactors involved in erythrocytes metabolism, such as glucose 6 phosphate dehydrogenase, flavin adenine dinucleotide, glutathione reductase and glutathione. Therefore, their deficiency triggers methemoglobinemia and hemolytic anemia. Genetic disorders affecting granulocytes are rare in horses, but a Pelget-Hüet anomaly has been reported. Primary immunodeficiencies described in horses and arising from defects in the immune system are severe combined immunodeficiency, X-linked agammaglobulinemia and Fell pony immunodeficiency syndrome. Because of the immunodeficiency, foals usually develop fatal infections during the first weeks or months of life, caused for opportunistic organisms. Prognosis of these animals is poor. The most common genetic defect of platelet is Glanzmann thrombasthenia, which results in prolonged bleeding time and hematoma formation. Spontaneous bleeding or impaired hemostasis after trauma or surgery are clinical findings in types 1 and 2 von Willebrand disease. Hemophilia A, resulting from a decreased activity of coagulation factor VIII has also been described in male horses of different breeds, being the most common genetic disorder affecting coagulation factor in the horse. Prekallikrein deficit, although described in some horses, is a rare genetic coagulation factor deficiency.

Keywords: Coagulation, Erythrocytes, Genetic blood disorders, Horse, Leukocytes, Immunodeficiencies, Platelets.

INTRODUCTION

Genetic disorders including congenital disorders, *i.e*., disorders present at birth or those having a late onset, possibly years after the birth, has low incidence in horses, compared with small animals and human beings [1]. Recently, important technological advances have been made in cases where the genetic disorder affects a specific breed and expresses developmental, congenital or lethal traits [2].

Deficiencies of red blood cells (RBC) enzymes as abnormality in glucose-6-phosphate dehydrogenase (G6PD) and flavin adenine dinucleotide (FAD) deficiency are genetic abnormalities affecting hemoglobin including methemoglobinemia and hemolytic anemia [3, 4]. Primary immunodeficiency disorders are genetically determined failures of immune defense that increase susceptibility to infectious agents, which is the main reason because of these horses are presented for veterinary diagnosis [5, 6]. The secondary infections accompanying the underlying immune disorder are difficult to manage and ultimately result in the demise of most immunodeficient horses [6]. Inherited platelet function disorders, alterations in the intrinsic contact system, and qualitative and quantitative defects in von Willebrand factor (vWF), although described in some horses, are rarely identified. A hereditary hemostatic defect implies a mutation within the gene encoding a specific hemostatic protein, leading to impaired synthesis or function of that protein and altering normal coagulation [7].

The current manuscript reviews the genetic alterations of blood cells and coagulation factors in horses, summarizes the molecular mechanisms of each, and updates information that facilitates diagnosis and management of affected horses.

1. ENZYMATIC ERYTHROCYTE DISORDERS IN THE HORSE

1.1. Glucose-6-Phosphate Dehydrogenase Deficiency

Equine erythrocytes are uniquely susceptible to oxidant-induced damage due to the use of inefficient mechanisms to correct and protect against oxidative

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damage [3, 8, 9]. Oxidants typically damage RBCs by oxidizing the heme iron in hemoglobin, reactive sulfhydryl, or unsaturated lipids in the membranes. The oxidation of the heme iron in hemoglobin to the ferric (Fe^{3+}) state generates methemoglobin, which is incapable of transporting oxygen. Methemoglobin can be enzymatically reduced back to the functional ferrous (Fe^{2+}) state, primarily by nicotinamide adenine dinucleotide (NADH)-dependent methemoglobin reductase [10].

Horses use a lactate-dependent pathway of methemoglobin reduction, which is less efficient than the glucose-dependent pathway of methemoglobin reduction utilized by most mammalian erythrocytes making horses more prone to the accumulation of methemoglobin [8]. Oxidation of sulfhydryl groups in the globin portion of hemoglobin can induce protein denaturation and the formation of Heinz body aggregates [3]. The oxidation of sulfhydryl groups and unsaturated lipids can also compromise the erythrocyte membrane integrity [9, 11]. Reduced glutathione (GSH) can protect erythrocytes against oxidant injury, being oxidized itself to a disulfide. However, horses, compared to other mammals, have a reduced ability to regenerate reduced GSH, presumably due to the decreased activity of glutathione reductase (GR) in equine erythrocytes [12]. Under normal conditions, equine erythrocytes have sufficient capability to prevent oxidative damage. However, increased levels of catalyzing oxidants in circulation, as may be seen following ingestion of an oxidizing toxin, may overwhelm the horse's ability to reduce methemoglobin and regenerate reduced GSH to prevent oxidative damage to erythrocytes, making horses more likely to develop hemolytic anemia and methemoglobinemia following ingestion of oxidizing toxins [3, 8, 13].

G6PD is involved in the first reaction of the pentoses route, catalyzing the conversion of glucose 6-phosphate (G6P) from anaerobic glycolysis into 6-phosphogluconate (6PG) and obtaining nicotinamide adenine dinucleotide phosphate (NADPH; reduced form) from of nicotinamide adenine dinucleotide phosphate (NADP; oxided form). This route is the main source of obtaining the reduced form of NADP in erythrocytes [11]. This mechanism protects erythrocytes against oxidative substances through of reactions catalyzed by the enzyme G6PD. A hemolytic anemia attributed to a severe G6PD deficiency was described by Stockham *et al*. [14] in an American saddle bred colt. This deficiency is an inherited disorder linked to the X chromosome, in which the decrease in enzyme activity results in hemolysis.

After the exposition of erythrocytes to acetylphenylhydrazine, horses with G6PG deficiency show RBCs morphologic abnormalities including eccentrocytosis, pyknocytosis, anisocytosis, macrocytosis, increased number of Howell-Jolly bodies and rare hemoglobin crystals [4, 14]. Nucleotide sequences of polymerase chain reaction (PCR)-amplified segments of the G6PD gene from the affected animals revealed a G to A mutation, that converts an arginine codon to a histidine codon [14].

1.2. Erythrocyte Flavin Adenine Dinucleotide Deficiency

In an adult Spanish Mustang mare and in a 7-year-old Kentucky mountain saddlehorse gelding Harvey *et al*. [3] and Harvey [4] reported respectively persistent methemoglobinemia, eccentrocytosis, and pyknocytosis that were not related to the consumption or administration of an exogenous oxidant. The methemoglobinemia was attributed to a deficiency in cytochrome-b5 reductase (Cb5R) activity, and the eccentrocytes and pyknocytes were attributed to a marked deficiency in reduced nicotinamide adenine dinucleotide phosphate-dependent GR activity that resulted in decreased reduced glutathione concentration within erythrocytes. FAD is a cofactor for GR and Cb_5R enzymes. Consequently, both RBC enzyme deficiencies in these horses can be attributed to decreased RBC FAD concentrations. FAD-deficient horses have persistent methemoglobinemia (25% to 46%), eccentrocytosis, pyknocytosis, and variable numbers of hemoglobin crystals. No Heinz bodies were observed in RBCs stained with new methylene blue. Hematocrits were normal or slightly decreased. The presence of eccentrocytes and pyknocytes in the absence of administered or consumed oxidants indicates deficient metabolic protection against endogenously generated oxidants. RBC biochemical abnormalities measured include decreased Cb_5R activity (about 40% of normal), decreased GSH concentration (about 60% of normal), and undetectable GR activity [3, 4, 11].

GR activity increased to a near-normal value after addition of FAD to the enzyme assay, indicating a deficiency of FAD in erythrocytes. The methemoglobinemia, eccentrocytosis, and pyknocytosis were attributed to deficiency of FAD in erythrocytes because the GR and Cb5R enzymes use FAD as a cofactor. The erythrocyte FAD deficiency results from a defect in riboflavin metabolism inside the erythrocytes and does not appear to affect other cells. This syndrome of methemoglobinemia and erythrocyte

membrane injury is secondary to erythrocyte FAD [3, 4]. In addition, eccentrocytes in horses have been observed in erythrocyte G6PD and FAD deficiency [3, 14, 15].

Eccentrocytes and pyknocytes are presumed to have shortened life spans in the circulation compared to normal RBCs [14, 16]. The mild anemia that was detected in the FAD–deficient mustang was likely the result of the rapid removal of damaged cells. The increased G6PD and pyruvate kinase (PK) activities in the mustang erythrocytes were attributed to the younger age of the circulating erythrocytes. The finding of erythroid hyperplasia in the bone marrow was interpreted as a compensatory mechanism of the hemolytic anemia [3, 15].

1.3. Other Enzyme Deficiencies

A trotter mare with a history of poor performance was found to have familial methemoglobinemia and hemolytic anemia associated with decreased erythrocyte GR and glutathione levels. The mare's dam, which also had a history of poor performance, was subsequently found to be similarly affected. Laboratory findings in both mares were similar to those found from two related trotter mares with persistent hemolytic anemia, methemoglobinemia, GR deficiency, and decreased GSH concentrations within RBCs. However, the GR deficiency did not appear to result from FAD deficiency, and the Cb_5R activity was reportedly normal [17].

2. GENETIC DEFECTS AFFECTING GRANULOCYTES

Diverse genetic defects affecting granulocytes, including alterations in functions (leukocyte adhesion deficiency), in granules (Chédiak-Higashi syndrome, mucopolysaccharidosis) and in oxidative metabolism (chronic granulomatous disease, glutathione peroxidase deficiency, 6-phosphate deficiency and myeloperoxidase deficiency) have been reported in small animals [18-22], but to the authors' knowledge, they have not been described in horses.

A genetic disorder characterized by failure of the mature granulocyte nuclei to lobulate, called Pelget-Hüet anomaly, has been described in the horse [23]. Granulocytes and monocytes in this anomaly present hyposegmented nuclei with condensed chromatin and no toxic changes in the cytoplasm. The nuclei of granulocytes might vary from round to oval or bilobulated. An autosomal dominant inheritance of Pelget-Hüet anomaly has been described in other species [24]. The diagnosis of this disorder is based on findings in granulocytes, with hyposegmented nuclei, with coarse mature chromatic patterns and cytoplasmic features of mature granulocytes. A transient condition similar to this anomaly has been reported in associated with infection, neoplasia or drugs administration and therefore, particular attention should be paid in order to distinguish between genetic and acquired conditions.

3. PRIMARY IMMUNODEFICIENCIES

Primary immunodeficiency disorders generally arise from a defect in the immune system and most frequently have a genetic basis. Several primary immunodeficiencies have been recognized in horses, including severe combined immunodeficiency (SCID), X-linked agammaglobulinemia, and Fell pony immunodeficiency syndrome [5].

3.1. Severe Combined Immunodeficiency

SCID is an autosomal recessive disorder in Arabians. The causative mutation is a 5 base pair deletion in the gene encoding DNA-protein kinase catalytic subunit (DNA-PKCS) on ECA 9. The effect of this deletion is the failure of maturation of both B and T lymphocytes [25-27]. These foals may appear clinically normal at birth but succumb to infection as protection from maternal antibodies wanes. Affected foals are therefore unable to mount pathogen specific cellular or humoral immune responses.

SCID is a fatal condition of both B (humoral) and T (cellular) cell dysfunction. This immunodeficiency may occur in Arabian foals (or breeds carrying Arab bloodlines), and manifests clinically by susceptibility to viral, bacterial, fungal, and protozoal organisms (*e.g*. adenovirus, coronavirus, *Rhodococcus equi*, *Pneumocystis carinii*, and/or *Cryptosporidium parvum*). Foals are normal at birth but soon develop fatal infections, particularly when circulating colostrum-derived antibody concentrations become low and do not survive beyond 5 months of age [5, 28-30].

The poor B and T cell development results in lymphopenia (< 1.000 cells/uL), marked serum IgM and IgA deficiency, and hypoplasia of lymphoid tissues (thymus, lymph node, spleen, mucosa-associated) [31, 32]. The disease is caused by the lack of activity of the enzyme DNA-dependent protein kinase (DNA-PK), which is required for gene rearrangement of the antigen-receptor on B and T lymphocytes. Absence of DNA-PK results in the elimination of lymphocyte

precursors, and affected foals are born without functional B and T lymphocytes [25, 27]. In Arabian horses, this mutation is also related to a higher incidence of tumors [33].

The DNA-PK enzyme defect results from a deletion mutation of the gene encoding the catalytic subunit. DNA isolated from blood or buccal swabs from horses of any age has been subjected to PCR using primers that produce a product that spans the area of the 5 base pair deletion in the gene encoding the DNA-PK, located on chromosome [33-35] DNA from a normal horse produces a 130 bp amplicon, while DNA from a SCID horse produces a 125 bp amplicon. Horses heterozygous for the disease will produce amplicons of both sizes [34]. This causes a block at the level of the differentiation of T and B lymphocytes, leading to profound immunodeficiency, making foals highly susceptible to secondary infections and causing death in their first months of life. Since the mode of inheritance of the genetic defect is an autosomal recessive trait, a genetic analysis should be performed in all Arabian and Arabian-crossbred horses used in reproduction. The appropriate planning of breeding of carriers prevents the outcome of affected foals and decreases the incidence of the mutant gene in the population.

3.2. X-Linked Agammaglobulinemia

Agammaglobulinemia is a rare immunodeficiency that has been early reported in Thoroughbreds and Standardbreds [36,37]. It has only been reported in males, suggesting an X-linked mode of inheritance similarly to X -linked agammaglobulinemia (XLA) in humans. XLA in humans is caused by a mutation in the Bruton tyrosine kinase (Btk) gene that is critical for normal B cell development. All cases described to date have occurred in males, suggesting but not proving an X-linked mode of inheritance in horses [38]. This complete absence of B lymphocytes and subsequent failure to produce immunoglobulins in affected horses make them suffer from recurrent bacterial infections, such as pneumonia, enteritis, laminitis and arthritis. Clinical signs begin between 2 and 6 months of age with most affected horses dying before 2 years of age from generalized infections. The two major laboratory findings are the lack of peripheral B cells and low or absent IgA, IgG, and IgM. Indeed, absence of serum IgM, IgA and IgG(T) and markedly reduced concentrations of IgG as low as 16 mg/dl characterize the immunodeficiency found in Thoroughbreds, Quarter Horses and Standardbreds [5, 39]. Other breeds might be susceptible to the immunodeficiency but have yet to be documented.

Although the immunodeficiency is caused by failed production of B-lymphocytes, affected horses live up to 19 months of age, and consequently, it has been concluded that T lymphocytes must be functional [5] or the combined immunodeficiency would cause the animals to die before four months of age [39]. Agammaglobulinemia has been proven to be a sex-linked (Y chromosome) immunodeficiency in humans [40] and although this fact has been assumed to be true also for in horses, the low incidence of the disorder makes difficult to prove this assumption. Currently, and to the authors' best knowledge, researchers in the horse in order to determine the genetic basis of agammaglobulinemia have not been conducted [5].

3.3. Fell Pony Immunodeficiency Syndrome

Foal o fell pony immunodeficiency syndrome (FIS), a fatal autosomal recessive disease found in Dale Pony, Fell Pony, and Gypsy horse breed. In each FIS case, the foals are clinically normal at birth, but start to weaken at 2-8 weeks [41] as they develop profound anemia [42] and do not have the ability to produce their own antibodies [43]. There is an almost total lack of B lymphocytes in the circulation or tissues, but with apparently normal levels of functional T lymphocytes [44-46]. The outcome is persistent opportunistic infections with no effective treatment and unfortunately, euthanasia is the preferred option.

FIS has been reported in ponies of diverse countries as Netherlands [47], Germany [48] and USA [49]. A single nucleotide polymorphism (SNP) in a sodium transporter (SLC5A3) was identified in a Dales pony foal with parents clinically normal [50]. The SNP is a functional alteration in an exon within the SLC5A3 gene based on PCR and sequencing to identify FIS carriers and early syndrome foals. This is currently available to all equine owners and can be performed simply on pulled hair samples, and therefore, there is no need for blood sampling. This syndrome, characterized by anemia and immunodeficiency, was firstly recognized in Fell pony foals [41, 47, 49]. Affected foals are apparently normal at birth, but the disease first manifests at two to eight weeks of age; the reported characteristic clinical signs include weakness, dyspnea, nasal discharge, poor growth, reduced appetite, diarrhea and anemia. A profound and progressive reduction in RBC, with hematocrits lower than 20% is a notable early feature.

B lymphocytes and erythrocytes are the most severely affected cell populations in ponies with FPI, and both undergo critical developmental stages in the bone marrow. The number of circulating lymphocytes is reduced and there is an increase in the number of polymorphonuclear cells [42]. Analyses of lymphocyte subpopulations show normal numbers of circulating T lymphocytes [44] but severely reduced numbers of circulating B lymphocytes [45]. There are also low concentrations of circulating IgM and IgA in the affected foal, while IgG concentrations could be variable [43, 49]. This last finding could reflect the presence of maternally derived IgG antibodies from colostrum. Typically, these changes persist for three to six weeks, with the foal becoming progressively weaker due to systemic infections and profound anemia. In fact, the hematocrit could decrease to as low as 3% [51]. FIS results in 100% mortality.

Pedigree analysis, incorporating the knowledge of affected animals, strongly suggests an autosomal recessive mode of inheritance [45]. Furthermore, pedigree analysis has identified the likely founder as a stallion from the 1950s that features in both the maternal and paternal ancestry of all FIS-affected foals [51, 52]. The condition may be caused by independent or common genetic abnormalities that affect both cell lines. FPS-affected foals lose the expression or function of a gene essential to hematopoiesis. Mouse models that resemble the condition in FPS-affected Fell Pony foals include SPI1/PU.1 and $EP300^{KIX}$ mutants. SPI1/PU.1 mutants die during late gestation or shortly after birth with impaired erythroblast maturation and a lack of B lymphocytes [53, 54]. However, macrophage, neutrophil, and T cell lineages are also affected in SPI1/PU.1 mutants. Mice with mutations in the $EP300^{KIX}$ domain that diminish binding to CREB1 and MYB proteins exhibit anemia, B cell deficiency, thymic hypoplasia, megakaryocytosis, and thrombocytosis [55].

4. GENETIC CONDITIONS AFFECTING PLATELETS AND COAGULATION FACTORS

4.1. Glanzmann Thrombasthenia

Hereditary platelet function defects includes abnormalities of platelet membrane receptors, signal-transduction pathways, granule secretion, or membrane phospholipid [56]. Glanzmann thrombasthenia (GT) is an inherited, intrinsic quantitative or qualitative defect in the heterodimer platelet membrane receptor αIIbβ3, which acts as fibrinogen receptor on the platelet membrane and consequently, it is essential for normal platelet aggregation [57]. This disorder has been described in Peruvian Paso horses, Quarter horses, Thoroughbred and Oldenburg horses [58-62]. Mutational analysis performed in Thoroughbred and Oldenburg horses identified that both horses were homozygous for a missense mutation, that led to a predicted amino acid change from arginine to proline in exon gene encoding αIIb [59, 61]. Mutational analysis in the Peruvian Paso horse identified a homozygous ten base pair deletion encompassing the last three base pairs of exon 11 and the first 7 base pairs of intron 11 of the gene encoding the glycoprotein αIIb. The mutation was predicted to affect normal splicing of intron 11 [62]. A compound heterozygote possessing both of the above described mutations has been described in the Quarter horse [58, 59].

The most common clinical signs of GT are associated with exaggerated bleeding manifesting as purpura, epistaxis, gingival bleeding, and prolonged hemorrhage after trauma or surgery. In most of the published reports, epistaxis was the main complaint [58-60, 62]. GT was suspected in the Oldenburg filly due to hematoma formation and excessive bleeding after arthroscopy and venipuncture [60].

Diagnosis of GT is based on normal platelet count and morphology and prolonged bleeding time. Platelet function analyzer PFA-100 is highly sensitive for detecting GT. The PFA assay uses collagen + adenosine diphosphate (ADP) and collagen (COL)/ADP embedded cartridges to mimic a damaged vessel endothelium. As citrated whole blood flows at a high shear stress rate through these cartridges, platelets bind, creating a platelet plug (closure time, CT). CT is prolonged in patients with GT [63]. Platelet aggregation in response to various agonists was markedly impaired in the Quarter horse diagnosed of GT [58].

A platelet function defect distinct from GT has been reported in Thoroughbreds [64,65]. Affected horses demonstrated prolonged thombotest (TBT), abnormal platelet aggregation to certain agonists, and impaired fibrinogen binding by flow cytometric assay. The physiologic and molecular bases of this defect is currently unknown.

A heritable bleeding diathesis associated with decreased thrombin generation by activated platelets was described in a 2-year old Thoroughbred mare. The mare showed platelet aggregation in response to thrombin and collagen [66].

4.2. Von Willebrand Disease

Von Willebrand disease (vWD) includes quantitative and functional defects of vWF. Both inherited quantitative and functional vWF defects have been reported in horses [67-69].

vWF is a high molecular weight glycoprotein synthesized by megakaryocytes and endothelial cells. It is found in platelets and endothelium and circulates in plasma bound to coagulation factor VIII. vWF functions to stabilize and to protect circulating coagulation factor VIII from immediate degradation by protease inhibitors, and also provides a scaffold for platelet adherence and formation of the platelet plug after endothelial damage occurs [70]. Patients with vWD typically present spontaneous bleeding from mucosal surfaces or impaired hemostasis after trauma or surgery. Clinical variability in phenotype is dependent on the amount of functional vWF present. Diagnosis is based on assessment of circulating vWF antigen concentrations (vWF:Ag), vWF function (based on ristocetin cofactor activity or collagen-binding capacity), evaluation of multimeric forms of vWF, and comparison of vWF:Ag to activity ratio [71].

Three distinct types of vWD have been described in people and dogs, but only two types have been reported in horses. Type 1 vWD is defined as a partial quantitative protein deficiency with diagnosis based on normal vWF multimeric structure and low levels of circulating vWF:Ag with a concomitant reduction in vWF function [70]. It has been reported in an Arabian filly and a Quarter horse colt [69], with multiple hematomas and hemarthrosis. Diagnosis of type 1 VWD is based on prolonged activated partial thromboplastin time (aPTT), decreased vWF:Ag activity (8%), reduced vWF function, and low-normal factor VIII:C activity. Maternal inheritance has been suspected [69]. Type 2 VWD is defined as a qualitative defect in vWF and can be further divided into subtypes 2A, 2B, 2M, and 2N [69]. Cases reports of type 2 vWD have been reported on a Quarter Horse filly [67] and on a Thoroughbred mare and her foal [68]. In these clinical cases, a diagnosis of vWD type 2A, consistent with a loss of platelet -dependent function due to abnormal multimers, was suspected [67, 68]. Diagnoses were made based on prolonged TBT, low plasma vWF:Ag with disproportionately severe loss of vWF function, and decreased concentrations of high molecular weight vWF multimers [68]. Type 3 vWD is an autosomal recessive disease and represents a severe quantitative defect of vWF characterized by immeasurable or extremely low levels of vWF [70]. No clinical cases of type 3 vWD have been documented in horses until now.

4.3. Inherited Coagulation Factor Deficiencies

Inherited defects caused by coagulation factor deficiencies identified in horses include deficiencies in coagulation factors VIII (hemophilia A), IX (hemophilia B), and combined factor deficiencies [72, 73].

The genes encoding coagulation factor VIII and IX are located on the X chromosome. Clinical disease primarily affects males with mutations occurring either as *de novo* stochastic events or as an X-linked mode of inheritance from phenotypically normal females. Both syndromes can manifest as mild, moderate, or severe clinical bleeding based on the percent of residual coagulation factor activity. Hemophilia A is being described as the most common inherited coagulopathy, reported in Thoroughbreds, Standardbreds, Quarter Horses, and Tennessee Walking horses and in Shetland ponies [7, 72-74]. In addition, Winfield and Brooks [75] showed an acquired hemophilia A caused by inhibitory antibodies against factor VIII in a Thoroughbred mare. Bleeding tendencies after minor injury and recurrent hemarthrosis have been associated with a poor prognosis [76]. In a Thoroughbred mare, Winfield and Brooks [75] showed hemorrhage and blood loss-induced anemia associated with the development of inhibitory antibodies against factor VIII that cause acquired hemophilia A.

Diagnosis is based on clinical signs, coagulation panel findings (prolonged aPTT with a normal platelet count and prothrombin time, PT), and decreased factor VIII coagulant activity (FVIII:C). The severity of disease varies inversely with the percent of FVIII:C activity. Severe disease has been associated with a FVIII:C activity lower than 10-15% [76].

In an early report, Hinton *et al*. [77] described a 2-month-old Arabian colt with clinical signs of epistaxis, hematoma formation, and excessive bleeding from injection sites. Coagulation profile revealed prolonged aPTT, decreased activity for VIII, IX, and XI factors and normal II, V, VII, and X factors. The colt was diagnosed with a multiple coagulation factor deficiency of the intrinsic pathway, although a single factor deficiency with secondary consumption of the remaining factors could not have been ruled out. Alterations in coagulation panels and coagulation factor activity were not found in the dam, sire, half-sister or brother of the affected colt.

Additional inherited intrinsic pathway defects include deficiencies in the contact activator prekallikrein (PK),

described in specific families of miniature and Belgian horses [78]. PK is a glycoprotein which functions in conjunction with high molecular weight kininogen (HMWK) and coagulation factor XII to form the intrinsic contact system [79]. PK circulates in plasma bound to HMWK. Activation of coagulation factor XII occurs due to contact of the negatively charged surface of damaged subendothelium with the PK-HMWK complex. Small amounts of activated factor XII cleave PK to kallikrein and thus acts as a source of autoactivation for additional coagulation factor XII. Kallikrein also augments the cleavage of HMWK to form bradykinin, an inflammatory mediator, and the activation of the plasminogen activator pro-urokinase [79]. Deficiencies in PK have an autosomal recessive mode of inheritance and are diagnosed via a prolonged aPTT and decreased level of serum PK (10-35% activity) [80] with normal HMWK and coagulation factor activity [78].

Tables **1**, **2** and **3** summarize the main characteristics of the genetic disorders that affect

Table 1: **Summary of the Characteristics of the Main Genetic Disorders Affecting Equine Erythrocytes [3, 4, 8, 13-17]**

Genetic Disorder Affecting Erythrocytes	Glucose-6-Phophate Dehydrogenase Deficiency (G6PDH)	Flavin Adenine Nucleotide Deficiency (FAD)	Other Enzyme Deficiencies
Breed	American saddle breed	Spanish Mustang, Kentucky mountain saddle horse	Decreased erythrocyte glutathion concentrations and decreased glutathion reductase activity not associated with flavin adenine nucleotide deficiency
Gender	Male		
Mutation /cause	Enzyme involved in anaerobic glycolysis and erythrocyte protection from oxidative damage. G to A mutation in the G6PDH gen		
Mode of inheritance	X-linked		
Clinical findings	Hemolytic anemia, methemoglobinemia	Mild to moderate anemia, methemoglobinemia	
Laboratory findings	Erythrocytes with morphological alterations (eccentrocytosis, pykocytosis, anisocytosis, macrocytosis, increased Howell-Jolly bodies, rare hemoglobin crystals)	Erythrocytes with morphological alterations (eccentrocytosis, pykocytosis, anisocytosis, hemoglobin crystals). Decreased glutathion concentrations. Indetectable glutathione reductase activity	

Table 2: Summary of the Characteristics of the Main Genetic Immunodeficiencies in the Horse [5, 25-52]

Genetic Disorder Causing Immunodeficiency	Severe Combined Immunodeficiency (SCID)	X-Linked Agammaglobulinemia (XLA)	Fell Pony Immunodeficiency Syndrome (FIS)
Breed	Arabian and cross Arabian	Thoroughbred, Standardbred, Quarter Horse	Fell and Dale pony and Gypsy horse breed
Gender	Both genders	Males	Both genders
Mutation /cause	5 base pair deletion in the gene encoding DNA-protein kinase catalytic unit Leads to failure in the maturation of B and T lymphocytes	Unknown in horses. In humans, mutation in the Bruton tyrosine kinase	A single nucleotide polymorphism in a sodium transport (SLC5A3)
Mode of inheritance	Autosomal recessive	X-linked	Autosomal recessive
Clinical findings	Increased susceptibility to infectious agents. Fatal infections when circulating colostrum-derived antibodies concentrations decreased. Opportunistic infections	Clinical signs start at 2-6 months of age. Death before 2 years. Recurrent infections, mostly caused by opportunistic agents	Clinical signs start a 2-8 weeks of age. Anemia. Infections caused by opportunistic agents.
Laboratory findings	Persistent lymphopenia. Deficit of IgM and IgA. Hypoplasia of lymphoid tissues.	Lack of peripheral B cells. Low or absent IgA, IgG and IgM concentrations	Anemia (hematocrit as low as 3-20%). Lymphopenia (B lymphocytes). Increased neutrophils numbers (infection). Low IgM, IgA concentrations. IgG concentrations variable from 4 weeks after waning of maternal colostrum derived antibody. T-lymphocytes not affected.

Table 3: Summary of the Characteristics of the Main Genetic Disorders Affecting Coagulation in the Horse [7, 56-79]

Genetic Disorder Affecting Coagulation	Glanzmann Thrombasthenia (GT)	Von Willebrand Disease (vWD)	Hemophilia	Others
Breed	Peruvian Paso, Quarter Horse, Thoroughbred, Oldenburg	Arabian, Quarter Horse	Thoroughbred, Standardbred, Tennessee Walking Horse, Quarter Horse, Shetland pony	Abnormal platelet aggregation in response to certain agonists
Gender	Both genders	Both genders	Males	
Mutation /cause	Defect in the platelet membrane receptor αIIbβ3, that acts as fibrinogen receptor on the platelet membrane (not described in Oldenburg)	Inherited quantitative and functional alterations in von Willebrand factor(vWF)	Deficiency in VIII factor: hemophilia A Deficiency in IV factor: hemophilia B	Impaired fibrinogen binding Decreased thrombin generation
Mode of inheritance	Autosomal recessive	Maternal inherence	De novo mutation or X-linked inheritance from phenotypically normal females	
Clinical findings	Bleeding. Epistaxis. Hematoma formation. Prolonged bleeding time	Spontaneous bleeding. Multiple hematomas. Impaired hemostasis after trauma or surgery	Bleeding of different intensity, from mild to severe	Combined deficiencies of several coagulation factors
Laboratory findings	Altered platelet aggregation in response to various agonists. Prolonged closure time	Type 1. Prolonged activated partial thromboplastin time. Reduced vWF:antigen activity. Reduced vWF function Type 2. Prolonged thombotest. Reduced vWF:antigen activity. Reduced vWF function	Prolonged activated partial thromboplastin time. Normal platelet count. Normal prothrombin time. Decreased factor VIII coagulant activity (FVIII:C)	Prekallikrein (PK) deficiency

equine erythrocytes, leukocytes and coagulation respectively.

CONCLUSIONS

Compared to small animals and humans, genetic diseases that affect blood cells and clotting factors have a low incidence. Despite this, it is imperative that the equine clinician know them, for a successful detection of the affected individual and their ancestry, in an attempt to control the dispersion of these disorders in the equine population.

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