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Case Report

A Possible EIPH and Sudden Death Hereditary Condition Detected in Thoroughbreds in Venezuela Report of Case

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Abstract

The objective of this study was to report a possible hereditary condition of Exercise-Induced Pulmonary Hemorrhage, collapse and sudden death detected in English Thoroughbred horses in Venezuela. Results case 1: Necropsy was performed on a 2-year-old English Thoroughbred horse (2006), with epistaxis, collapse in training and sudden death with severe massive hemothorax, rupture of the segmental bronchial arteries, with edema, pulmonary congestion and petechial hemorrhage, to confluent ecchymotic and subserosal petechial hemorrhages were observed in the dorsocaudal pulmonary lobes. Histopathological lesions showed severe congestion, marked interstitial edema, and acute pulmonary hemorrhage due to rupture of focal bronchial arterioles by vascular rhexis. Case 2: Necropsy was performed on a 2-year-old Thoroughbred horse (2008), with epistaxis, collapse in the race and sudden death with severe massive hemothorax, rupture of the segmental bronchial arteries, with edema, pulmonary congestion and confluent petechial to ecchymotic hemorrhage, subserosal petechial hemorrhages were observed in the dorsocaudal pulmonary lobes. Histopathological lesions of the lungs showed severe congestion, marked interstitial edema and acute pulmonary hemorrhage due to rupture of focal bronchial arterioles, hemorrhage due to vascular rhexis. In the review of the pedigree in both cases the mother and maternal grandfather coincided, in two different stallions in 2006 and in 2008. The kinship tests by DNA study confirmed the kinship. In conclusion, the clinical history, macroscopic and histopathological presentation were compatible with a diagnosis of bilateral epistaxis, collapse and sudden death associated with exercise-induced pulmonary hemorrhage, a possible hereditary condition confirmed by the parentage study.

Keywords: *Epistaxis; EIPH; Hereditary; Sudden*

Introduction

Epistaxis i.e. bleeding from the nose in racing horses, has been observed by horsemen since at least the seventeenth century [1]. In the history. Bleeding Childers, born about 1716, was one of the first documented bleeders [2]. Horsemen of the time understood that this bleeding affected the health and performance of their racing stock [3]. Exercise-associated sudden deaths (EASDs) are deaths occurring unexpectedly during or immediately after exercise [4], but in some cases collapse and sudden death not associated with exercise may occur. Epistaxis and Exercise-Induced Pulmonary Haemorrhage (EIPH) is a major cause of poor performance in the equine Athlete [5]. All manifestations of EIPH other than bilateral or unilateral epistaxis, collapse including acute/sudden death due to EIPH, require scientific tools and expertise to identify as being EIPH related [1]. Exercise-induced pulmonary haemorrhage does not have a single aetiologic factor such as race, distance of race, sport, training, age, sex, environment or horse management, but it is supported by the coexistence of multiple predisposing factors and many authors agree that the occurrence of EIPH is caused by effort, training or career [5]. Bleeding from the nose in exercising horses has been identified in historical texts dating back to the 1500s, and racehorses have experienced this condition dating back to the foundation sires of the Thoroughbred breed [3]. Inbreeding in Thoroughbred race horses can somehow play a role in the development of vascular and cardiac malformations that mostly go unreported if they occur in the early stages of life, but are occasionally seen in necropsies [6]. The first report published on the incidence of epistaxis in a group of racing Thoroughbreds in South Africa was in 1950 [7]. Some research show significant genetic lines prone to certain phenotypic or genotypic traits could possibly be prone to vascular hypertension [6]. Since aortic and pulmonary trunk ruptures occurred in three Friesian horses which were descendants from the same sire, a genetic cause cannot be excluded [8]. A study has shown that epistaxis as related to EIPH in the Southern African Thoroughbred sires has a strong genetic basis [7]. The 2009 AAEP (American Association Equine Practitioner) statement-genetic-defects [9] clearly defines the following terms: Congenital defects: Congenital defects include all undesirable traits and pathologic conditions present at birth whether they are genetic or due to intra-uterine events that result from extra-uterine influences. Congenital defects do not necessarily indicate inheritance; they simply indicate that the defect was present at birth. Inherited tendencies: There are characteristics in horses that are influenced by a wide variety of genes, whose pattern of inheritance is complex and whose expression has strong environmental influences. Genetic defects: Genetic defects are pathologic conditions of proven genetic origin. These may be the result of a mutation in a gene of major effect or mutations in multiple genes (polygenic) whose effects combine to produce a deleterious or undesirable result. The degree to which some traits are expressed in horses carrying particular mutations can be influenced by environmental factors. This is called incomplete penetrance. Undesirable traits: An undesirable trait, as designated by certain breed registries, is a condition or behavior which may or may not be present at birth, may develop over time, may or may not be a genetic defect, but precludes registration of that animal. Systematic postmortem evaluation of racehorses has focused primarily on the detection of preexisting conditions associated with fatal musculoskeletal injury (FMSI); however, apparently healthy horses also die suddenly or collapse on the track, often during exercise [10]. The cardiac molecular autopsy is not currently available for horses, but researchers have started working toward developing genetic tests to screen for potential inherited arrhythmogenic disorders that may lead to SCD in horses. This diagnostic tool will hopefully help to determine if inherited cardiac arrhythmogenic disorders may play an important role in horses, as they do in humans [11]. Although cardiac conditions are frequently suspected as a cause of death, is common the news in the newspapers when collapsing and a high competition horse dies, SD racehorses are often autopsied negative; however, previous studies have been limited due to inconsistent or insufficient cardiac sampling and lack of controls. While not excluding a genetic basis for SD, analysis of the genotypes (GGP Equine 70 K Array) of cases and controls did not reveal significant differences in allele frequencies at any locus. Most SD racehorses were autopsied negative; further research using standardized protocols and controls is needed to understand the underlying causes of SD, which is crucial to protecting the viability of racing [10]. Venezuelan Thoroughbred Racing data suggests that the frequency of sudden death associated with Exercise Induced Pulmonary Hemorrhage (EIPH) is related to the altitude at which racing occurs [12]. We performed a clinical and toxicological study in 19 cases of epistaxis associated with pulmonary hemorrhage induced by exercise at the Racetrack "La Rinconada", Caracas, Venezuela, however was not possible to detect drugs in 10 horses who had epistaxis [13], which is possible EIPH and sudden

death hereditary condition in these horses in Venezuela. Practical experiences in Venezuela suggest a tendency of horses with epistaxis and sudden death associated with EIPH to a group of stallions and mares [12]. Pulmonary hypertension related-EIPH, cardiovascular and early atherosclerosis revealed a high trend for future research on diet versus genetics associations with hypertensive equine athletes on parental lines crossing relationship [14]. Our unpublished studies suggest lines of hypertensive horses with a predisposition to Epistaxis and EIPH, with follow-up of the lines of stallions and mares, with the complete identification of parental lines crossing relationship of horses that have suffered a collapse and sudden death associated with EIPH.

Aim of the Study

The aim of this study was to report a possible EIPH and sudden death hereditary condition detected in Thoroughbreds in Venezuela.

Report of Case

A necropsy was performed in a 2 years old (2006), Thoroughbred horse, with epistaxis, collapse in training and sudden death with severe massive hemothorax (approximately 5 liters), following rupture of the segmental bronchial arteries, with associated edema, pulmonary congestion and hemorrhage petechial to equimotic confluent and subserosal petechial hemorrhages were observed in the dorso-caudal lung lobes associated with EIPH. These histopathological lesions showed on lungs severe congestion, marked interstitial edema, and acute pulmonary hemorrhage due to rupture of focal bronchial arterioles, including red blood spilled, associated to EIPH. The pedigree was reviewed (Copent Garden/Keep Running). Two years later a necropsy was performed in a 2 years old (2008), Thoroughbred horse, with epistaxis, collapse in a race and sudden death with severe massive hemothorax (4 liters approximately), foolwong rupture of the segmental bronchial arteries, with associated edema, pulmonary congestion and hemorrhage petechial to equimotic confluent and subserosal petechial hemorrhages were observed in the dorso-caudal lung lobes associated with EIPH. These histopathological lesions of the lungs showed severe congestion, marked interstitial edema, and acute pulmonary hemorrhage due to rupture of focal bronchial arterioles, including red blood spilled, associated with EIPH. The pedigree was reviewed (Draw/Keep Running), stallions and products at the database of the Stud Book of Venezuela and the kinship test in the Department of Veterinary Integrative Biosciences, Texas A&M University, USA. The two cases of epistaxis and sudden death have the same broodmare (grandfather broodmare) in common, which is why it was confirmed by DNA kinship testing of each of the horses and parents. However, of the 8 broodmare products, two with different stallions presented epistaxis and sudden death. Three products of the same broodmare with 3 different stallions have not presented epistaxis and sudden death to date. Broodmare KEEP RUNNING (VEN) b. M, 1997 {1-n} DP = 9-4-13-0-0 (26) DI = 3.00 CD = 0.85 - - Starts, 4 Wins, - Places. Broodmare Family Summary: 1-b (1), 1-g (1), 1-n (6), 1-o (2), 1-w (1), 1-x (5), 1-k (3), 2-s (1), 2-f (1), 2-n (1), 3-l (3), 3-j (1), 3-m (1), 4-n (1), 4-m (2), 5-f (1), 8-g (2), 8-d (2), 8-f (2), 8-h (3), 9-c (1), 11-g (1), 13-c (7), 14-f (2), 16-g (4), 22-b (5) (https://www.pedigreequery.com/keep+running).

Products	Stallion	Broodmare	Date	N° DNA
No Name	Draw	Keep running	26/03/2004	-
*Brother Forever	Copent Garden	Keep Running	27/03/2006	18300
Pequeño Ronald	Draw	Keep Running	17/03/2007	18397
*The Brothers	Draw	Keep Running	30/03/2008	38783
La Libanesa	Runspastum	Keep Running	30/03/2009	50352
Walla Walla	Bocca Al Lupo	Keep Running	24/02/2010	53174
The Clown	Draw	Keep Running	13/02/2011	61660
Nathana	Runspastum	Keep Running	22/01/2012	1400456

Table 1: *Products by year, stallions, broodmare, date and DNA number.*

**Epistaxis and sudden death.*

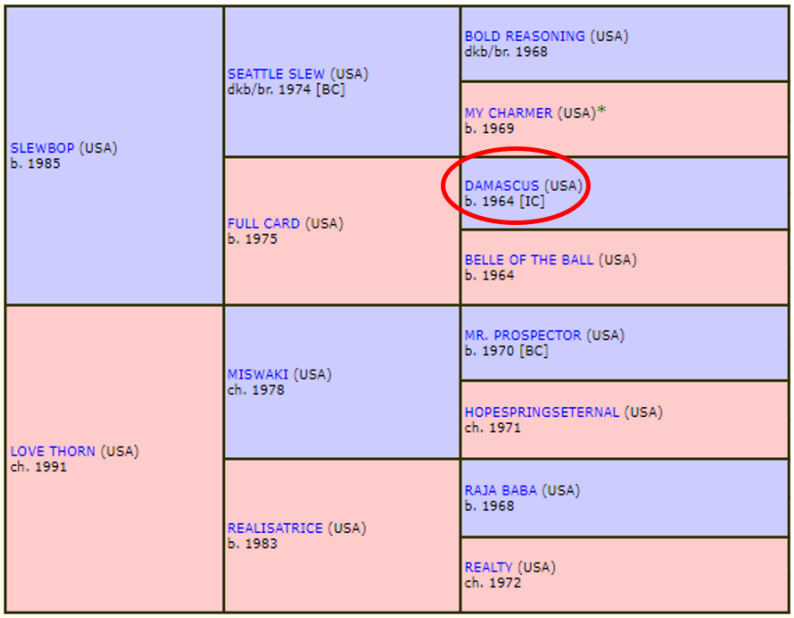

Figure 1: *Broodmare pedigree (indicating with the circle the maternal great-grandfather).*

Source: https://www.pedigreequery.com/.

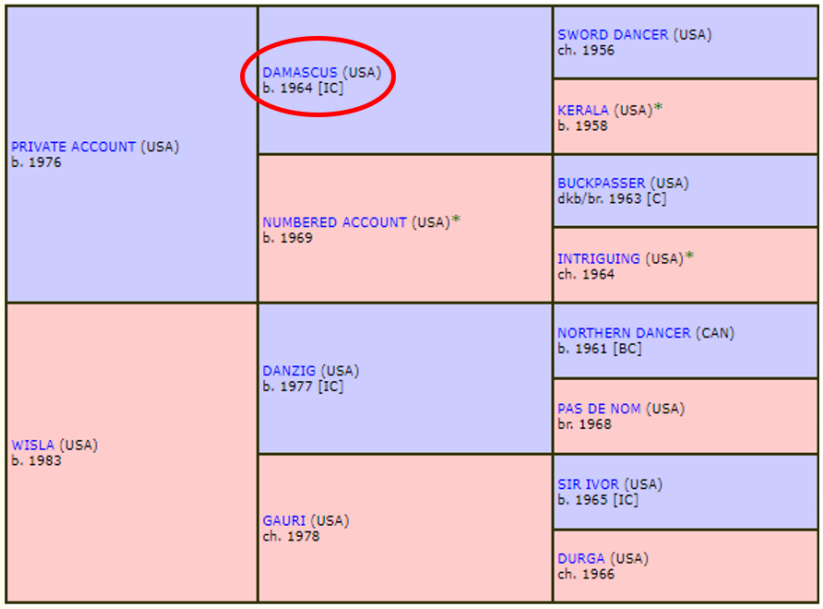

Figure 2: *Stallion pedigree (pointing with the circle the paternal grandfather).*

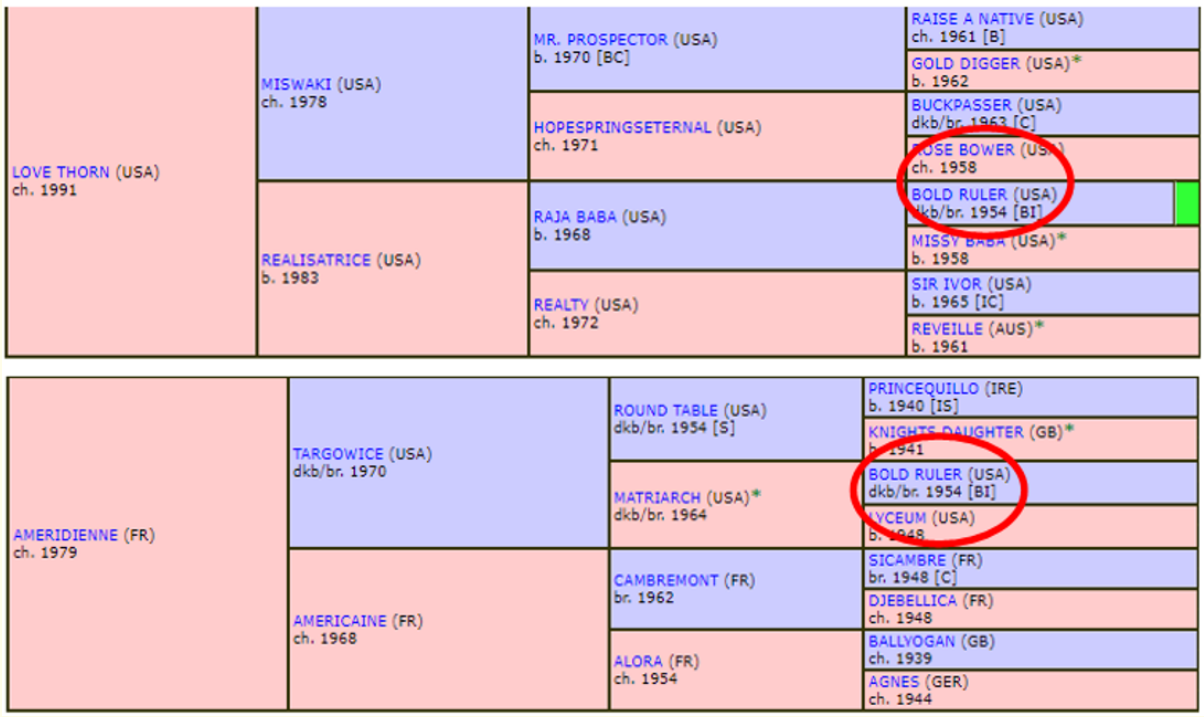

Figure 3 and 4: *Broodmare and Stallion pedigree (marking with the circle the great-great-grandfather in common, for great-grandmother in the Broodmare and for the great-grandfather in the Stallion).*

Discussion

Genetic bleeding disorders can have a profound impact on a horse's health and athletic career, as well as how it affects the image of the spectacle of horse racing and competitions these diseases include haemophilia A, von Willebrand disease, prekallikrein deficiency, Glanzmann's Thrombasthenia and Atypical Equine Thrombasthenia. Exercise-induced pulmonary haemorrhage also has a proposed genetic component [15]. Evidence suggests genetic and non-genetic links to EIPH expressed as epistaxis [16]. Genetic variants are transmitted to offspring and their frequency might increase within a family [4]. In the first case of a horse with epistaxis and sudden death (2006), the maternal great-great-grandfather coincides with the maternal great-great-grandfather of the second stallion (Figure 1). Therefore, the frequency of such variants might increase with the inbreeding factor [4]. Exercise-induced pulmonary haemorrhage also has a proposed genetic component [15], however, there are many aspects to study and elucidate. Higher inbreeding could have a negative impact on racing performance [4]. In this second case, in the revision of the pedigree of the broodmare, the maternal great-grandfather coincides with the paternal grandfather of one of the stallions for the horse that collapsed in 2008 (Figure 3 and 4). Although multiple analyses have suggested that non-genetic factors may lead to the development of this condition, relatively little consensus has been reached regarding its genetic aetiology [16]. In the absence of genetic tests, bleeding disorders are typically diagnosed by measuring platelet function, von Willebrand factor, and other coagulation protein levels and activities. For autosomal recessive diseases, genetic testing can prevent the breeding of two carriers [15]. Postmortem evaluation of racehorses has focused primarily on musculoskeletal injuries; however, horses also die suddenly on the track (sudden death [SD]) [10]. Necropsy in sudden death associated to EIPH, results in some cases were severe

massive hemothorax, foolwong rupture of the segmental bronchial arteries, with associated edema, pulmonary congestion and hemorrhage petechial to equimotic in many cases confluent [17-19] and subserosal petechial hemorrhages were observed in the dorso-caudal lung lobes associated with EIPH. These histopathological lesions generally showed severe congestion, marked interstitial edema, and acute pulmonary hemorrhage due to rupture of focal bronchial arterioles, including red blood spilled, is possible to observe areas of pulmonary emphysema and EIPH [17-19], these findings represent the diagnostic key in cases of sudden death in racehorses [20].

Conclusion

In conclusion necropsy gross and histopathologic appearance, were consistent with a diagnosis of sudden death associated with Exercise-Induced Pulmonary Haemorrhage a possible hereditary condition.

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