Case Report
Aniridia in Two Related Tennessee Walking Horses

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Aniridia in horses is rare and has previously been reported to be genetically transmitted in Belgian horses and Quarter horses. This paper describes the defect in 2 related Tennessee Walking horses, with special reference to new findings regarding the molecular genetics of ocular development and how they might relate to equine aniridia. In addition to aniridia, these 2 horses possessed additional ocular abnormalities including cataracts and dermoid lesions. Euthanasia was elected, and the eyes were examined histologically. Iris hypoplasia, atypical dermoids, and cataracts were confirmed in both horses. Due to the heritability of aniridia in horses, breeding of affected animals is not recommended.

1. Introduction

Aniridia is a rare condition marked by partial or complete absence of the iris. This condition has been reported in horses [6–11], cattle [1], laboratory animals [2, 3], and humans [4, 5]. In Belgian horses [6] and Quarter horses [7], the defect has been reported to be genetically transmitted as an autosomal dominant trait, but at least one case in a Swedish Warmblood was not dominantly inherited [8]. In humans, the anomaly either presents as a familial condition with autosomal-dominant inheritance or is sporadic [4, 5]. Affected animals are usually photophobic with absent direct and indirect pupillary light responses bilaterally, and they often have additional ocular abnormalities including dermoid lesions and cataracts. Dermoid lesions, like many instances of aniridia, form during foetal development, and our understanding of the molecular genetics of ocular development has improved since the last case report of aniridia in horses [8]. Therefore, the purpose of this report is to describe the clinical and histologic features of aniridia in 2 related Tennessee Walking horses, especially considering "new" information about the genetics of ocular involvement.

2. Case Presentation

Two Tennessee Walking horses were presented to the University of Tennessee Equine Hospital for bilateral ocular abnormalities. Horse A was a 15-year-old mare, and horse B was her 12-month-old female offspring. Very limited history was available because both animals were rescued. Visual deficits had been recognized in both animals prior to presentation, and the new owners had noticed bilateral ocular opacities in both horses. On ophthalmic examination of horse A, both direct and indirect pupillary light responses were absent in both eyes. However, the horse did have positive menace responses bilaterally. The tips of the ciliary processes were visible in both eyes, and the iris could not be identified. The corneas showed evidence of chronic keratitis bilaterally with mild vascular infiltration of the cornea at the dorsal aspect. Fine cilia-like hairs were protruding from the superior corneoscleral limbus of the left eye, consistent with a limbal dermoid. There were also bilateral immature nuclear cataracts. Cataracts hid portions of the fundus, but those portions that were evaluable were normal.
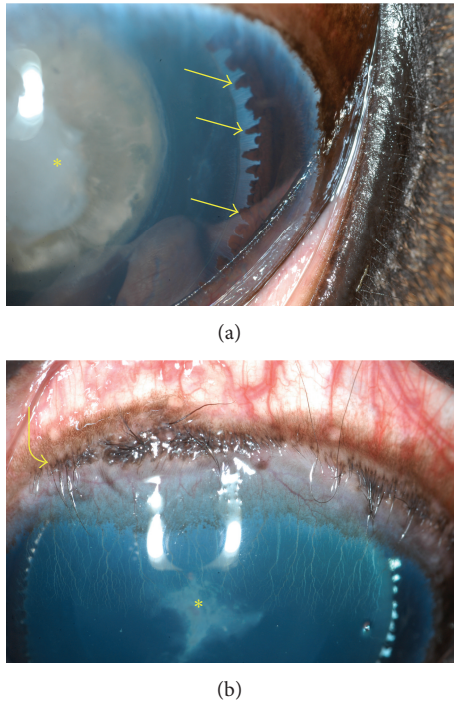
(a)

(b)

FIGURE 1: Horse B. (a) Left eye. Due to the absence of any grossly visible iris, the ciliary processes are easily seen (arrows). An immature nuclear cataract is also present (asterisk). (b) Right eye. Short hairs emanating from the corneoscleral limbus are considered variants of limbal dermoids (curved arrow). An incipient cataract is also present (asterisk).
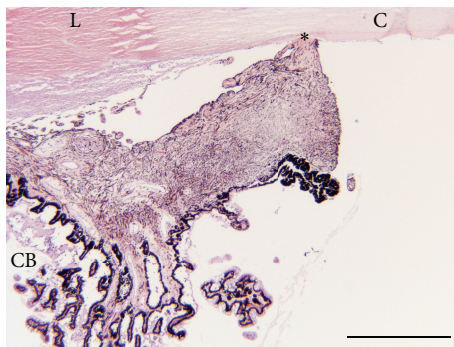

FIGURE 2: Horse A. The iris is markedly blunted and focally adhered to Descemet's membrane (peripheral anterior synechia) (asterisk). For orientation, C: cornea, L: limbus, and CB: ciliary body. Hematoxylin and eosin. Bar = 2 mm.

Ophthalmic examination of horse B, the yearling offspring of horse A, revealed similar findings. There was no evidence of an iris, and the ciliary processes were easily seen (Figure 1(a)). Chronic keratitis was present bilaterally, and limbal dermoid lesions were more pronounced than those in horse A (Figure 1(b)). Incipient to immature cataracts were present bilaterally.

Both horses were diagnosed with bilateral aniridia with chronic keratitis, limbal dermoids, and cataract formation. The rescue organization elected euthanasia for both animals due to the poor prognosis for improvement in long-term vision. Following euthanasia, the eyes of both animals were harvested and fixed in Davidson's solution.

3. Histopathology

In both eyes (one from each horse), the iris leaflets were present but markedly blunted (iris hypoplasia) (Figure 2). The blunted iris was frequently adhered to Descemet's membrane (peripheral anterior synechia) (Figure 2). The iris sphincter muscle was absent, and only poorly developed remnants of the dilator muscle were apparent with a Masson's trichrome stain (Figure 3). There were occasional nerve bundles within the iris leaflets. The iridocorneal angle was otherwise normal, but horse B had erythrocytes (haemorrhage) within the angle. On the posterior surface of the iris, the normally heavily pigmented, bilayered epithelium was disorganized and varied from poorly to heavily pigmented (Figure 3). The ciliary body and ciliary processes were within normal limits.

Horse A had mild, limbal, superficial corneal vascularization on one side of the eye; the clinically noted limbal dermoid was not present in the section. At the limbus of horse B, there was a single hair follicle with an associated sebaceous gland, consistent with a limbal dermoid. The surrounding collagen was haphazardly arranged and contained scattered blood vessels, lymphocytes, and plasma cells.

There was artifactual retinal detachment in both horses. Grossly, both horses had bilateral lens opacities; however, only the lens from the foal (horse B) was examined microscopically. There was splitting of the anterior lens capsule and lens epithelial cells metaplasia and hyperplasia. No other histopathologic lesions were present in the lens.

4. Discussion

Aniridia was first reported in horses in 1955 in a Belgian stallion and his offspring [6]. The defect identified in this group of related horses was heritable and passed via an autosomal dominant mode. Aniridia has also been described in a group of related Quarter horses, also with autosomal dominant inheritance [7, 9]. In single case reports in a Thoroughbred colt [10] and Welsh-Thoroughbred cross filly [11], hereditability was undetermined. Hereditability was undetermined for 5 in a series of 6 cases from Sweden, and dominant hereditability with complete penetrance was ruled out in one Swedish Warmblood. In humans, aniridia is inherited in about two-thirds of the cases and sporadic in the remainder [4]. In the inherited forms, the majority are autosomal dominant [4]. Although it is impossible to make a conclusion about inheritance in the 2 horses in this report, the presentation in a mare and its foal makes hereditability highly likely, and rarity of the syndrome makes dominant inheritance most likely.

The underlying pathophysiology of aniridia is not known with certainty. During ocular organogenesis, the epithelial layers of the normal iris are derived from the neuroectoderm of the anterior rim of the optic cup, while the stroma is derived from mesenchymal tissue of neural crest origin [12].
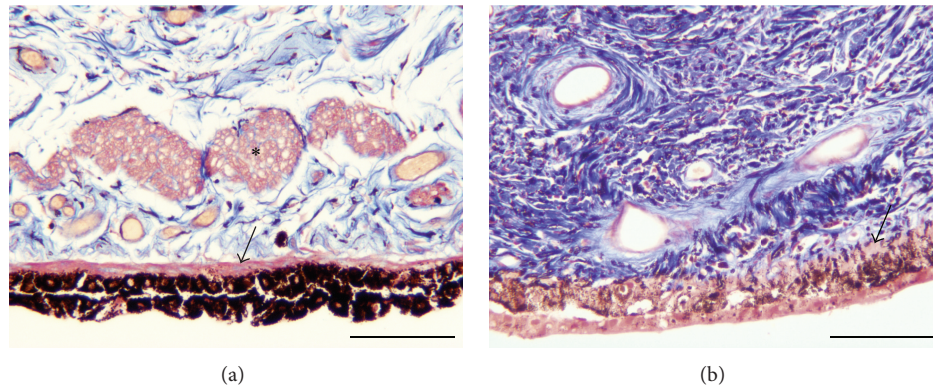
(a)　　　　　　　　　　　　　　(b)

FIGURE 3: (a) Control horse. Normal portion of the posterior surface of the pupillary margin of the iris with both the dilator muscle (arrow) and sphincter muscle present (asterisk). Masson's trichrome. Bar = 200 μm. (b) Horse B. Posterior surface of the iris with thin dilator muscle (arrow); the sphincter muscle was absent. Note also the poorly pigmented and disorganized epithelium on the posterior surface of the iris. Masson's trichrome. Bar = 200 μm.

Histologically, epithelium and stroma are both deficient in aniridia, so it is possible that defects in epithelial development prevent normal stromal maturation or that stromal maldevelopment causes failure of normal epithelial development [5]. A third theory suggests that aniridia is a result of excessive remodelling, with normal iris formation being followed by inappropriate iris tissue regression [13].

In humans, most cases are transmitted via autosomal dominant inheritance and are linked to defects in the *PAX6* gene, one of a family of transcriptional regulators that has a central role in controlling the development of the eye [4, 5]. Most mutations (nonsense mutations, splice mutations, frameshift deletions, etc.) cause premature translational termination on one of the alleles, resulting in haploinsufficiency with decreased expression of gene product [4, 5]. Because a critical dose of PAX6 protein is necessary to initiate transcription of target genes [14], the reduced amount could prove critical in preventing normal iris development. A high, continuous expression of *PAX6* in tissues of ectodermal origin (e.g., iridial epithelium) directly affects the regulation and structure of these tissues during organogenesis of the eye but is also necessary for the expression of signalling molecules that act on cells of mesenchymal origin (e.g., the iris stroma). In addition, a low and transient expression of *PAX6* is observed in cells of mesenchymal origin during development of the iris and other anterior segment tissues [15]. This favours a hypothesis that simultaneous defects in epithelial and mesenchymal development are involved in aniridia, with the former probably being more important. Missense mutations are relatively rare and result in a variety of phenotypes, including corneal dystrophy, Peter's anomaly, foveal hypoplasia, ectopia pupillae, congenital nystagmus, and presenile cataract [5]. Sporadic mutations also occur and may be associated with nephroblastoma (Wilms' tumour), genitourinary abnormalities, and mental retardation [4, 5]. While most of our knowledge about *PAX6* structure and function comes from humans and laboratory rodents, *PAX6* protein function is highly conserved across bilaterian species [4]. Therefore, it is easy to assume that most of the genetic features of aniridia described in humans would apply to horses as well. Another equine ocular developmental disorder, multiple congenital ocular anomalies, also features maldevelopment and hypoplasia of the iris, but that syndrome appears to be clinically and genetically distinct from the equine aniridia syndrome [16, 17].

Clinically, aniridia in humans is usually found in association with other ocular defects such as cataracts, glaucoma, keratopathy, optic nerve hypoplasia, ectopia lentis, nystagmus, and photophobia [5]. The foregoing discussion of the importance of *PAX6* on ocular organogenesis focuses on the iris, but *PAX6* is equally important in the development of the cornea [18], lens [19], optic nerve/retina [20], and iridocorneal angle [15]. Multiple ocular defects are therefore not surprising. Both of the cases in this report had cataracts, corneal pathology, and limbal dermoids, and similar findings are common in previously published equine cases [7–10]. The dermoids were clinically atypical in that the aberrant hairs did not emanate from a skin-like mass of tissue but rather appeared in a regular row along the limbus and were very much like a row of cilia. The precise embryological errors leading to the development of the various presentations of dermoids are unclear, but it has been hypothesized that the pathogenesis of limbal dermoids may be related in part to aberrant development and fusion of the lids, with displacement of lid elements to the limbus [21], which would certainly correlate with the clinical appearance in our cases.
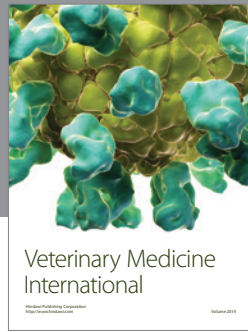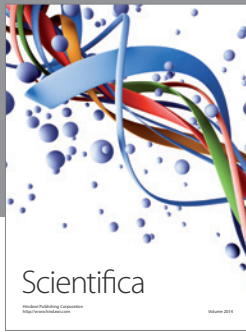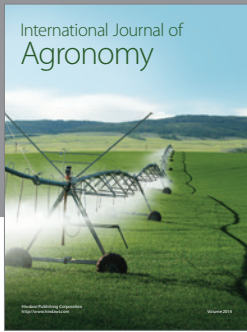
Aniridia is a complex heritable disorder of horses that has been reported in Belgians, Quarter Horses, and now in Tennessee Walking horses. The disorder most commonly follows an autosomal dominant mode of inheritance and results in impaired vision of affected animals due to chronic keratitis and cataract formation. There is no known treatment of the condition for horses; affected animals are managed based on clinical symptoms as they arise. Although horses have been reported to perform well with the condition [10], affected animals should not be used for breeding purposes.

Acknowledgment

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