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Hoof wall separation disease: A Review

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Summary

Hoof wall separation disease (HWSD) is a genetic defect in Connemara ponies characterised by separation and cracking of the dorsal hoof wall. The disease can result in chronic inflammation, severe lameness and laminitis. Affected ponies typically show clinical signs within the first six months of life. The disease is inherited as an autosomal recessive trait. The genetic mutation is a frameshift mutation in the gene *SERPINB11*, (c.504_505insC). Carriers are completely normal, only ponies that are homozygous for the mutation will have clinical signs of the disease. Within the Connemara breed, carrier frequency has been estimated at 14.8% and the mutation has not been identified in other breeds at this time. While there is no definitive cure for HWSD, management through targeted hoof care and the use of special shoes may be beneficial. Additionally, environmental management may lessen the severity of clinical disease in affected ponies. Genetic testing of Connemara ponies is required for all new registrations.

This review of Hoof wall separation disease (HWSD) in Connemara ponies describes the clinical presentation, histopathologic findings, genetic discovery and resulting DNA test and management considerations for affected ponies.

Keywords

horse; Connemara; genetics; laminitis; recessive

Clinical Presentation

Typically, clinical signs of HWSD include dorsal hoof wall splitting on the weight-bearing surface and sole proliferation that develop within the first six months of life. The outer hoof wall splits and separates at the sole and the hoof wall may develop a frayed appearance (Figure 1). Affected ponies exhibit weight-bearing problems and present shoeing challenges, as nails cannot be maintained in the hoof wall due to splitting. Proliferative horn can develop on the sole of the hoof since the ponies are forced to bear the majority of their weight on the soles of their hooves. All four hooves are typically affected, but they can show varying

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Authorship

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degrees of splitting. The coronary band, sole, and white line appear healthy. In severe cases, ponies may develop recurrent abscesses and laminitis (Finno *et al.* 2015).

The clinical presentation can vary widely between individuals. Some ponies are minimally affected, with only small amounts of hoof wall fraying notable during sudden environmental changes from dry to wet or vice versa. These ponies may have successful athletic careers without a high degree of maintenance. Other ponies can be severely affected and it may be difficult to manage their comfort level even if they are not used for any performance activities. These ponies may suffer from chronic lameness, abscessation or laminitis. Despite the wide range of clinical disease severity, the causative genetic mutation is the same. There may be interacting genetic alterations or epigenetic phenomena that lead to this phenotypic heterogeneity, as is observed in human medicine (Wolf 1997).

Histopathologic Findings

Hooves from HWSD-affected ponies show variable degrees of splitting within the dorsal hoof wall, most prominent along the distal margin. The hoof wall horn is brittle and easily fragmented. The coronary band is completely normal, and the white line is intact, with no hyperemia or scarring. The dorsal hoof wall separation is outside of the white line. There are no histologic abnormalities apparent in the coronary band, periople and proximal lamina. Laminitis, with associated coffin bone rotation or sinking, may be identified in severe cases.

Genetic Discovery

Parents of HWSD affected ponies appeared normal, suggesting an autosomal recessive mode of inheritance. A genome-wide association study (GWAS) using the first-generation single-nucleotide polymorphism (SNP) DNA genotyping array was performed in 2015 using 15 HWSD Connemara cases and 17 controls (Finno *et al.* 2015). A genome-significant region of association was identified on chromosome 8 (chr8) within an ~1.7 Mb window. Two affected and two unaffected Connemara ponies underwent whole-genome sequencing (average of 6x coverage) and 363 potential associated single nucleotide variants (SNVs) and 28 associated insertions and deletions (indels) were identified in the region of association on chr8. Variants within or adjacent to genes were prioritised for further investigation and 22 variants (17 SNVs and 5 indels) were then genotyped in a larger group of 23 affected ponies and 27 obligate carriers. Of these, only four variants were unique to the 23 affected ponies, including a 1-bp insertion, resulting in a frameshift mutation in *SERPINB11* (c.504_505insC,p.Thr169Hisfs*3). Gene expression studies then demonstrated that gene expression of *SERPINB11* was significantly downregulated in coronary band tissue from HWSD affected ponies as compared to controls.

Once the mutation was identified, 324 Connemara ponies that were unrelated to affected animals were genotyped and the carrier frequency was calculated at 14.8% (Finno *et al.* 2015). Heterozygous animals are all phenotypically unaffected, confirming an autosomal recessive mode of inheritance. For Connemara ponies that are homozygous for the mutation and thereby affected, the severity of the phenotype ranges from mild, with a cleft between the dorsal hoof wall and white line but no overt lameness, to severe, with proliferative solar

horn and associated laminitis. Penetrance is complete for HWSD but expressivity can be variable.

The exact mechanism by which SERPINB11 maintains dorsal hoof wall structure is unknown. The serine protease inhibitor family, which includes SERPINB11, could potentially inhibit proteolytic cleavage of residues in the terminally differentiating hoof wall layer. Thus, a loss of SERPBIN11 could result in a loss of peptidase inhibition and structural failure of the hoof wall upon impact. An alternative theory is that SERPINB11 may play a role in relative keratinocyte proportions in the equine hoof wall, thereby weakening the overall structure and allowing the most distal end to fragment.

Management of HWSD

For mild cases of HWSD, frequent hoof care and trimming can maintain soundness. In more severe cases, the dorsal hoof wall may entirely separate, leading to repeated stress of the innermost layer of the lamellar interface, which can result in laminitis. The splitting of the dorsal hoof wall appears to worsen when environmental conditions change from dry to wet or vice versa. Many owners are able to manage cases with frequent trimming and glue-on shoes.

With the availability of a DNA test for HWSD in the Connemara breed, the Connemara Pony Breeders Society requires genetic testing for all new registrations, unless they are the progeny of recorded non-carrier parents. For testing not related to registration, hair samples (with roots attached) can be submitted to the UC Davis Veterinary Genetics Laboratory. Owners should avoid breeding carriers to other carriers, but they may breed carriers to non-carriers to maintain desirable traits and maintain genetic diversity in the breed.

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Abbreviations

GWAS	Genome-wide association study
HWSD	Hoof wall separation disease
Indel	Insertion/deletion
SNP	Single nucleotide polymorphism
SNV	Single nucleotide variant

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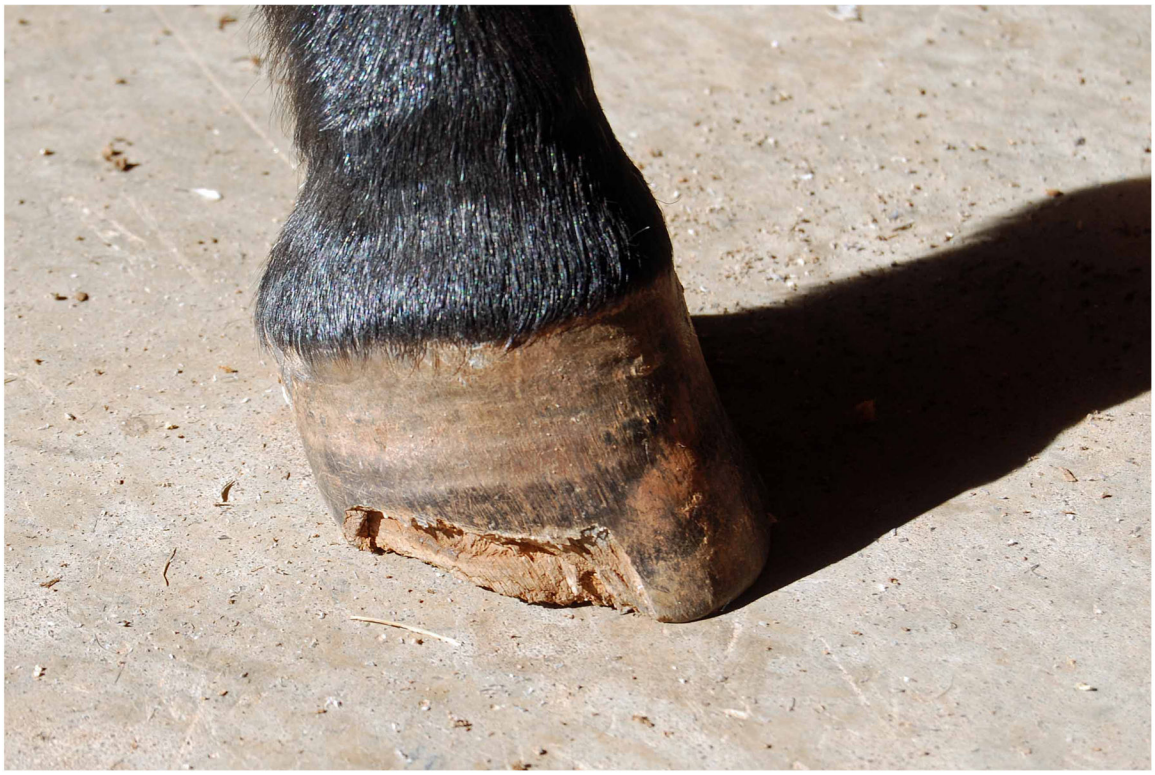

Figure 1:
The hoof of a HWSD-affected pony.