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Review

Bovine spastic paresis: A review of the genetic background and perspectives for the future

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ABSTRACT

Bovine spastic paresis (BSP) is a sporadic, progressive neuromuscular disease that is thought to affect all breeds of cattle. The disease manifests as a unilateral or bilateral hyperextension of the hind limb due to increased muscle tone or permanent spasm of mainly the gastrocnemius and/or the quadriceps muscle. Clinical signs only appear in rising, standing and moving animals, which is an important diagnostic feature. Although several medical treatments have been described, surgical procedures such as neurectomy or tenectomy are generally indicated. Even though complete recovery can be achieved, BSP-affected animals should not be used for breeding, since BSP is commonly considered a hereditary disease. The condition therefore negatively affects animal welfare, economics and breeding. When first described in 1922, BSP was already assumed to be heritable, and this assumption has been perpetuated by subsequent authors who have only discussed its possible modes of inheritance, which included monogenetic and polygenetic modes and gene–environment interactions. Besides some clinical aspects and the consideration of the tarsal joint angle as a BSP-correlated trait, this review mainly focuses on the assumed genetic aspects of BSP. Evaluation of the published literature demonstrates that to date, irrevocable proof for the assumed heritability of BSP is still missing. The assumption of heredity is further contradicted by known allele frequencies and incidences of proven hereditary diseases in cattle, such as arachnomelia or bovine spinal muscular atrophy. Consequently, future research is needed to determine the cause of spastic paresis. Procedures that will help test the null-hypothesis ('BSP is not hereditary') and possible modes of inheritance are discussed in this review.

Introduction

Bovine spastic paresis (BSP) was first reported in 1922 by Hamoir and Wester (Wester, 1922; Dietz, 1971; Fankhauser et al., 1972; Touati et al., 2003; Vertenten, 2006). Hamoir (1922) described BSP as a contraction of the gastrocnemius muscle, the extensor of the tarsal joint, which was assumed to be a defect of the N. tibialis and the N. fibularis (Huskamp and Daniels, 1970; König and Liebich, 2001). Initially spastic paresis was referred to as 'contracted Achilles tendon', 'straight hock' and 'Elso heel' (Denniston et al., 1968). 'Elso II 34' was an elite East Friesian sire born in 1903, with an especially high breeding value for fat performance. Assuming the disease is heritable, Elso II 34 is said to be *the* sire of BSP in the Friesian breed (Wiesner, 1960; Rieck and Leipold, 1965). In 1932, Götze introduced the term 'spastic paresis', which has since been established in the literature and is now the commonly used term (Rosenberger, 1939).

Since the first description of BSP almost 100 years ago, several studies concentrating on the pathogenesis and aetiology of this disease have been conducted. Based on the results of these studies, most authors assumed a hereditary nature of BSP. Reliable evidence for the genetic basis of BSP, however, has not been found. Accordingly, BSP is considered as a defect of yet unknown status regarding possible Mendelian heredity in the OMIA database.[1]

In addition to presenting an overview of clinical aspects (clinical signs, diagnosis, treatment), this manuscript aims to review the existing hypotheses of the potential causes of BSP. The main focus will be on different genetic hypotheses and the usefulness of the tarsal joint angle as a BSP-correlated trait. Moreover, future perspectives and general reflections concerning hereditary diseases in general, and particularly BSP itself, will be presented. These aspects will then be discussed in general comments on potential risks for hereditary diseases posed by the common practice of artificial insemination and in BSP-specific reflections opposing the heredity of

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[1] See: Online Mendelian Inheritance in Animals, OMIA. Faculty of Veterinary Science, University of Sydney. http://omia.angis.org.au/ (OMIA 000928-9913; accessed 22 June 2016).

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BSP. Furthermore, proposals for future research that might help resolve the cause of spastic paresis are presented.

Clinical aspects

BSP is a sporadic neuromuscular disease that is assumed to affect many, if not all, breeds of cattle (Götze, 1932; Formston and Jones, 1956; Wheat, 1960; van Gastel-Jansen and Frederik, 1962; Love and Weaver, 1963; Rasbach, 1963; Roberts, 1965; Bouckaert and De Moor, 1966; Leipold et al., 1967; Denniston et al., 1968; Gadgil et al., 1970; Arnault, 1983; Browning et al., 1986; Thomason and Beeman, 1987; Harper, 1993; Gentile, 2000; Vlaminck et al., 2000; Gentile et al., 2002; Gentile and Testoni, 2006; Miura et al., 2009; De Vlamynck et al., 2014). The disease mostly occurs at the age of 3–8 months and manifests itself in a progressive hyperextension of the hind limb(s) caused by spasms of certain muscles, especially the gastrocnemius and the quadriceps femoris muscle (Dirksen, 1970; Gentile, 2000; Touati et al., 2003; Gentile and Testoni, 2006). Due to different patterns of muscle involvement, some authors distinguish between BSP-G (gastrocnemius muscles), BSP-Q (quadriceps muscles) and BSP-M (mixed; quadriceps and/or other muscles) (Keith, 1981; Harper, 1993; Touati et al., 2003; Vertenten, 2006; De Vlamynck et al., 2014). Furthermore, clinical signs can be observed either unilaterally or bilaterally and, depending on their onset, are referred to as the 'early form' (Fig. 1) or the 'late form' of BSP. The early form, which is the more frequent type of BSP, occurs in calves <8 months old and can be treated by surgery. The late form manifests itself at 2–6 years of age (Rieck and Leipold, 1965; Dirksen et al., 2006). For economic reasons, it has been recommended that bilaterally affected animals with a bodyweight of at least 200–300 kg should not be treated surgically, but rather be slaughtered (Nuss, 1991).

As clinical signs only appear in rising, standing and moving, but never in recumbent animals, careful observation of the animal combined with palpation of the spastic muscles is crucial for the diagnosis of BSP. Additional diagnostic methods, more extensive descriptions of clinical signs and different hypotheses regarding pathogenesis are reviewed in De Vlamynck et al. (2014). Surgical treatments for BSP include total neurectomy, partial tibial neurectomy, triple tenotomy and triple tenectomy. The most commonly used treatment is tenotomy (Nuss, 1991; Dirksen et al., 2006), but there are also descriptions of medical treatments, surgical methods and their success-rates in the literature (De Vlamynck et al., 2014). However, independent of any treatment success, animals affected by BSP should generally not be used for breeding (Dirksen, 1970). BSP thus not only causes economic damage but also losses in breeding animals (Vlachos, 1974; Koberg and Laiblin, 1988). Moreover, BSP is a serious animal welfare problem since BSP-affected animals experience considerable pain.

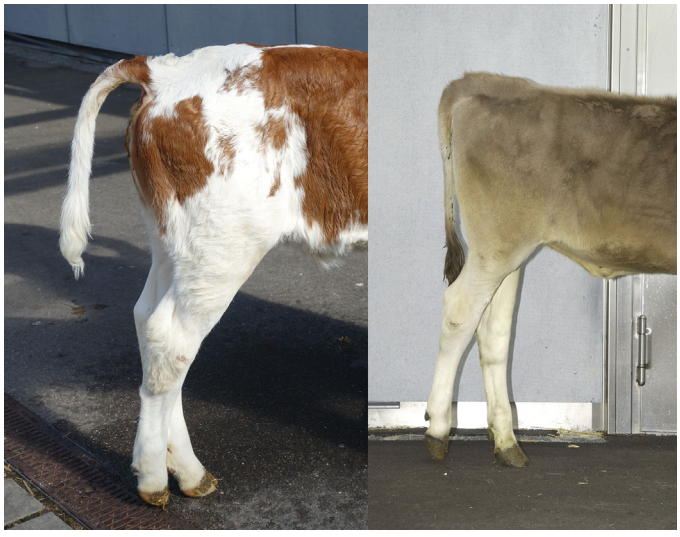

Fig. 1. Cattle with early form of bovine spastic paresis of the right hind limb. Spastic paresis with very mild clinical sings (left); spastic paresis with advanced clinical signs (right).

BSP: Arguments for heredity

Although definitive proof is lacking, heredity of BSP has been assumed almost throughout all the literature on the subject. Most authors, however, simply assume this without conducting their own heritability analyses (Schmahlstieg and Mätzke, 1962b; Roberts, 1965; Leipold et al., 1967; Baker, 1968; Matousková et al., 1972; Keith, 1981; van Huffel et al., 1986; De Vlamynck et al., 2014). Here we concentrate on publications that actually investigated the hereditary aspect of BSP and drew conclusions based on their own observations (see also Appendix: Supplementary material). Where obvious, deficiencies of the respective studies are discussed.

Most authors, particularly in Germany, share the opinion that the elite East Friesian sire Elso II 34 was the true originator of BSP (Baird et al., 1974; Dirksen et al., 2006). The large number of affected animals among the bull's offspring caused the Veterinary University of Hannover to start a breeding experiment using a selected descendant of this sire. In 1932, Götze published his first observations before the untimely death of the chosen bull, which led to the premature termination of the breeding experiment. He stated that spastic paresis could be caused hereditarily due to its familial occurrence and supported this theory with the example of several calves with spastic paresis, which were all descendants of a single sire that had been affected by spastic paresis that resolved following medical treatment. However, his conclusions were based on observations only and the number of affected calves was not reported. He specifically stated that his observations were not based on perfect pedigrees. Seven years later, Rosenberger (1939) confirmed the heredity assumption of Götze (1932) by means of herd book analysis. He supported his statement with pedigree certificates and with comparable breeding experiments in other species, in particular examinations of spastic paralysis in rabbits (Nachtsheim, 1937). Similar to Götze (1932), Rosenberger (1939) did not mention the number of animals and/or pedigrees that were part of his herd book analysis. Rosenberger (1939) further extended the hypothesis of the hereditary nature of spastic paresis by assuming a recessive mode of inheritance.

Besides Elso II 34, Formston and Jones identified a second bull as the suspected origin of BSP, based on the pedigrees of groups of affected animals. The authors claimed that BSP in British cattle had its origin in the Schwarzbunt breed, especially in the Dutch Adema line of the bull 'Adema 197' (Formston and Jones, 1956; Köppe, 1956; Dawson, 1975).

Regarding pedigree analysis, it needs to be taken into consideration that at that time: (1) there was no genetic verification of paternity; (2) knowledge of genetics in general and specific knowledge on segregation analyses were very abstract; and (3) there were no computers for efficient analysis of large amounts of data. Thus, segregation analyses that included unaffected animals and their pedigrees were not possible (Hill and Knott, 1990). However, in order to prove that a distinct ancestor is more frequent in affected than in unaffected individuals, unaffected animals need to be considered.

Gadgil et al. (1970) observed five affected animals stemming from different farm sections of the Institute of Agriculture (Anand, Gujarat State, India) and suggested an autosomal recessive mode of inheritance with incomplete penetrance. He justified this hypothesis with the observation that the common ancestor of the affected bullocks