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Review

Bilateral convergent strabismus with exophthalmus (BCSE) in cattle: An overview of clinical signs and genetic traits

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Abstract

Bilateral convergent strabismus with exophthalmus (BCSE) is a heritable eye defect prevalent in many cattle breeds and known worldwide. BCSE shows a progressive course often terminating in complete blindness. The onset of the defect can sometimes be slowly progressing (late in life) and, as the first signs of the defect are frequently not noticed prior to first breeding, prevention cannot be achieved only by exclusion of affected animals from the breeding program.

This paper provides an overview of the clinical signs, histopathology and genetics of BCSE, its distribution in different cattle breeds and analyses the association between milk production traits and US Brown Swiss. There were different modes of inheritance proposed for BCSE, but although an autosomal dominant major gene is considered most likely in German Brown cattle, an association with milk production traits could not be found. Comparative molecular genetic approaches could help to characterize the responsible genes for this ocular disease in cattle.

Keywords: Cattle; Strabismus; Inheritance; Candidate gene; Comparative genomics

1. Introduction

Bilateral convergent strabismus with exophthalmus (BCSE) is an eye disorder affecting many cattle breeds worldwide. The defect is heritable and of relatively high incidence, particularly in Holstein and German Brown cattle (Schütz-Hänke et al., 1979; Distl et al., 1991; Distl and Gerst, 2000; Holmes and Young, 1957; Power, 1987; Regan et al., 1944; Vogt and Distl, 2002). BCSE can become a significant problem because of its progressive course, which most often leads to complete blindness due to anterior-medial rotation of both eyeballs and, as a consequence of this rotation, the pupils disappear at the inner angle of the orbits. This can cause changes in the behaviour of the affected animals, such as aggressiveness, shying or panic in everyday situations, or reluctance to walk to the milking parlour or to pasture.

Cattle showing clinical signs of BCSE may be suspected of having bovine spongiform encephalopathy (BSE) as both conditions have similar clinical signs, such as an insecure gait, trembling when forced to walk and shyness, as well as strabismus of the eyes. Due to the impact of BCSE, the breeding of animals suspected to be carriers is not allowed by German animal welfare laws. However, sufficiently early detection is not yet possible and efficient preventive measures have to be developed to reduce the occurrence of BCSE.

The objective of the present paper is to provide an overview of the phenotypic form of strabismus in cattle, to review its prevalence, associations with other characteristics, and reported mode of inheritance. We will also discuss histological findings in connection with human molecular genetic candidate genes useful for further research work.

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2. Strabismus and exophthalmus in cattle

Strabismus is defined as the permanent or temporary deviation of the eyes from their normal visual axis. The signs of strabismus can manifest congenitally or later in life. In both human and veterinary medicine, paralytic and non-paralytic forms of strabismus are distinguished.

Concomitant (non-paralytic) strabismus is due to a functional disturbance of the ocular apparatus and can be congenital or caused by disease. Deviation from the visual axis does not vary with ocular movements, and the function of individual eye muscles is usually intact. The paralytic strabismus (incomitant strabismus) is due to paralysis of one or more ocular muscles and leads to limited eye motion and thus to different angles of the axes of the eyes.

The most frequently observed manifestation of strabismus is convergent strabismus (esotropia), with eyes deviating medially. Strabismus in cattle can be caused by congenital defects, space-occupying processes within the orbit, neurological diseases, muscular impairment, metabolic diseases or intoxication (e.g. by phosphoric acid ester, seeds of *Aesculus octandra* (Magnusson et al., 1983)).

Exophthalmus is the abnormal prominence of an eyeball of normal size and can be caused by congenital deformity of the scull or by defects of the suspension apparatus of the eyeball, paralysis of the extraocular muscles (e.g. a defect of the abducens nerve, lesions of the musculus retractor bulbi) or space-occupying processes within the orbit.

3. Clinical signs of bilateral convergent strabismus with exophthalmus (BCSE) in cattle

The signs of bilateral convergent strabismus with exophthalmus (BCSE) were first described in cattle by Koch (1875) at the end of 19th century. BCSE is characterised by a bilateral symmetric, permanent rotation of the eyeballs in an anterior-medial direction, which results in a permanent deviation of the visual axis. Bilateral convergent strabismus is accompanied by slight to severe laterodorsal exophthalmus. According to Power (1987), this is due to the oval shape of the bovine eye, the transverse diameter of which is greater than its axial diameter (Sisson, 1953) so the eyeball protrudes when it is rotated. Epiphora is often seen, particularly in cattle with advanced BCSE (Vogt, 2000). In many cases, the visible sclera shows a secondary dark pigmentation (Veenendal, 1958; Schütz-Hänke et al., 1979). Parts of the lateral rectus muscle or even the retrobulbar fat pad (Schütz-Hänke et al., 1979) can become visible in severely affected animals (Schütz-Hänke et al., 1979). There are no known reports on treatment of BCSE.

The degree of deviation of both eyes from the normal visual axis can be determined by the amount of sclera permanently visible in the temporal corner of the eye. Vogt and Distl (2002) proposed a four-stage scale for classifying affected animals: stage 1, with <25% of the visible eyeball filled with sclera; stage 2 from 25% to 50%; stage 3 from 50% to 75%; and stage 4, with >75% filled (Fig. 1). Mild forms of BCSE (stage 1) are more difficult to diagnose than advanced stages. For the diagnosis of stage 1 BCSE, the animal has to be carefully watched from a distance of 1–2 m for several minutes at least. The animal's sense of orientation may be intact in mildly affected individuals in spite of the limited field of vision (Miles, 1932), but animals showing stage 3 or 4 BCSE are generally disoriented and have an insecure gait (Distl et al., 1991; Gerst, 1996). Handling of these animals is difficult due to their limited vision. Farmers describe affected cows as 'shy', 'leery', 'jumpy' and 'wild'. BCSE causes economic losses from the animals' decreased market value and the fact that they and their progeny cannot be used as breeding animals (Distl and Gerst, 2000).

Fig. 1. Bilateral convergent strabismus with exophthalmus (BCSE), stage 4, in a German Brown cow.

4. Differential diagnoses for BCSE

Several similar clinical pictures caused by other factors have been described in the literature. Magnusson et al. (1983) reported the case of a calf which developed bilateral dorsomedial strabismus after being fed with seed of *Aesculus octandra* Marsh. Ventromedial strabismus was found in four animals showing clinical coccidiosis (Jubb, 1988). Bovine leukosis occasionally causes tumours which sometimes affect the central nervous system and lead to strabismus with exophthalmus if their position is retrobulbar (Power, 1987).

Distl and Scheider (1994) reported a full sibling pair of male Highland cattle showing divergent unilateral strabismus (DUS), which is assumed to be inheritable. The reason for this eye defect was a 40° ventral displacement of the

insertion of the lateral rectus muscle. Julian (1975) described a case of divergent bilateral strabismus with hydrocephalus in a Holstein calf. At birth the calf showed strabismus concurrent with several other abnormalities.

5. Occurrence and prevalence of bovine strabismus

BCSE has been observed in different cattle breeds, including the German Brown, Jersey, Shorthorn, Ayrshire, Bulgarian Grey, Irish Friesian, German Fleckvieh, German Black and White, and Dutch Black Pied (Distl et al., 1991; Distl and Gerst, 2000; Holmes and Young, 1957; Mintschev, 1965; Power, 1987; Regan et al., 1944; Schütz-Hänke et al., 1979; Vogt and Distl, 2002).

Generally, at birth no signs of the defect are present as these tend to develop later in life. According to Holmes and Young (1957), the earliest manifestation of the defect is usually at the age when the heifers are in calf and often not until after calving, although those investigators also report one calf affected at birth. Regan et al. (1944) observed BCSE earliest in one six-month-old calf, but all other animals were at least one year old. The first clinical signs of BCSE were found in cattle from at least one year of age up to 10 years and Gerst and Distl (1997, 1998) found it too difficult to ascertain an age limit after which all affected animals would have started showing signs of BCSE. The condition generally shows a progressive course that advances at an individual speed and which may be interrupted by long, apparently stable periods (Holmes and Young, 1957; Gerst, 1996). Given a sufficiently long lifetime, affected animals can become completely blind.

The incidence of BCSE in German Brown cattle was estimated by Gerst and Distl (1997) to be 0.9% in adult cows and 0.1% in young animals. As there are fewer data for the German Black and White and German Fleckvieh breeds, only tendencies can be estimated for these breeds. However, the incidence of BCSE in German Black and White cattle seems to be higher and that of German Fleckvieh lower than in German Brown cattle.

Vogt and Distl (2002) analysed the influence on his offspring of an unproven German Brown sire used for artificial insemination (AI) and affected by BCSE. There was a significant relationship between the paternity of this sire and the occurrence of BCSE in his female progeny. The incidence of BCSE was 8.33% when the descendants were 4–5 years of age (Vogt and Distl, 2002) and increased to nearly 50% when the progeny was examined at 7–8 years. Assuming this AI sire was a heterozygote carrier of an autosomal dominantly inherited defect, the observed incidence fits well to the expectation of 50% affected (O. Distl and S. Mömke, unpublished data) not as shown.

6. Analysis of US Brown Swiss and milk production trait associations

It is remarkable that the proportion of US Brown Swiss blood in affected German Brown animals was up to 7% higher than in unaffected animals of this breed (Gerst and Distl, 1998), and a potential association was suspected between BCSE and the in-crossing of US Brown Swiss bulls. However, in a subsequent study, Vogt and Distl (2002) did not find a significant influence of the percentage of US Brown Swiss blood on the occurrence of BCSE in data from about 130 herds. Therefore, it is not clear whether the spread of BCSE is caused by the intensive use of US AI bulls in the German Brown population. The defect definitely cannot be caused solely by the in-crossing of US Brown Swiss sires, since BCSE has also been observed in maternal families without US Brown Swiss blood (Distl, 1993).

No associations were found in German Brown cattle between BCSE and milk, fat and protein traits. Nor was the prevalence of BCSE in cows associated with higher or lower breeding values for milk production traits, so it is unlikely that there was a selection advantage for cows with BCSE (Distl and Gerst, 2000; Vogt, 2000). It seems therefore improbable that there was an indirect selection for BCSE caused by higher milk performance in affected cows. It also appears unlikely that there is a close genetic linkage of the defect allele for BCSE and a major gene for milk yield (Distl and Gerst, 2000).

7. Mode of inheritance

As early as 1885, BCSE in cattle was assumed to be an inherited defect. Barrier and Brissot (1885) described the case of a cow with one descendant showing a similar occurrence of strabismus and exophthalmus. Jakob (1920) advised farmers to exclude animals affected with BCSE from breeding. However, both the mode of inheritance as well as the number of contributing genes was controversially discussed for several decades.

Regan et al. (1944) were the first to collect systematic records on the defect. They compared the ancestry of two male and seven female affected animals of a Jersey cattle herd owned by the California Agricultural Experiment Station. Most of the affected animals were inbred progeny (sire-daughter matings) of three different, apparently unaffected sires. The progeny of bulls from strabismus-free lines mated with affected cows did not show the defect. Regan et al. (1944) supposed that strabismus in cattle was caused by one autosomal recessive gene. This thesis was only partly affirmed by Holmes and Young (1957), who observed BCSE in three groups of Shorthorn and Ayrshire cattle, which included more than 20 affected individuals. Those investigators could not exclude the possibility of a recessive gene causing BCSE because their material was not sufficiently extensive. Using regressive logistic models of segregation analysis, Distl et al. (1991) examined 107 animals of the German Brown cattle breed and found a major gene model influenced by additively acting genes. Complex segregation analysis was employed to study additional 10 pedigrees, including 184 German Brown individuals (Distl, 1993). When the data were corrected for non-random ascer-

tainment the results showed that an autosomal dominant major gene was the most likely explanation for the segregation of BCSE-affected cattle within the pedigrees.

Gerst and Distl (1997) found that the defective dominant allele segregated mainly within cow families and herds. The analysis of the flow of the major gene through the pedigrees of German Brown cattle was consistent with an autosomal dominant mode of inheritance with incomplete penetrance of 70% (Gerst, 1996). For this model, the frequency of the BCSE gene was estimated as $f = 0.008$ for the available cattle population. Vogt and Distl (2002) supposed that complete penetrance for a single autosomal dominant gene causing the disease was unlikely, due to the variable age of manifestation of BCSE in cattle. A mitochondrial DNA defect responsible for BCSE might be an alternative hypothesis for the mode of inheritance of BCSE. This latter hypothesis can be excluded only by showing transmission of BCSE from an affected bull to his progeny. Our unpublished data on two German Brown AI sires affected by BCSE with more than 40 affected daughters in about 35 different herds did not provide evidence for maternal cytoplasmatic inheritance. Nearly 50% of the examined 75 descendants of these two AI-sires were affected by BCSE.

8. Histopathological findings

Knowing the pathogenesis of a defect can help to assign it to a specific gene that causes the same or similar findings in other species, and a histopathological examination can be most helpful. In the case of BCSE-affected animals, the defect was suspected in the lateral rectus muscles (Barrier and Brissot, 1885) or in the supplying nerves and appropriate nuclear regions (Jakob, 1920). Mintschev (1965) diagnosed BCSE in Bulgarian Grey cattle and proposed that the defect was probably caused by lesions of the N. abducens. Pathomorphological investigation by Schütz-Hänke et al. (1979) revealed no differences in the eyes, eye muscles and the N. abducens between affected and unaffected individuals. However, those investigators' histomorphological examinations of the nucleus of N. abducens showed that the number of nerve cells in both nuclear regions of the abducens nerve is decreased in animals with clinical signs of BCSE and that this induces paresis of the lateral rectus muscles and the lateral part of the retractor bulbi muscles.

Histological examination of the lateral and medial rectus muscles of affected cattle eyes revealed "ragged red fibres", which are indicators for muscle defects and can be associated with mitochondrial DNA defects (Vogt, 2000). Since "ragged red fibres" are not exclusively signs of mitochondrial DNA defects but can also be shown in other defects in the metabolic chain of the muscle, clarification of the pathogenesis depends on molecular genetic approaches and/or examination of tissue sections by electron microscopy for the detection of deformed organelles and characteristically arranged inclusions.

9. Human paralytic strabismus in comparison with bovine BCSE

It has become apparent that there are extensive genetic homologies between humans and even distantly related species. Great progress has been made in the comparative gene map between humans and cattle such that syntenic genomic regions can be identified with high precision. Genes causing defects, e.g., BCSE that have already been identified in man can be used as candidate genes for the clarification of BCSE in cattle. Progressive external ophthalmoplegia (PEO) in man has striking similarities to BCSE in cattle. PEO refers to a group of disorders characterised by ptosis and slowly progressive bilateral immobility of the eyes (Sorkin et al., 1997), and is considered to be the most frequent form of mitochondrial encephalomyopathies in humans (Deschauer et al., 2001). In many cases, the onset of the disease is in adolescence or adulthood.

Based on age of onset and severity of clinical symptoms, patients with PEO are divided into three groups. The most severe variant is called Kearns–Sayre syndrome and is characterised by an infantile, childhood or adolescent onset. The second is the milder, chronic PEO with an adolescent or adult onset. The third is isolated chronic PEO with an adult onset and mild symptoms. PEO are monogenic autosomal dominant (adPEO) or autosomal recessive (arPEO) defects caused by mutations of different genes. For polymerase (DNA directed) gamma (POLG) different autosomal mutations were found (Van Goethem et al., 2001), whereby some of them were dominant and others recessive. For solute carrier family 25, member 4 (SLC25A4) (Kaukonen et al., 2000; Napoli et al., 2001; Komaki et al., 2002) and progressive external ophthalmoplegia 1 (PEO1, chromosome 10 open reading frame 2, C10orf2) (Spelbrink et al., 2001) the mutations were only autosomal dominant. Furthermore, a mutation in the endothelial cell growth factor/platelet-derived (ECGF1) gene causes an autosomal recessive PEO (Nishino et al., 1999; Vissing et al., 2002). Since all proteins required for replication of the mitochondrial genome are encoded by nuclear genes, defects in these genes will cause mtDNA loss or deletion, which leads to tissue dysfunction (Soumalainen and Kaukonen, 2001). Because of their high energy consumption and dependence on oxidative energy, ocular tissues are affected especially often by mitochondrial defects (Mojon, 2001). Furthermore, mitochondrial point mutations have been suggested which are passed on maternally (Deschauer et al., 2001).

The genes with dominantly acting mutations causing PEO in humans were chosen as candidate genes for BCSE in cattle (Hauke, 2003). After localisation of POLG, SLC25A4 and PEO1 (C10orf2) on bovine chromosomes BTA21q17-q22, BTA27q14-q15 and BTA26q13-q21, microsatellite markers were developed and tested for allelic co-segregation with the BCSE phenotype. Neither these markers nor evenly distributed microsatellite markers on

the respective bovine chromosomes showed significant linkage with BCSE. Thus, these candidate genes could be excluded as responsible for bovine BCSE.

A whole genome scan has to be completed for the BSCE-causing genes to be identified. Comparative genomics can then be used as a very effective approach towards unravelling the genetic basis of bovine BCSE. When the genes with their causal mutations for BCSE are identified, breeding strategies can be developed to eradicate this defect in cattle. Furthermore, new insights may be gained into the causes and pathogenesis of strabismus, possibly leading to therapeutic measures.

10. Conclusions

Bilateral convergent strabismus with exophthalmus (BCSE) is caused by an autosomal dominant major gene in Brown German and possibly in other cattle breeds. This inherited eye disease cannot usually be diagnosed in calves, heifers or young bulls, so these animals may spread the defect in the cattle population before they can be excluded from breeding. The development of a gene test is necessary to identify affected animals at an early age. Three candidate genes causing dominantly inherited progressive external ophthalmoplegia (adPEO) in man have been excluded. A whole genome scan has to be completed for the BSCE-causing genes to be identified. Comparative genomics can then be used as a very effective approach towards unravelling the genetic basis of bovine BCSE.

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