GENETIC DISEASES OF THE BROWN CALVES

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The Authors describe the clinical findings and the pathological features of the most important genetic diseases typical in Brown calves, and namely: Spinal Muscular Atrophy, Spinal Dysmyelination, Congenital Myopathy and Arachnoidima. In the context of a research project on calf neurodegenerative diseases carried out by the Institutions mentioned in the title in collaboration with ANARB (Italian Brown Cattle Breeders’ Association) and financed by the University of Bologna, the authors are carrying out a surveillance plan for the genetic diseases in Brown cattle, mainly but not exclusively affecting the nervous system.

The purpose of this presentation is to awaken the veterinarians to the importance of inviting the Brown farmers to report any abnormal birth or unusual disease in young calves that occurs in their herds. At present the availability of genetic tests for detecting the carriers is restricted to Spinal Muscular Atrophy and partially to Spinal Dysmyelination; for the other diseases only the report of affected animals, and therefore the emerging of clinical cases, can allow a retrospective identification of carrier animals.

LE MALATTIE GENETICHE DEL VITELLO DI RAZZA BRUNA

Gli Autori descrivono le caratteristiche cliniche e morfo-logiche delle più importanti malattie genetiche del vitello di razza Bruna, e precisamente dell’Atrofia Muscolo Spinale, della Dismielogenesi Spinale, della Miopatia Congenita e dell’Arachnoidima.

L’interesse degli Autori nei confronti di queste malattie è inserito in un progetto di ricerca sulle malattie neurodegenerative del vitello svolto in collaborazione con l’Associazione Nazionale Allevatori Razza Bruna (ANARB).

Con la nota si intende sottolineare l’opportunità, da parte dei veterinari operanti sul campo, di sollecitare gli allevatori di razza Bruna a riferire qualsiasi caso di vitello malformato o di patologie neonatali insoliti. Poiché prove di tipo genetico sono disponibili esclusivamente per l’Atrofia Muscolo Spinale, solo la pronta segnalazione di tali evenienze patologiche può consentire, in maniera retrospettiva, l’individuazione dei potenziali portatori.

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Acknowledgements
Investigation supported by University of Bologna (funds for selected research topics)

Introduction
Brown cattle (Brown Swiss, Braunvieh, Italian Brown) have experienced the occurrence of undesirable genetic defects in the last decades.

The first and possibly the most known is the Progressive Degenerative Myeloneuropathy ("Weaver Syndrome"). We shall not deal with this disease for two reasons: firstly because clinical signs usually begin at about 6-8 months of age; secondly because a marker-assisted selection has reduced the occurrence of the disease noticeably in the last years.

The objects of this work are the genetic diseases of young calves, such as Spinal Muscular Atrophy, Spinal Dysmyelination, Congenital Myopathy and Arachnoidima. These have become a matter of considerable concern for the Brown breeders' associations all over the world. A brief review of the location of lesions and their relationship to clinical signs is provided in order to improve the skills of bovine practitioners in recognizing and differentiating them from non-inherited conditions.

Spinal Muscular Atrophy
Spinal Muscular Atrophy (SMA) is a progressive lethal disease affecting humans and a variety of mammalian species, among them cattle. Bovine-SMA has been reported mainly in advanced backcrosses between American Brown-Swiss and European Brown cattle breeds (El-Hamidi and coll., 1989; Nielsen and coll., 1990; Dirlsen and coll., 1992; Stocker and coll., 1992; Tryer and coll., 1993; Winter and coll., 1999; Testoni and coll., 2002), but was described also in Brown related cross-calves (Agerholm and Basa, 1994) and in Holstein-Friesian calves (Furmola and coll., 1997).

The condition is characterized by severe muscular neurogenic atrophy, progressive quadriaparesis, and sternal recumbency. In 2002 we described the first case of Bovine-SMA in Italy which occurred in a Brown calf brought to our attention because of respiratory distress and recumbency (Testoni and coll., 2002); another 5 cases have been reported to us more recently. SMA at present represents the most worrisome concern for the Brown breeders' associations.

The initial signs, symmetric weakness of the rear legs, locomotion difficulties and slight dyspnea, appear at 3-4 weeks of age. The course of the disease is progressive and calves become increasingly weaker and progress to paraparesis and finally tetraparesis. Animals usually look alert and show good appetite and normal suckle reflex. Urination and defecation are in the physiological range. Death occurs after 2-4 weeks, usually as a consequence of respiratory failure due to atrophy of the respiratory muscle. Bronchopneumonia is a frequent complicating disease, and contributes to the spontaneous death of the affected animals.
Histo-pathologically, the condition is mainly characterised by muscle fibre atrophy, axonal degeneration of the spinal cord as well as neuronophagia and degeneration and loss of motor neuron in the grey matter of the ventral horns (especially brachial and lumbosacral regions); additionally, severe vascular degeneration in the midbrain and motor central cortex can be observed (Troyer and coll., 1992; Lasak, 1996; Sisó and coll., 2003).

There is clear evidence that bovine-SMA is inherited as an autosomal recessive disorder. The extensive usage of American Brown Swiss carriers to upgrade European Brown cattle breeds has to be considered the cause of the spread of the defective alleles. Most of the reported cases could be traced back to an American Brown Swiss bull named “Meadow View Destiny” (Medugorac and coll., 2003).

Medugorac and coll. (2003) managed to map the gene causing bovine-SMA to Chromosome 24. The same authors suppose that the apoptosis-inhibiting protein BCL2 might be the most promising positional candidate gene causing bovine-SMA. A marker-assisted test based on four microsatellite markers has recently become available in order to detect carriers of this undesirable nature (Gene Control GmbH, Grub, Germany: Berchtold, 2001 and 2002; Medugorac and coll., 2003).

**Spinal Dysmeliaization**

Spinal Dysmeliaization (SD) is another congenital and genetic neurological disorder affecting Brown or cross-bred calves upgraded with American Brown Swiss (Hafner and coll., 1993; Agerholm and coll., 1994; Stockler and coll., 1996).

Affected animals have congenital remnants (on the contrary to SMA) and mostly lie in a lateral position with a slight to moderate opisthotonos. Rear limbs are held in extension and on pressing the interdigital skin they react by stretching or kicking. The hind limb remain typically extended also if calves are able to maintain the sternal position. Although the animals do not try to use them they are attentive to their surroundings. Main reflexes are normal, as are appetite and feces and urine delivery.

Histo-pathologically the disorder is mainly characterized by bilateral symmetrical dysmeliaization in the white matter of the spinal cord (granular layer, dorsolateral spinocerebellar tract, subcommissural tract), especially at the level of the cervical intumescences (Hafner and coll., 1993; Agerholm and Andersen, 1993; Pfleger, 1999). Typically, the subcortical areas have a more pronounced dysmeliaization than the deeper parts (Agerholm and coll., 1994). Moreover the number of axons within the affected tracts is reduced. Myelination of dorsal and ventral nerve roots appears normal.

Slight muscular atrophy may appear as a consequence of inadequate innervation. Similarly to the bovine-SMA, SD is an autosomal recessively inherited defect (Agerholm and Andersen, 1995).

There is evidence that SD might be traced back to an American Brown Swiss bull named White Cloud Jasons Elegant born in 1966 (Agerholm and Andersen, 1995; Stockler and coll., 1996).

Nissen and coll. (2001) mapped SD to bovine chromosome 11, and hypothesized that a mutation in the EGR4 (early growth response) gene could be responsible for the defect. Subsequently they questioned what they had hypothesized regarding the EGR4 gene, and failed to provide evidence of its role in SD (Nissen and coll., 2003).

A marker-assisted test based on five markers has been recently developed in order to detect carriers of this undesirable character (Gene Control GmbH, Grub, Germany: announcement in the Rinderzucht Braunsch, 9(2):36, 2003). It is however limited to some genetic lines.

**Arachnomelia**

Arachnomelia ("spider-legs") is a congenital abnormality of the skeletal system giving the animal a spindly look. Although the first reports of this condition date back to the seventies/eighties (Rack and Shade, 1975; Brem and coll., 1984; König and coll., 1987) the disease has been insufficiently analysed and, except for those descriptions, we failed to find other experimental research in the veterinary literature. In 1989 Leipold and Steffen drew the attention of Brown-cattle breeders and veterinarians to the disease, but only in recent years has the disease again begun to worry the breeders’ associations all over the world.

We have recently described the first cases of Arachnomelia in Italy (Testoni and coll., 2003); all calves (three) traced back to the same sire (Tommy). After these reports many Brown-cattle Italian breeders have reported the occurrence of other cases of Arachnomelia; all cases were offspring of Tommy or Amarauto. As both these bulls have been widely used for artificial insemination in Italy, ANARB (Associazione Nazionale Allevatori di Razza Bruna) expects many other cases of Arachnomelia in the future. Brown calves affected with Arachnomelia have major lesions in the skeletal and muscular system. Most affected calves are born dead and only a few live for a few hours.

The most important pathologic findings are: facial deformities (i.e. brachynia inferior and concave rounding of the dorsal profile of the maxilla); bone dolichostenomelia; angular deformities in the distal part of the hind legs; muscular malformations.

Bones of the legs appear to be more fragile than normal and spontaneous fracture during calving may injure the dam. Although we failed to find precise information in the literature, the pathogenesis of the disease seems to overlap that of the Marfan Syndrome in human medicine (Arachnodactyly): in this context a defect in the metabolism of the connective tissue is involved.

However the clinical findings recorded in calves affected by Arachnomelia usually differ from the typical picture of the human “Marfan patients" (dolichostenomelia with high fragility of long bones, defects of the heart and main arteries, ectopia lenta), and for this reason we think that the clinical identification between the bovine Arachnomelia and the human Marfan Syndrome is inopportune. Moreover, contrary to the almost undisturbed vitality of human patients, bovine Arachnomelia has a rapidly lethal course. It should be kept in mind that a true Bovine Marfan Syndrome more closely resembling human Marfan syndrome has also been described in cattle (Potter and coll., 1995; Potter and Besser, 1994).

Regarding the aetiology, although it has not been possible to find candidate genes until now, the condition is attributed to a simple autosomal recessive inheritance. The origin of this defect was postulated to be an American Brown Swiss bull or a cow of the same breed (König and coll., 1987).

At the moment there is neither a chromosomal nor biochemical test to detect the carriers of this defect.
Congenital Myopathy

A further congenital skeletal muscle disorder suspected to have a hereditary etiology was described by Hafner and coll. (1996) and named Congenital Myopathy (CM). Similarly to SMA and SD, affected calves (6) were upgraded with American Brown Swiss bulls. The animals show rapidly progressing muscular weakness and become recumbent within 2 weeks of birth. If assisted animals can maintain the quadrupedal stance for short time, showing muscular trembling and pendent head (Dirksen G., 2002).

Clinically the disease is very similar to bovine-SMA and only the pathological changes allow its definitive diagnosis. Calves afflicted with CM show characteristic signs of primary muscular disorders (rhabdomyopathy), such as marked variation in muscle fibre size, internally located nuclei, fibre splitting and broadened extracellular spaces (Hafner and coll., 1996; Lusak, 1996).

References