GENETIC DISEASES OF THE BROWN CALVES

Gentile A., Testoni S. (*), Castagnaro M (**)

Veterinary Clinical Department - Bologna - Italy
(*) Department of Veterinary Clinical Science – Padua - Italy
(**) Department of Public Health, Comparative Pathology and Veterinary Hygiene – Padua - Italy

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 Arachnomelia.
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 carring 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 morfologiche delle più importanti malattie genetiche del vitello di razza Bruna, e precisamente dell'Atrofia Muscolo Spinale, della Dismielogenesi Spinale, della Miopatia Congenita e dell'Aracnomelia.
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 s'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 inusuali. 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.

Gentile Arcangelo
Dipartimento Clinico Veterinario, Via Tolara di Sopra 50, 40064 Ozzano Emilia – Bologna (Italia).
Tel: 0039 051 792803; fax: 0039 051 792793; email: agentile@vet.unibo.it

Aknowledgements
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 Myeloencephalopathy ("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 and 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 Dysmielination, Congenital Myopathy and Arachnomelia. 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; Dirksen and coll., 1992; Stocker and coll., 1992; Troyer and coll., 1993; Winter and coll., 1999; Testoni and coll., 2002), but was described also in Brown related cross-calves (Agerholm and Basse, 1994) and in Holstein-Friesian calves (Pumarola and coll., 1997).
The condition is characterized by severe muscular neurogenic atrophy, progressive quadriparesis, 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 dyspnoea, 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 characterized 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 lumbo-sacral regions); additionally, severe vacuolar degeneration in the midbrain and motor central cortex can be observed (Troyer and coll., 1992; Lassak, 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; Medugorak and coll., 2003).

Spinal Dysmielination

Spinal Dysmielination (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; Stocker and coll., 1996).
Affected animals have congenital recumbency (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 pressuring 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 rise they are attentive to their surroundings. Main reflexes are normal, as are appetite and faeces and urine delivery.
Histo-pathologically the disorder is mainly characterized by bilateral symmetrical dysmielination in the white matter of the spinal cord (gracile funiculus, dorsolateral spinocerebellar tract, sulcomarginal tract), especially at the level of the cervical intumescences (Hafner and coll., 1993; Agerholm and Andersen, 1995; Pfluger, 1999). Typically, the submeningeal areas have a more pronounced dysmielination 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 can 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; Stocker 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 Braunvieh, **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 spidery look. Although the first reports of this condition date back to the seventies/eighties (Rieck and Shade, 1975; Brem and coll., 1984; König and coll., 1987) the disease has been insufficiently analyzed 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 Amaranto. As both these two 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. brachygnatia inferior and concave rounding of the dorsal profile of the maxilla); bone dolichostenomelia; angular deformities in the distal part of the hind legs; muscular atrophy; cardiac 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 (Arachnodactylia): 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 lins), 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., 1993; 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 inheritability. 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 aetiology 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; Lassak, 1996).

References

Agerholm J.S. and Andersen O. (1995) "*Inheritance of Spinal Dysmielination in calves*" J. Vet. Med A, **42**:9-12.

Agerholm J.S. and Basse A. (1994) "*Spinal muscular atrophy in calves of the Red Danish dairy breed*" Vet. Rec., **134**:232-235.

Agerholm J.S., Hafner A., Olsen S., Dahme E. (1994) "*Spinal dysmyelination in cross-bred Brown Swiss calves*" J. Vet. Med. A, **41**:180-188.

Berchtold J. (2001) "*SMA-Gentest kommt auf den Markt*" Rinderzucht Braunvieh, **7**(2):18.

Berchtold J. (2002) "*Fast alle Prüfstiere SMA-frei geprüft*"" Rinderzucht Braunvieh, **8**(2):64-65.

Brem G., Wanke R., Hondele J. and Dahme E. (1984) "*Zum Auftreten des Arachnomelie-Syndroms in der Brown-Swiss x Braunvieh Population Bayerns*" Berl. Münch. Tierärztl. Wschr., **97**:393-397.

Dirksen G. (2002) "*Primäre konnatale Myopathie*" in: Innere Medizin und Chirurgie des Rindes, Dirksen G., Gründer H.D. e Stöber M., Berlin, Parey Buchverlag, 2002, pag. 889.

Dirksen G., Doll K., Hafner A., Hermanns W. and Dahme E. (1992) "*Spinale Muskelatrophie (SMA) bei Kälbern aus Brown Swiss x Braunvieh-Kreuzungen*" Dtsch. Tierärztl. Wschr., **99**:168-175.

El-Hamidi M., Leipold H. W., Vestweber J. G. E. and Saperstein G. (1989) "*Spinal Muscular Atrophy in Brown Swiss calves*" J. Vet. Med. A, **36**:731-738.

Hafner A., Dahme E., Obermaier G., Schmidt P. and Dirksen G. (1993) "*Spinal Dysmyelination in new-born Brown Swiss x Braunvieh calves*" J. Vet. Med. B, **40**:413-422.

Hafner A., Dahme E., Obermaier G., Schmidt P., Doll K. and Schmahl W. (1996) "*Congenital myopathy in Braunvieh x Brown Swiss calves*" J. Comp. Path., **115**:23-34.

König H., Gaillard C., Chavaz J., Hunziker F. and Tontis A. (1987) "*Prüfung von Schweizer Braunvieh-bullen auf das vererbte Syndrom der Arachnomelie und Arthrogrypose (SAA) durch Untersuchung der Nachkommen im Fetalstadium*" Tierärztl. Umschau, **42**:692-697.

Lassak T. (1996) "*Vergleichende myopathologische Studien an Braunvieh x Brown Swiss Kälbern mit Spinaler Dysmielogenese (SDM), Spinaler Muskelatrophie (SMA) und Kongenitaler Myopathie (CM)*" Vet. Med. Diss., München.

Leipold H.W. e Steffen D. (1989) "*Sindrome of Arachnomelia and Arthrogryposis (SAA) in Brown Swiss Calves*" Brown Swiss Bull., september 1989, pagg.86-87.

Medugorac I., Kempter J., Russ I., Pietrowsky D., Nüske S., Reichenbach H-D., Schmahl W. and Förster M. (2003) "*Mapping of the bovine spinal muscular atrophy locus to Chromosome 24*" Mamm. Genome, **14**:383-391.

Nielsen J.S., Andresen E., Basse A., Christensen L.G., Lykke T. and Nielsen U.S. (1990) "*Inheritance of Bovine Spinal Muscular Atrophy*" Acta Vet. Scand., **31**:253-255.

Nissen P.H., Shukri N.M., Agerholm J.S., Fredholm M. and Bendixen C. (2001) "*Genetic mapping of spinal dysmielination in cross-bred American Brown Swiss cattle to bovine Chromosome 11*" Mammalian Genome, **12**:180-182.

Nissen P.H., Thomsen B., Offenberg H., Thomsen P.D. and Bendixen C. (2003) "*Cloning and characterization of the bovine EGR4 gene and evaluation as candidate gene for bovine spinal dysmielination*" Animal Genetics, **34**: 124-131.

Pfluger K. (1999) "*Spinale Dysmielisierung neugeborener Kälber der Rasse Deutsches Braunvieh. Eine morphometrische Studie*" Vet. Med. Diss., München.

Potter K.A. and Besser T.E. (1994) "*Cardiovascular lesions in bovine Marfan syndrome*" Vet. Pathol., **31**:501-509.

Potter K.A., Hoffman Y., Sakai L.Y., Byers P.H., Besser T.E., and Milewicz D.M. (1993) "*Abnormal fibrillin metabolism in bovine Marfan syndrome*" Am. J. Pathol., **142**:803-810.

Pumarola M., Anor S., Majo N., Borras D. and Ferrer I. (1997) "*Spinal muscular atrophy in Holstein-Friesian calves*" Acta Neuropathol. (Berl.), **93**:178-183.

Rieck G.W. and Shade W. (1975) "*Die Arachnomelie (Spinnegliedrigkeit), ein neues erbliches letales Mißbildungssyndrom des Rindes*" Dtsch. Tierärztl. Wschr., **82**:342-347.

Sisó S., Pumarola M. and Ferrer I. (2003) "*Cell death and decreased synaptic protein expression in the ventral horn of Holstein-Friesian calves with Spinal Muscular Atrophy*" J. Comp. Path., **128**:132-139.

Stocker H., Ossent P., Heckmann R. and Örtle C. (1992) "*Spinale Muskelatrophie bei Braunvieh-Kälbern*" Schweiz. Arch. Tierheilk., **134**:97-104.

Stocker H., Pusterla J.B., Lutz H. and Ossent P. (1996) "*Eine neue Erbkrankheit beim Braunvieh in der Schweiz: Spinale Dysmielinisierung (SDM) bei festliegenden Kälbern*" Schweiz. Arch. Tierheilk., **138**:295-300.

Testoni S., Cavicchioli L., Ferro S. and Gentile A. (2003) "*Tre casi di aracnomelia in vitelli di razza Bruna*" Atti Soc. It. Buiatria, **35**:113-121.

Testoni S., Gentile A., Castagnaro M. and Lugli M. (2002) "*Atrofia Muscolo Spinale del bovino. Su di un caso in un vitello di razza Bruna*" Ob. Doc. Vet., **23**:25-29.

Troyer D., Cash W.C., Vestweber J., Hiraga T. and Leipold H.W. (1993) "*Review of spinal muscular atrophy (SMA) in Brown Swiss cattle*" J. Vet. Diagn. Invest., **5**:303-306.

Troyer D., Leipold H. W., Cash W. and Vestweber J. (1992) "*Upper motor neurone and descending tract pathology in bovine Spinal Muscular Atrophy*" J. Comp. Path., **107**: 305-317.

Winter P., Bago Z., Podstatzky L. and Speckbacher G. (1999) "*Spinale Muskelatrophie bei einem Brown-Swiss Kalb - Fallbericht*" Wien. Tierärztl. Mschr., **86**:83-87.