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PREVALENCE OF ANTIBODY TO MALIGNANT CATARRHAL FEVER VIRUS IN WILD AND DOMESTIC RUMINANTS BY COMPETITIVE-INHIBITION ELISA

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ABSTRACT: A competitive-inhibition ELISA (CI-ELISA), based on a monoclonal antibody to an epitope conserved among malignant catarrhal fever virus (MCFV) strains of both wildebeest and sheep origin, was used to determine the prevalence of antibody to MCFV in selected domestic and wild ruminants, both free-ranging and captive, from the USA. We evaluated 2528 sera from 14 species between 1990 and 1995, including 80 pronghorn antelope (*Antilocapra americana*), 339 bighorn sheep (*Ovis canadensis*), 103 bison (*Bison bison*), 17 black-tailed deer (*Odocoileus hemionus columbianus*), 395 domestic cattle (*Bos taurus*), 291 domestic goats (*Capra hircus*), 680 domestic sheep (*Ovis ammon*), 323 elk (*Cervus elaphus*), 41 llamas (*Lama glama*), 21 mouflon sheep (*Ovis montanus*), 54 mountain goats (*Oreamnos americanus*), 101 mule deer (*Odocoileus hemionus*), 20 muskox (*Ovibos moschatus*), and 63 white-tailed deer (*Odocoileus virginianus*). A high seroprevalence (37 to 62%) was observed in domestic sheep, domestic goats, muskox, and some bighorn sheep populations. Seroprevalence in these species was generally age-related: a very low seroprevalence was present in these animals under one year of age. A low seroprevalence (2% to 13%) was found in clinically-susceptible species such as domestic cattle, deer, elk and bison, supporting the concept that significant numbers of non-lethal infections occur among clinically susceptible ruminants.

Key words: Malignant catarrhal fever, gammaherpesvirus, ruminants, wildlife, antibody prevalence, competitive-inhibition ELISA.

INTRODUCTION

Malignant catarrhal fever (MCF) has been known for many years as a dramatic, often lethal, systemic viral infection of cattle and many species of wild ruminants (Plowright, 1968). Its hallmarks are widespread lymphoproliferation and inflammatory vascular lesions (Rossiter, 1985). Based on the reservoir ruminant species from which the causative virus arises, two major epizootiological entities of the disease have been described: wildebeest-associated (WA) and sheep-associated (SA) MCF, between which there are no significant differences in clinico-pathological features (Plowright, 1990). The etiologic agent for WA-MCF has been isolated (Plowright et al., 1960), characterized as a gammaherpesvirus (Plowright et al., 1965), and

named alcelaphine herpesvirus 1 (AHV-1) in reference to the principal reservoir host, wildebeest (*Connochaetes* spp., subfamily Alcelaphinae) (Roizman et al., 1981). A relatively large number of related species-adapted variants of the gammaherpesviruses reside as persistent infections in members of subfamilies of Bovidae: Alcelaphinae, Hippotraginae, Caprinae and Ovibovinae (Reid, 1992). For example, a distinct but closely-related group of the viruses, termed Alcelaphine herpesvirus-2 (Roizman et al., 1981), exists in a number of species of antelope other than the wildebeest and have not been reported to cause disease in other ruminants under natural conditions (Mushi et al., 1981). To date, the etiologic agent for SA-MCF has not been isolated. However, based on circumstantial evidence domestic sheep

(*Ovis ammon*) (subfamily Caprinae) may serve as a reservoir and transmit the virus to susceptible ruminants such as domestic cattle (*Bos taurus*), deer (*Odocoileus* spp.), and bison (*Bison bison*) (Plowright, 1990). The demonstration of SA-MCF virus DNA with sequence similarity to Epstein-Barr virus and *Herpesvirus saimiri* in leukocytes from normal sheep and SA-MCF-affected cattle (Baxter et al., 1993) supports the idea that sheep are indeed carriers of a gammaherpesvirus. Based on its antigenic and base sequence similarity to AHV-1, the putative SA-MCF agent has been tentatively classified as ovine herpesvirus 2 (OHV-2) (Roizman, 1992).

More than 150 species in the suborder Ruminantia are susceptible to MCF virus infection (Heuschele, 1988). Clinical disease has been described in over 30 of these species, including domestic and wild ruminants, some of which are threatened or endangered (Heuschele, 1988). Diagnosis and control of MCF has been hindered by a lack of reliable screening tools for epizootiological surveys and by its clinical similarity to several other diseases of ruminants. Application of newly-developed specific assays for MCFV antibody (Li et al., 1994) and DNA (Baxter et al., 1993) promises to overcome these impediments and to answer some of the intriguing questions posed by this ill-defined group of viruses that have eluded research efforts for many years. Our objective was to determine the prevalence of MCFV antibody in domestic and wild ruminants, using the recently developed competitive-inhibition ELISA (CI-ELISA), based on a monoclonal antibody to an epitope specific to, and conserved among, all strains of MCF virus examined to date.

MATERIALS AND METHODS

The Minnesota isolate of MCFV (MN-MCFV), originally derived from a cow with clinical MCF in Minnesota, USA (Hamdy et al., 1978), and fetal mouflon sheep kidney (FMSK) cells were kindly provided by Dr. Werner Heuschele, Center for Reproduction of Endangered Species, Zoological Society of San

Diego, San Diego, California, USA. The viral antigens were prepared by infection of FMSK cell monolayers in 900 cm² roller bottles or 150 cm² flasks at a multiplicity of infection of 0.1. When 80 to 90% of the cells had cytopathic effects, the supernatant was harvested, clarified by centrifugation at 4300 × G for 30 min, and virus pelleted at 125,000 × G for 90 min through a 2-cm 35% (w/w) sucrose column. The pellets were resuspended in phosphate-buffered saline (PBS), sonicated and the supernatant collected after clarification at 6,000 × G for 5 min, stored at -20 C. Protein concentration was determined by BCA protein assay (Pierce, Rockford, Illinois, USA).

We collected 2528 serum samples from 14 species in 11 states of the USA for assay of antibody to MCFV by CI-ELISA (Table 1). Of these, 826 were from white-tailed deer (*Odocoileus virginianus*), black-tailed deer (*Odocoileus hemionus columbianus*), elk (*Cervus elaphus*), pronghorn antelope (*Antilocapra americana*) and bighorn sheep (*Ovis canadensis*) and were kindly provided by Drs. David Hunter, Wildlife Health Laboratory, Idaho Department of Fish and Game, Boise, Idaho, USA; Philip Schladweiler, Wildlife Laboratory, Montana Department of Fish, Wildlife and Parks, Bozeman, Montana, USA, and William Foreyt, Department of Veterinary Microbiology and Pathology, Washington State University, Pullman, Washington, USA. Samples from mountain goats (*Oreamnos americanus*) and domestic llamas (*Lama glama*) were provided by Dr. W. Foreyt. We collected 680 sera from domestic sheep (*Ovis ammon*) in California, Georgia, Idaho, Kentucky, Montana, North Dakota, Tennessee, Washington, and Wyoming (USA): 170 of these were from eight flocks of sheep with known histories of association with cases of clinical MCF in cattle (*Bos taurus*), white-tailed deer, or bison. Twenty-one sera were collected from a group of mouflon sheep (*Ovis musimon*) associated with a case of clinical MCF in sika deer (*Cervus nippon*) in Washington. The bison serum samples were collected from ranches in Montana and Washington. Domestic goat (*Capra hircus*) sera were collected from a closed Saanen goat herd at Washington State University. Another 238 sera from domestic cattle were selected randomly from the archived serum banks of Washington Animal Disease Diagnostic Laboratory, Washington State University, having been submitted with clinical diagnoses other than MCF. In addition, 157 serum samples were collected from cattle with known history of contact with domestic sheep in Montana, Washington and Wyoming. Samples from muskox (*Ovibos moschatus*) were

TABLE 1. Summary of numbers and state of origin of serum samples collected from ruminants for malignant catarrhal fever virus seroprevalence studies between 1990 and 1995.

Common name	Scientific name	Number of serum samples	State of origin
Bighorn sheep	<i>Ovis canadensis</i>	339	California, Idaho, Montana, Washington, and Wyoming
Bison	<i>Bison bison</i>	103	Montana and Washington
Black-tailed deer	<i>Odocoileus hemionus columbianus</i>	17	California
Domestic cattle	<i>Bos taurus</i>	395	Montana, Washington, and Wyoming
Domestic goats	<i>Capra hircus</i>	291	Washington
Domestic sheep	<i>Ovis ammon</i>	680	California, Georgia, Idaho, Kentucky, Montana, New York, North Dakota, Tennessee, Washington, and Wyoming
Elk	<i>Cervus elaphus</i>	323	California, Idaho, Montana, Washington, and Wyoming
Llama	<i>Llama glama</i>	41	Washington
Mouflon sheep	<i>Ovis musimon</i>	21	Washington
Mountain goats	<i>Oreamnos americanus</i>	54	Idaho and Washington
Mule deer	<i>Odocoileus hemionus</i>	101	California, Idaho, Montana, Washington, and Wyoming
Muskox	<i>Ovibos moschatus</i>	20	Alaska
Pronghorn antelope	<i>Antilocapra americana</i>	80	California and Wyoming
White-tailed deer	<i>Odocoileus virginianus</i>	63	Idaho, Montana, Washington, and Wyoming
Total		2,528	

kindly provided by Dr. John Blake, University of Alaska, Fairbanks, Alaska, USA.

Procedures for competitive-inhibition ELISA (CI-ELISA) were described by Li et al. (1994). Briefly, 96-well polystyrene plates (Immulon 4, Dynatech Lab, Inc., Chantilly, Virginia, USA) were coated at 4 C for 18 to 20 hr with 0.25 µg of the Minnesota isolate of MCFV antigen/well in 50 µl of 50 mM carbonate-bicarbonate buffer (pH 9.6). After blocking with 20% nonfat milk in PBS at 24 C for 2 hr and washing with PBS with 0.1% Tween-20, 250 µl of 1:10 dilution of test serum and 50 µl of monoclonal antibody (0.2 µg) were added and incubated at 24 C for 1 hr. The wells were washed three times with PBS/Tween-20, and incubated with alkaline phosphatase antimouse immunoglobulin G (Sigma Chemical Co., St. Louis, Missouri, USA) at 24 C for 1 hr. After a final wash, 50 µl of substrate buffer containing 1 mg/ml p-nitrophenyl phosphate (Sigma Chemical Co.) were added, and incubated for 60 min; the optical density at 414 nm (OD₄₁₄) was determined. All sera were run in triplicate. A panel of sera from sheep or cattle defined as negative by an absence of MCFV antibody on indirect immunofluorescence (Li et al., 1994) and immunoprecipitation (Li et al., 1995a) was included in each run as controls in

all tests. Data interpretation was similar to that described previously (Li et al., 1994): when the mean of the three replicate OD readings of a serum was more than 3 SD below the mean of a panel of six negative control sera (from sheep or cattle) run in triplicate, the serum was considered positive for MCFV antibody. This assay is highly specific for MCFV viruses, having been tested in several animal species against numerous ruminant pathogens (Li et al., 1994).

Data were analyzed by chi-square goodness-of-fit test (Ott, 1993). Statistical significance was determined as $P < 0.05$.

RESULTS

A low percentage (0 to 9%) of seropositivity occurred in bison, black-tailed deer, white-tailed deer, mule deer, and elk (Table 2). There were no apparent differences in seroprevalence between groups of the same species, regardless of state of origin (data not shown). A relatively high percentage, 124 (37%) of 339 bighorn sheep, were seropositive. A significant ($P < 0.001$) difference was detected between desert bighorn sheep (*Ovis canadensis nel-*

TABLE 2. Prevalence of malignant catarrhal fever virus antibody in certain wild ruminant sera collected in the USA between 1990 and 1995.

Species	Number positive/ number tested	Prevalence (%)
Bison	2/103	2
Black-tailed deer	0/17	0
Elk	30/323	9
Llama	0/41	0
Mountain goats	0/54	0
Mule deer	2/101	2
White-tailed deer	2/63	3
Pronghorn antelope	20/80	25
Bighorn sheep	124/339	37 ^a
Muskox	8/20	40
Mouflon sheep	13/21	62

^a Including 28 desert bighorn sheep (0% positive) and 26 peninsular bighorn sheep (65% positive) from California.

soni) from California and other populations of bighorn sheep, which included Rocky Mountain bighorn sheep (*Ovis canadensis canadensis*) and peninsular bighorn sheep (*Ovis canadensis cremnobates*): none (0%) of 28 desert bighorn sheep had antibodies, compared to 124 (40%) of 311 bighorn sheep in other populations (Table 2). Seroprevalence levels did not appear to be related to whether the sheep flocks had ever been associated with cases of clinical MCF ($P > 0.15$) (Table 3). A high seroprevalence was present in animals over 1 yr of age, whereas antibody was rarely detected in animals less than 1 yr of age (Table 4). The difference between the two age groups was statistically significant ($P < 0.001$). A similar pattern was observed in the muskox, although sample numbers were small. A difference ($P < 0.001$) was observed between cattle with a history of contact with domestic sheep and cattle with no known history of association with sheep (Table 3).

DISCUSSION

It is becoming apparent that MCF agents represent members of a group of related gammaherpesviruses that exist as enzootic infections in many ruminant species (Metzler, 1991). Viruses of this group are a potentially important impediment,

TABLE 3. Prevalence of malignant catarrhal fever virus antibody in certain domestic ruminant sera collected in the USA between 1990 and 1995.

Species	Number positive/ number tested	Prevalence (%)
Cattle (no known contact with sheep)	10/238	4 ^a
Cattle (known history of contact with sheep)	21/157	13 ^a
Domestic goats	177/291	61
Domestic sheep (no known association with cases of clinical MCF)	282/531	53 ^b
Domestic sheep (associated with cases of clinical MCF)	88/149	59 ^b

^a A difference between cattle with no known history of association with sheep and cattle with a known history of sheep contact was significant at $P < 0.001$.

^b No significant difference detected between domestic sheep associated with caes of clinical MCF and those without known association ($P > 0.15$).

not only to domestic cattle or farmed deer, but also to propagation of endangered ruminant species in the wild, in captivity, or on game farms. Prevalence studies have been severely constrained in the past by deficiencies in available seroassays for MCF viruses (Heuschele and Seal, 1992). Although no bona fide SA-MCFV isolate is yet available, we have identified an epitope conserved among all MCFV strains

TABLE 4. Relationship between malignant catarrhal fever virus antibody prevalence and age among certain domestic and wild ruminants in the USA (sera collected between 1990 and 1995).

Species	Less than 1 year old ^a		Over 1 year old ^a	
	Number positive/ number tested	Prevalence (%)	Number positive/ number tested	Prevalence (%)
Domestic sheep	2/77	2.5	227/250	91
Domestic goats	0/28	0	102/137	74
Bighorn Sheep	1/21	4.8	63/116 ^b	54
Muskox	0/10	0	8/10	80
Total	3/136	2	400/513	78

^a Significant difference observed between the age groups (less than 1-yr old and over 1-yr old) ($P < 0.001$).

^b Not including any California desert bighorn sheep.

examined (Li et al., 1994). This has enabled production of an efficient CI-ELISA for identification of animals infected with any of the known MCF viruses.

Based on this CI-ELISA, we found evidence for a wider host range for MCF viruses than formerly suspected, including several species of wild ruminants such as muskox and some populations of bighorn sheep. There also was a large difference in antibody prevalence between clinically-susceptible species such as cattle and deer (6%), and carrier species such as domestic sheep and domestic goats (56%). Cattle and deer with clinical MCF can recover from the disease (Milne and Reid, 1990). Our data support these other studies that there is a significant level of non-lethal infection in these clinically susceptible species (O'Toole et al., 1994).

There is a degree of uncertainty about whether MCF occurs naturally in free-ranging deer (Blake et al., 1990). The prevalence of antibody in this study was low, in the range of 0 to 3%. The data from this study are evidence that MCFV infection indeed exists among free-ranging deer albeit the prevalence of antibody was low. Jessup (1985) reported a case of suspected MCF in a free-ranging black-tailed deer from California. Anti-MCFV antibodies were recently demonstrated in this animal by CI-ELISA (H. Li, unpubl.). Malignant catarrhal fever is the most important infectious disease affecting game farm-raised red deer (*Cervus elaphus*) in New Zealand (Mackintosh, 1992). Several incidences of MCF have occurred in cervids in North America in recent years resulting in significant mortality (Brown and Bloss, 1992). These observations and the present study emphasize the need for caution in management and the advisability of avoiding co-habitation between cervid and ovine species in zoos, on game farms, and in the wild.

Small numbers of free-ranging deer, elk, and bison were seropositive; these animals were once infected by MCF viruses. Whether these animals had recovered

from a non-lethal disease, or the infection was entirely subclinical is unknown. Although a clear association between age and seroprevalence has been observed in domestic sheep (Li et al., 1994), the difference in seroprevalence between desert bighorn sheep (0%) and other populations of bighorns (40%) (Table 2) seems not to be associated with the age of the animals, since most of the desert bighorn sheep examined were adults. The explanation for this observation is not known, but factors such as location and management efforts specific to these populations need further exploration. The difference in seroprevalence between mountain goats (0%) and muskox (40%) (Table 2), both members of subfamily Caprinae, is intriguing. The reason for the difference is not apparent, but could relate to the differences in population density or social interactions between members of these two species.

Sheep-associated MCF in cattle often occurs during or shortly after lambing season (Buxton and Reid, 1980), which is similar to the pattern of WA-MCF. Lambs might play the same role in transmission as wildebeest calves (Mushi and Rurangirwa, 1981). The notion that sheep are infected at early age and serve as a source of transmission, similar to wildebeest, has recently been challenged because Li et al. (1995b) have shown that lambs are infected not at an early age, but sometime in later life. The present study supports the concept that the MCFV infection in sheep is age-related: similar seroprevalence patterns were observed among domestic goats, muskox, mouflon sheep, and some populations of bighorn sheep. If lambs can be ruled out as a source of transmission, the peaks of SA-MCF occurrence during lambing season may be due to enhanced virus shedding by ewes undergoing stress during the periparturient period. Whether domestic goats, muskox, and some populations of bighorn sheep are capable of serving as sources of virus transmission to clinically susceptible species in nature has not been determined. The amplification of

a DNA fragment from peripheral blood lymphocytes of domestic goats using OHV-2-specific polymerase chain reaction primers (Wiyono et al., 1994) provided evidence that domestic goats and sheep are infected with the same or very closely-related viruses. Moreover, several recent MCF cases of captive deer have been only associated with mouflon sheep (Bienvenu and Helie, 1992).

Based on this study as well as others (Rossiter, 1981), a high prevalence of antibody to MCFV exists in domestic sheep, mouflon sheep, domestic goats, and certain subpopulations of bighorn sheep. Although domestic sheep, for example, are virtually all infected, transmission of the virus is not a predictable event. On some ranches, cattle are pastured with sheep for many years without occurrence of MCF, whereas on other farms the disease problems are relatively frequent when cattle and sheep are housed in contact. This is evidence for multifactorial influences on disease expression.

Based on our data, MCFV is more prevalent among captive and wild ruminants in North America than previously thought. The results support the need for more research in this area, and the necessity of care in management to avoid mixing species susceptible to clinical MCF with species that may be MCFV carriers.

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