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Review

Morbilliviruses and Morbillivirus Diseases of Marine Mammals

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Summary: In recent years, serious disease outbreaks among seals and dolphins were attributed to infection with established or newly recognized morbilliviruses. The first identification of a morbillivirus as causative agent of mass mortality among marine mammals was in 1988, when the previously unrecognized phocine distemper virus (PDV) caused the death of 20,000 harbor seals (*Phoca vitulina*) in northwestern Europe. A similar epizootic among Baikal seals (*Phoca sibirica*) in Siberia in 1987 was later attributed to infection with canine distemper virus (CDV). A morbillivirus isolated from stranded harbor porpoises (*Phocoena phocoena*) between 1988 and 1990 proved to be yet another new member of the genus *Morbillivirus*, distinct from PDV and CDV and more closely related to rinderpest virus and peste-des-petits-ruminants virus: porpoise morbillivirus. A similar virus, dolphin morbillivirus, was the primary cause of mass mortality among striped dolphins (*Stenella coeruleoalba*) in the Mediterranean from 1990 to 1992. In this review, current knowledge of the genetic and antigenic relationships of these viruses is presented, and the origin and epizootiological aspects of the newly discovered morbilliviruses are discussed. In addition, the possible contributory role of environmental contaminant–related immunosuppression in the severity and extent of the different disease outbreaks is discussed. **Key Words:** Marine mammals—Morbillivirus—Distemper—Immunotoxicology.

MORBILLIVIRUS INFECTIONS IN PINNIPEDS

In 1988, an apparently contagious disease spread among harbor seals and gray seals (*Halichoerus grypus*) in northwestern Europe. Disease symptoms included respiratory, gastrointestinal, and neurological disorders and were often complicated by secondary parasitic, bacterial, or viral infections. Among harbor seals, the disease was accompanied by mortality levels of >60% in some areas, while in gray seals mortality was relatively low. The first indication of the involvement of a morbillivirus in the outbreak came from serological studies on paired serum samples, in which canine distemper virus (CDV)-neutralizing antibodies were found in the serum of affected animals (41). On the basis of these serological data, in combination with the clinical signs and pathological lesions found in infected seals, which appeared to be quite similar to those observed in dogs with canine distemper, it was concluded that a "morbillivirus closely related if not identical to CDV" was the primary cause of the outbreak (38). Virus isolation and subsequent char-

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acterization demonstrated that the virus was not identical to CDV but should be considered a new member of the genus *Morbillivirus*, now referred to as phocine distemper virus (PDV) (10,32,54). Finally, Koch's postulates were fulfilled when seals proved to be protected from fatal challenge infection by vaccination with an inactivated CDV vaccine, and the virus could be reisolated from the sham-vaccinated animals in this experiment (40,57).

After the identification of PDV as causative agent of the northwestern European epizootic, a similar outbreak among Baikal seals in Siberia (Lake Baikal), which started in 1987, could also be attributed to infection with a morbillivirus (18,39). Initially, it was suspected that an epizootiological link existed between this virus, which was tentatively called PDV-2, and the northwestern European virus, which we will refer to here as PDV-1. PDV-2, like PDV-1, could be isolated from organ materials and caused mild clinical symptoms in specific-pathogen free (SPF) dogs (54). However, comparison of PDV-1, PDV-2, and CDV with respect to biological, morphological, protein chemical and antigenic properties confirmed that PDV-1 was a morbillivirus different from CDV, and revealed only minor differences between PDV-2 and CDV (54). Nucleotide sequence homologies of the nucleoprotein, phosphoprotein (P), matrix, hemagglutinin, and fusion (F) protein genes between PDV-1 and CDV ranged from 65 to 85% (8,19,28,47,58). Comparison of the PDV-2 F gene with other morbillivirus F genes for which sequence data are available confirmed a 91% similarity to the complete CDV F gene, and a 97% similarity when only the coding regions of the F gene were compared. This is a level of sequence variation similar to that observed, for example, when geographically different isolates of RPV are compared (58).

MORBILLIVIRUS INFECTIONS IN CETACEANS

When in 1988 porpoises that had been stranded along the Irish coast were shown to be morbillivirus antigen positive (26) and the virus involved was subsequently isolated from animals stranded along both the Irish and Dutch coasts (34,56), it was assumed that the virus would be identical to PDV-1. In 1990 we also found evidence for a morbillivirus infection in a white-beaked dolphin (*Lagenorhyncus albirostris*) that had become stranded on the Dutch coast, by detecting morbillivirus antigen in the lungs of this animal (unpublished observation). In that same year, large numbers of striped dolphins started to wash ashore along the coasts of the western part of the Mediterranean Sea (14,53). The epizootic progressed eastward to reach the Turkish coast in 1992. Virus isolates were compared with PDV-1 and CDV and with the above-mentioned porpoise isolates. It was shown that the dolphin and porpoise viruses were quite similar, but both were distinct from PDV-1 and CDV. They were subsequently named dolphin morbillivirus (DMV) and porpoise morbillivirus (PMV) (52,56). Comparison of a sequence of the P gene encoding the RNA editing site from all presently known members of the genus confirmed that DMV and PMV were closely related members of the genus, but quite different from the other members. They form a distinct lineage more closely related to the ruminant morbilliviruses (RPV and PPRV) than to the carnivore morbilliviruses (4).

Phylogenetic trees of the presently known morbilliviruses, based on sequence analysis of the F genes and this P gene region, show the phylogenetic relationship of the newly discovered viruses with the established members of the genus (Fig 1). Experimental infection studies showed that not only dogs but also ruminants (cow, sheep, and goats) were susceptible to infection with DMV and PMV, which caused a mild leukopenia (56). Pre–exposure to DMV or PMV protected dogs from developing CDV viremia and clinical signs upon fatal CDV challenge (56). It was speculated to be unlikely that DMV or PMV would infect ruminants or dogs under natural circumstances, since morbillivirus infections generally seem to be restricted to one order of mammalian species (7). It is interesting to note that in recent years, CDV has been found in many carnivorous species, including seals (18,39), javelinas (2), and large cats both in zoos (3) and in the wild (21).

ORIGIN AND EPIZOOTIOLOGY OF THE NEWLY RECOGNIZED MORBILLIVIRUSES

The origin of PDV-1 was the subject of extensive speculation during and after the outbreak in 1988. Initial speculation about a possible link with CDV infections in sled dogs in Greenland, or with the PDV-2 (CDV) outbreak among seals in Siberia, could readily be dismissed after the characteriza-

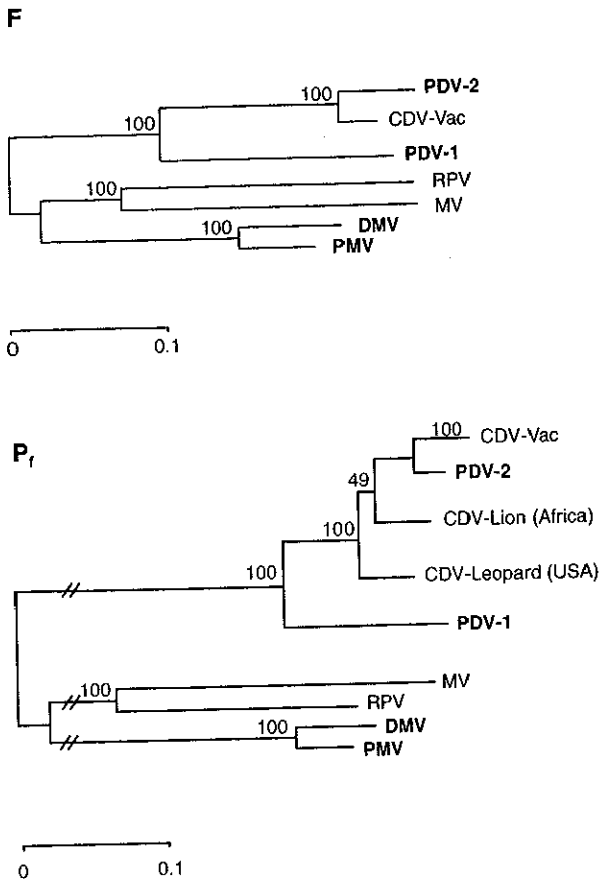

FIG. 1. Unrooted phylogenetic tree of the fusion protein encoding region (F) and a fragment of the gene encoding the polymerase-associated protein (P_f) of several morbilliviruses. Genetic distances between the nucleotide sequences were calculated according to Kimura's two-parameter method (27) and used to construct phylogenetic trees employing the neighbor-joining principle (46). Branch lengths are drawn in proportion to genetic distances, as indicated by bars. The robustness of the tree was tested by bootstrap analysis (17) using 2,000 replications (23). Numbers at nodes represent bootstrap percentages. Values >95% indicate a statistically significant separation of the respective cluster from the rest of the tree. All calculations were carried out using the "MEGA" PC program (29). Selected sequences were aligned by "Pileup" included in the GCG software package (release 8.0), setting gap weights to 3.0 and gap length weights to 0.1. Sequences were extracted from the GenBank database (accession numbers given between brackets) or from recent publications. F: phocid distemper virus type 2 (PDV-2, no. L07075), canine distemper virus vaccine strain Onderstepoort (CDV-Vac, no. X65509), phocid distemper virus type 1 (PDV-1, no. D10371), rinderpest virus (RPV, no. Z30700), measles virus (MV, no. U03655), dolphin morbillivirus (DMV, no. Z30086), porpoise morbillivirus (PMV, no. X80757). P_f: the aligned fragments correspond to positions 420–807 (388 bases) of the measles virus P gene mRNA; CDV-Vac (no. X51869), PDV-2 (33), CDV isolated from a lion of the Tanzanian Serengeti National Park (21), CDV isolated from a captive Chinese leopard from the U.S.A. (22), PDV-1 (no. D10371), MV (no. M89920), RPV (no. X68311), and DMV and PMV (4). Viruses that naturally infect marine mammals are indicated by bold typeface.

tion of the virus as a new member of the genus. However, interspecies transfer of the virus is still considered the most likely cause of the outbreak. In sero-epizootiological studies, the presence of a virus closely related, if not identical, to PDV-1 was shown in several North American marine mammal populations (15,16,45). The virus could have been transmitted by Arctic harp seals (*Phoca groenlandica*), a species that is in contact with both the North American and European seal populations and has been shown to be infected with a PDV-like virus (13,48). Interestingly, a mass migration of harp seals southward to continental European fishing waters was observed in the period directly preceding the 1988 outbreak. Since virus characterization studies showed that PDV-2, the virus that was isolated from Baikal seals, should be considered a strain of CDV, the origin of this virus was probably a local terrestrial carnivore. Speculation that the origin might have been a vaccine strain of CDV used to vaccinate local dogs had to be dismissed, since nucleotide sequences of PDV-2 P genes showed a closer relationship to European wild-type strains than to the vaccine strain used in that area (33). A similar event may have taken place in the Antarctic region in 1955, when a mass mortality among crab-eater seals (*Lobodon carcinophagus*) was possibly related to a simultaneous distemper outbreak among sled dogs. Support for this assumption came from serological studies showing the presence of CDV neutralizing antibodies in these animals (5).

Serological studies have shown that morbilliviruses similar to DMV and PMV are enzootic among many cetacean populations (56). Recent retrospective immunohistochemical studies have suggested the involvement of a morbillivirus in an epizootic among bottle-nose dolphins (*Tursiops truncatus*) along the U.S. Atlantic coast in 1987 (30). Based on the phylogenetic distinctness from other morbilliviruses, it may be concluded that it is unlikely that the PMV/DMV lineage has a recent origin in terrestrial animals (Fig. 1). The phylogenetic relationship between the different morbilliviruses of aquatic mammals largely parallels the phylogenetic relationship of the animal species they infect (55). Common viral ancestors may have acquired access to phylogenetically related animal species on the basis of biological similarities: CDV and PDV-1 probably share a common ancestor, which is also likely to be the case for the PMV/DMV and the RPV/PPRV lineages.

INVOLVEMENT OF ENVIRONMENTAL POLLUTION

Morbilliviruses have probably been enzootic in pinniped and cetacean species for a long time. In general, when these viruses have not been present in a certain population for a long period and consequently no specific immunity is present, an introduction by interspecies transmission may lead to severe outbreaks accompanied by mass mortalities (36,37). However, other factors may have played a role in the recently observed incidence of mass mortalities among marine mammals.

Studies in laboratory animals have shown that exposure to certain environmental contaminants may lead to increased susceptibility to infectious agents (59,61). The mammalian immune system has long been recognized as a sensitive target for persistent toxic chemicals accumulating in the food chain, including polychlorinated biphenyls, -dibenzo-*p*-dioxins and -dibenzofurans, hexachlorobenzene, dieldrin, β-hexachloro-cyclohexane, and dichlorodiphenyl-trichloroethane (DDT). As top predators, seals and dolphins inhabiting coastal waters of industrialized regions are known to accumulate high levels of some of these xenobiotics (31,50) and may therefore be at particular risk. These high contaminant burdens have been associated with several physiological abnormalities, including skeletal deformations (6,35), reproductive toxicity (24, 25,42) and hormonal alterations (9,49). While high levels of xenobiotics in affected animals suggest that contaminant-induced immunosuppression may have affected the severity and extent of the morbillivirus epizootics (1,20), no direct cause-and-effect relationship could be established.

We have addressed this issue in a controlled experiment, in which young harbor seals were fed fish contaminated through the food chain of different marine regions. During a 2½ period, two groups of 11 harbor seals each were fed herring from the heavily polluted Baltic Sea or the relatively uncontaminated Atlantic Ocean. Intakes of contaminants were three to ten times higher in seals fed Baltic herring (12), which led to significantly higher blubber levels in this group of seals after 2 years on the respective diets. During the feeding study, blood samples were taken at regular intervals, and functional immunological parameters were compared. Results showed an impairment of immune function in the seals fed on polluted Baltic herring (12), as evidenced by suppressed natural killer (NK) cell activity (44) and suppressed T lymphocyte mediated responses (11,43). Since NK cells play an important role in the first line of defense against virus infections (60) and T lymphocytes are important in the clearance of virus infections in general and morbillivirus infections in particular (51), we have postulated that environmental contaminants rendered seals inhabiting certain polluted areas more susceptible to morbillivirus infections, and may thus have affected the severity and extent of the disease outbreaks. In addition, other secondary factors, including changes in climate, population densities, food stocks and migration patterns, may also have played a role in the outcome of the epizootics.

CONCLUSIONS

In the past decade, a seemingly high incidence of previously unrecognized morbillivirus infections among marine mammal populations has been unraveled. This may in part be attributed to the increased interest in the health status of marine mammals, but it may also be related to an increased susceptibility of marine mammals to virus infections resulting from environmental contaminant–related immunosuppression.

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