WILEY InterScience® DISCOVER SOMETHING GREAT
Reviews in Medical Virology

Rev. Med. Virol. (in press)
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/rmv.526

REVIEW

Involvement of morbilliviruses in the pathogenesis of demyelinating disease

G. J. Sips[1], D. Chesik[1], L. Glazenburg[1], J. Wilschut[2], J. De Keyser[1]* and N. Wilczak[1]

[1]*Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
[2]*Department of Medical Microbiology, Molecular Virology Section, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*

SUMMARY

Two members of the morbillivirus genus of the family *Paramyxoviridae*, canine distemper virus (CDV) and measles virus (MV), are well-known for their ability to cause a chronic demyelinating disease of the CNS in their natural hosts, dogs and humans, respectively. Both viruses have been studied for their potential involvement in the neuropathogenesis of the human demyelinating disease multiple sclerosis (MS). Recently, three new members of the morbillivirus genus, phocine distemper virus (PDV), porpoise morbillivirus (PMV) and dolphin morbillivirus (DMV), have been discovered. These viruses have also been shown to induce multifocal demyelinating disease in infected animals. This review focuses on morbillivirus-induced neuropathologies with emphasis on aetiopathogenesis of CNS demyelination. The possible involvement of a morbillivirus in the pathogenesis of multiple sclerosis is discussed. Copyright © 2007 John Wiley & Sons, Ltd.

Received: 6 July 2006; Revised: 23 October 2006; Accepted: 2 November 2006

INTRODUCTION

The morbillivirus genus consists of a group of single-stranded, negative-sense RNA viruses belonging to the family *Paramyxoviridae* [1]. Until 1988 the genus was thought to consist of only four members; measles virus (MV), rinderpest virus (RPV), peste-des-petits ruminants virus (PPRV) and canine distemper virus (CDV). Since then, three other members of the morbillivirus genus have been discovered, all infecting aquatic mammals, dolphin morbillivirus (DMV), porpoise morbillivirus (PMV), both strains of the member cetacean morbillivirus (CeMV), and phocine distemper virus (PDV) [2,3] (Figure 1). This is the first time that members of this genus have been shown to infect aquatic animals, possibly demonstrating their ability to mutate and shift between hosts quickly [4]. The morbillivirus genus as a whole has a wide host range (Figure 2), as have most of its members, and cross-species infections have been reported on several occasions, sometimes with devastating outcomes [4–8].

In the following sections, we describe the neuropathology of these viral infections as most members of the genus exhibit a high degree of neurovirulence [9]. In particular, we focus on demyelination of the CNS, which may be relevant for the pathogenesis of multiple sclerosis (MS) [5,10–20]. To understand pathologies of the CNS and the concept of demyelination properly, one needs to have a basic knowledge of normal CNS functioning. Therefore, we briefly outline the normal cellular organisation of the CNS.

CELLULAR ORGANISATION OF THE CNS

The CNS is divided into two types of cells: neurons and neuroglia (Figure 3). The neurons are

*Corresponding author: Dr J. De Keyser, Department of Neurology, University Medical Center Groningen, Hanzeplein 1, 9713GZ Groningen, The Netherlands. E-mail: j.h.a.de.Keyser@neuro.umcg.nl

Abbreviations used
ADEM, acute disseminated encephalomyelitis; ALS, amyotrophic lateral sclerosis; CDE, canine distemper encephalitis; CDV, canine distemper virus; CeMV, cetacean morbillivirus; DMV, dolphin morbillivirus; EAE, experimental allergic encephalomyelitis; EEG, electro encephalo gram; F, fusion; H, haemagglutinin; L, large; M, matrix; MBP, myelin basic protein; MIBE, measles inclusion body encephalitis; MS, multiple sclerosis; N, nucleocapsid; P, phospholipid; PDV, phocine distemper virus; PMV, porpoise morbillivirus; PPRV, peste-des-petits ruminants virus; RPV, rinderpest virus; SSPE, subacute sclerosing panencephalitis

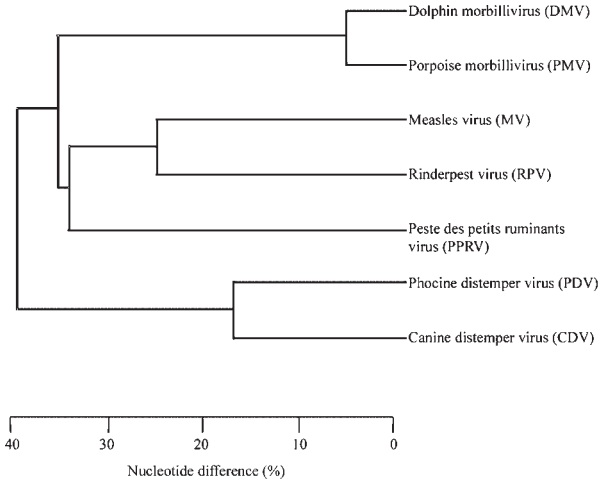

Figure 1. Phylogenetic tree showing the interindividual relationships between the different morbilliviruses, based on sequence analysis of genes encoding the H protein. Converging lines mark possible locations of ancestral viruses within the genus. Reproduced with kind permission of Reference 211

the cells in which the actual signal transduction takes place. A neuron typically consists of a cell body with dendrites, conducting incoming information from other neurons, and axons, conducting information towards other neurons [21]. The neuronal cell bodies are located in the cortex or grey matter, which, with a thickness of only a few millimetres, makes up the outer brain. The axons which connect the cortex with other parts of the brain and the spinal cord are located in the inner brain, commonly referred to as white matter. The neuroglia outnumber neurons by a factor of 10. There are four subtypes of neuroglia in the CNS, ependymal cells, oligodendrocytes, microglia and astrocytes. Ependymal cells line the ventricles of the CNS and by beating their cilia, which are located on the apical cell membrane, help to circulate the CSF.

Oligodendrocytes are essential for the formation and maintenance of myelin sheaths, which are wrapped around the axonal membranes. Due to the presence of these isolating myelin layers,

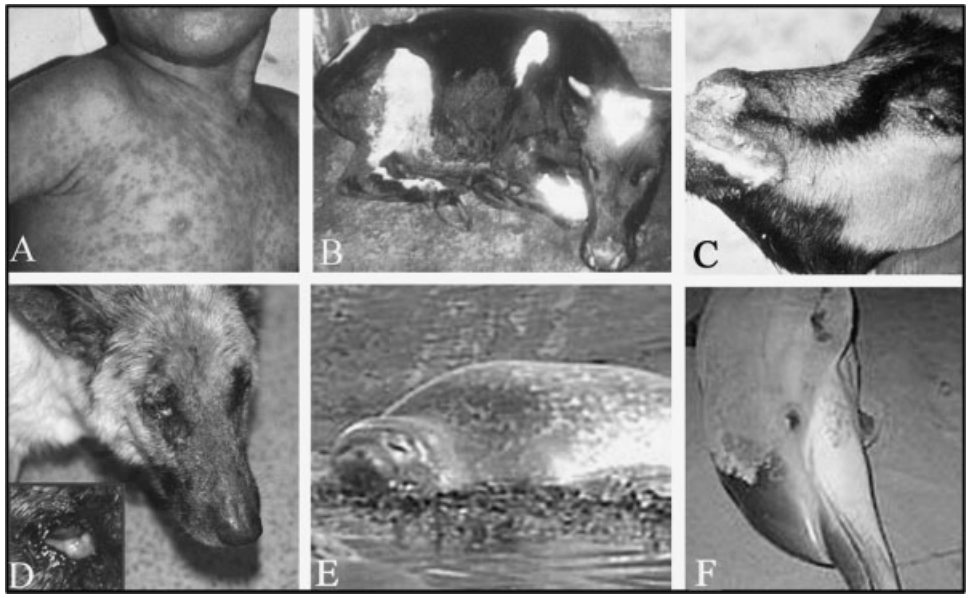

Figure 2. An overview of the species most commonly affected by the different morbilliviruses. (A) Characteristic rash on the chest of a child infected with MV. Courtesy of the Clinical Virology Network (www.clinical-virology.org). (B) A cow, markedly depressed due to infection with RPV. Courtesy of the Foreign Animal Disease Diagnostic Laboratory, Plum Island Animal Disease Center, NY, USA. (C) A goat infected with PPRV; notice the swollen lips and exudate in the nostrils. Courtesy of Professor T.U. Obi, Department of Veterinary Medicine, University of Ibadan, Nigeria. (D) Mucopurulent ocular discharge in a dog infected with CDV. Courtesy of Professor D.E. Brooks, College of Veterinary Medicine, University of Florida, FL, USA. (E) A harbour seal (Phoca vitulina) stranded on the British coast as a result of PDV infection. (F) a stranded striped dolphin (Stenella coeruleoalba). Courtesy of the Irish Whale and Dolphin Group

DOI: 10.1002/rmv

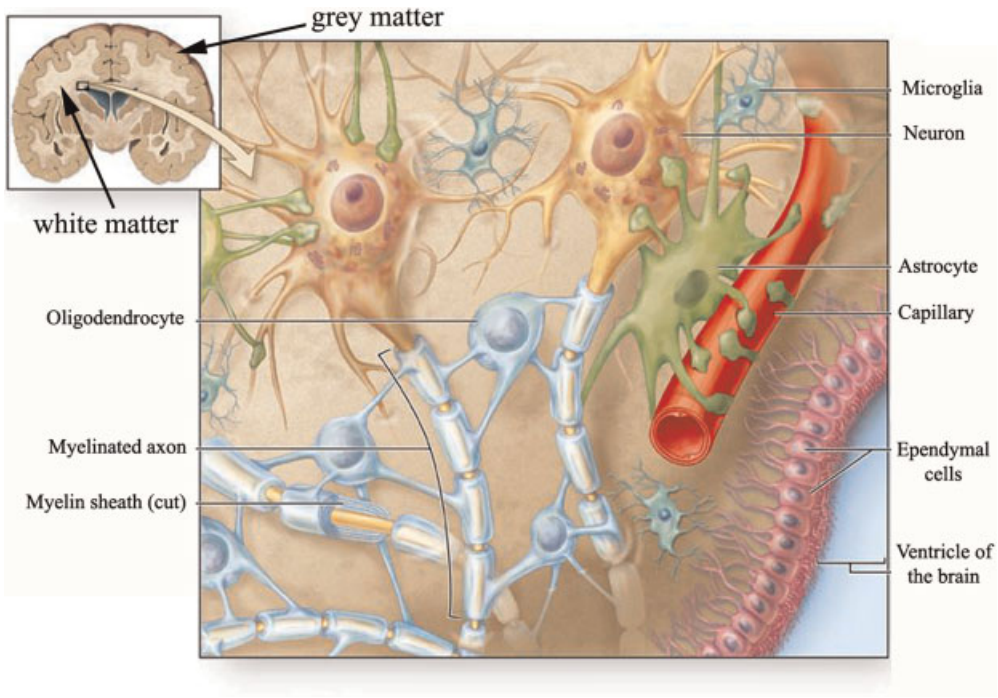

Figure 3. The cellular organization of the CNS; reproduced from McKinley M, O'Loughlin V. Human Anatomy. McGraw-Hill: New York, 2006; Chapter 14 (with kind permission of Mc-Graw Hill).

interrupted at regular intervals by the so-called nodes of Ranvier, the speed and efficacy of signal transduction between neurons is increased greatly. Where myelin is lost, as is the case in demyelinating disease, the CNS starts to dysfunction heavily because of the distorted signal transduction in affected axons [21]. Microglia are the 'macrophages' of the CNS and become recruited and activated during infection or injury. They are physiologically and embryologically unrelated to the other cell types of the CNS [21]. Astrocytes are the most numerous glial cells. Connected with their feet-ends to the blood brain barrier and their other ends to the other CNS cell types, they are the main supportive cells of the CNS, providing energy and nutrients to other CNS cell types and playing an essential role in normal homeostasis and the maintenance of physiological electrolyte gradients within the CNS [21].

MEASLES VIRUS

MV is probably the most well-known member of the morbillivirus genus. The virus naturally infects humans, mostly children, and is extremely contagious with a basic reproduction number, that is the number of secondary cases following an index case in a susceptible population, of more than 15 [22]. Although effective vaccination programmes have been set up in most developed countries, the virus remains responsible for the death of nearly 800 000 children each year, mostly in the developing world [23]. Before the introduction of vaccines and a global eradication programme coordinated by the WHO [24], death rates may have been as high as 7–8 million children annually. Apart from its clear potential to cause disease in susceptible humans, interestingly, MV is also being studied as a potential oncolytic agent. The results of pre-clinical studies regarding the oncolytic efficacy of MV, as well as future perspectives, have recently been reviewed [25].

MV consists of a 100–300 nm long virion surrounded by a lipid envelope. The viral genome consists of six transcriptional units, encoding two non-structural proteins and, as in most morbilliviruses, six structural proteins [5] (Figure 4). Three structural proteins, the nucleocapsid (N), phospholipid (P) and large (L) protein, are associated

DOI: 10.1002/rmv

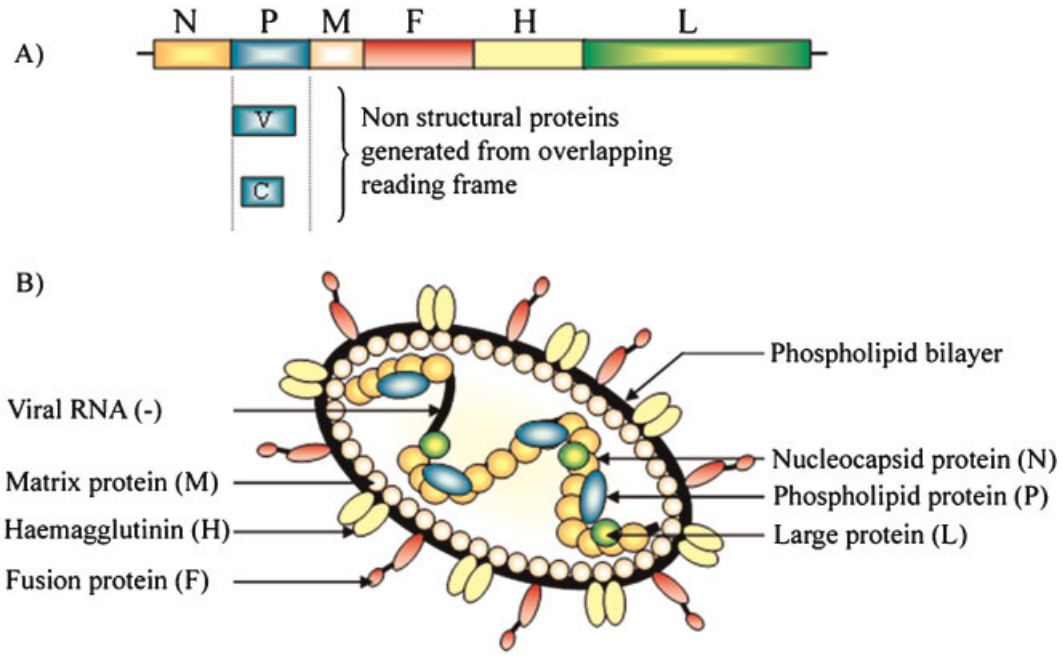

Figure 4. Measles genome map showing the different proteins encoded by MV (A) as well as their structural representation. (B) Reproduced with kind permission of Reference 35

with the viral RNA and make up a helical ribonucleoprotein (RNP) complex. The haemagglutinin (H) and fusion (F) envelope glycoproteins form oligomeric spikes, which protrude from the viral surface and are visible by electron microscopy. The H protein binds to cellular receptors whereas the F protein mediates virus entry into host cells. Most virus-neutralising antibodies are directed against the H protein of the envelope [26,27]. The inside of the membrane is coated by a hydrophobic protein named the matrix (M) protein. This protein serves several roles and is particularly involved in virus budding and transcription regulation [28,29]. Many genomic sequences have been obtained for both wild-type and vaccine strains of MV, which mostly differ in nucleotide sequences encoding the terminal part of the N protein and the entire H protein [30–33]. In spite of these differences in genotype, the virus exists as a single serotype and infection with one strain provides life-long protection from disease caused by all strains. Within the morbillivirus genus, MV is phylogenetically most closely related to RPV [1].

MV spreads within aerosol droplets and, after inhalation, initially replicates in the upper respiratory tract. Secondly, cells of the immune system become infected, which are the main route for further virus spread [34]. Apart from its direct effects on the immune system, MV also has indirect, longer-lasting effects on the immune system, in which the interaction between several viral proteins and the human host seems to play a role [35,36]. As a result, patients with measles develop a clear immunosuppression, which can last up to 6 months after an acute infection and increases their susceptibility to secondary infections [35].

General symptoms of an acute MV infection consist of a maculopapular rash, dry cough, coryza, fever, conjunctivitis and photophobia, usually preceded by characteristic spots on the mucosal surface of the mouth, called Koplik spots (Figure 2). The most serious complications of MV infection occur within the CNS, which may take three forms: acute disseminated encephalomyelitis (ADEM), measles inclusion body encephalitis (MIBE) and subacute sclerosing panencephalitis (SSPE), the last two occurring months or even years after acute infection and being invariably fatal [5,37,38].

Acute disseminated encephalomyelitis

ADEM is not an exclusive complication of MV infection and has also been seen following infections with other pathogens [39–44]. In measles, it occurs about 5–6 days after the initial rash in about

DOI: 10.1002/rmv

1/1000 infected children [38–44]. In vaccinees and children under 2 years of age it is less common [5,38–40]. Symptoms occur once the initial rash has disappeared and consist of a sudden recurrence of fever, decreased consciousness, seizures and multifocal neurological signs. The disease has an abrupt onset, often reaching its peak within the first 24 h. Mortality is about 20% [19]. The electro encephalo gram (EEG) is usually slow but nonspecific, given the fact that in half of all cases of measles infection, even including uncomplicated infections, EEG changes are seen [19,39]. The CSF usually shows a mild elevation of protein and mononuclear cells, but is normal in about one-third of patients [19,39]. The clinical diagnosis of ADEM is strongly suggested by a close temporal relationship between an infectious incident or an immunisation and the onset of leukoencephalopathic neurological symptoms [19,39]. Particularly helpful are acute signs of newly developed extensive, multifocal and subcortical white matter abnormalities on magnetic resonance images (MRI) of the brain [39,40,45] (Figure 5).

The major differential diagnosis of ADEM is multiple sclerosis [35]. No virus has as yet been demonstrated in the brains of children who died from ADEM [38,39,46] and, because of its rarity, ADEM has been very hard to study.

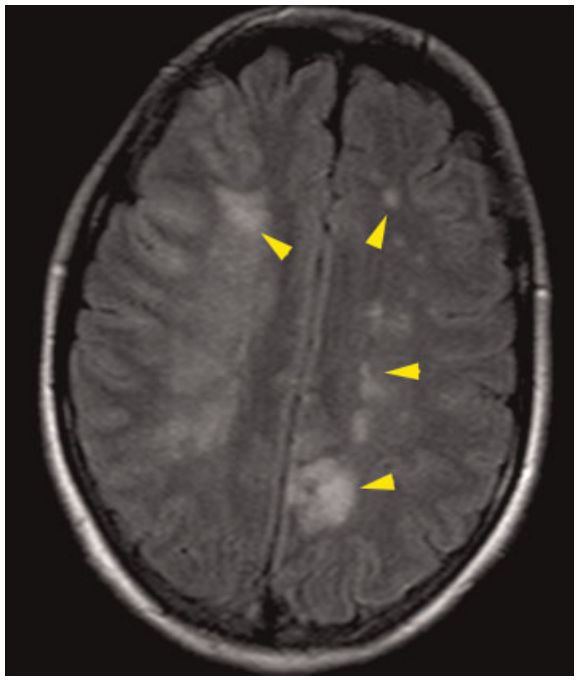

Figure 5. Axial MRI scan in a case of ADEM showing multifocal subcortical white matter lesions (arrows)

The pathology of ADEM consists of a pattern of widespread perivascular demyelination and infiltration of mononuclear cells. Histologically, the pattern of demyelination resembles that observed in experimental allergic encephalomyelitis (EAE), an animal model of MS [47,48]. The exact pathological mechanism of this demyelination remains unclear. An autoimmune reaction has been suggested, but at present there is no consensus about the exact aetiopathology of ADEM [5,38,39].

Measles inclusion body encephalitis

MIBE usually occurs between 2 and 6 months after MV infection in immunocompromised patients [5,37,38,49–51] and can follow both wild-type virus infection and vaccination [5,38,49–54]. Patients are usually present with focal seizures and altered mental state. Prognosis is poor with a 76% mortality rate and all survivors retain a persistent neurological disorder [51].

Characteristic neuropathologic changes are glial cell proliferation and focal necrosis, with varying degrees of perivascular inflammation. Intranuclear and/or intracytoplasmatic inclusion bodies are often present [38,51]. The diagnosis of MIBE can only be confirmed *post mortem*, by RT-PCR for MV RNA or by immunohistochemistry. A few cases have been described in which MIBE followed vaccination and here dysgammaglobulinaemia or a pre-existing undiagnosed immune abnormality was suggested to be a predisposing factor [53,54].

The mechanism of viral spread and persistence in the brain in MIBE patients is not well understood [5,38]. MIBE is not associated with an increased antibody response to measles, as might be expected in immunocompromised patients, and oligoclonal bands are not present in the CSF [5,38,51].

The most recent case report of MIBE described the death of an immunocompromised boy who had previously received stem cell therapy for chronic granulomatous disease [55]. Neither patient nor donor had recently been exposed to MV, received recent MV vaccination or had recently visited an endemic area. Brain biopsy on day 53 post-transplantation demonstrated numerous eosinophilic intranuclear inclusion bodies and

DOI: 10.1002/rmv

minimal perivascular inflammatory infiltrates. Inclusions of varied sizes were seen in astrocytes, oligodendroglial cells and neurons. Electron microscopic examination showed that the inclusions were clusters of relatively long, curved, tubular structures consistent with paramyxovirus nucleocapsids. Extensive demyelination of axons was seen.

Subacute sclerosing panencephalitis

SSPE is thought to complicate about 1/1 000 000 cases of MV infection [5,19,38], although areas of high incidence (1/10 000-1/25 000 cases) have been reported [56]. SSPE occurs approximately 5–10 years after initial MV infection, infection under the age of 2 being a risk factor [57–60]. There is a male preponderance of SSPE with a male/female ratio of 2.5:1 [61]. In the early stage, children present with loss of attention span and neurological symptoms, typically stereotyped myoclonic jerks. As the disease progresses, they gradually slide into a vegetative state and eventually die from the infection [62]. SSPE is an example of a chronic defective CNS infection [63].

The first report of the disorder was in the early 1930s, describing characteristic viral inclusions [64]. The association with MV came later when the inclusions were shown to be MV-specific [65]. Inclusions are present in both cytoplasm and nuclei of infected neurons [66] and, in later stages of SSPE, small numbers of oligodendrocytes, astrocytes and endothelial cells seem to become infected as well [67]. It is thought that these inclusions are in fact sites of transcription and replication, but their exact nature has yet to be determined. The disease is characterised by extremely high anti-measles antibody titers in both serum and CSF, with the finding of intrathecally-synthesised MV-specific oligoclonal bands [63,68]. Antibodies to structural proteins of MV, especially N, F and H, are present in concentrations almost 10 times higher than those seen in acute infection [69]. As the name of the disease suggests, histologically, there is a widespread chronic inflammatory infiltrate of small lymphocytes and plasma cells, often in perivascular cuffs. The white matter shows focal demyelination and widespread astrogliosis, which are also the histopathological hallmarks of MS. White matter abnormalities can also be detected by MRI, especially in the late phase of the disease. White matter abnormalities consist of high signal intensity areas on T2-weighted images which, especially in the early phase, tend to be located in the occipital and parieto-occipital lobes [62,70,71] (Figure 6).

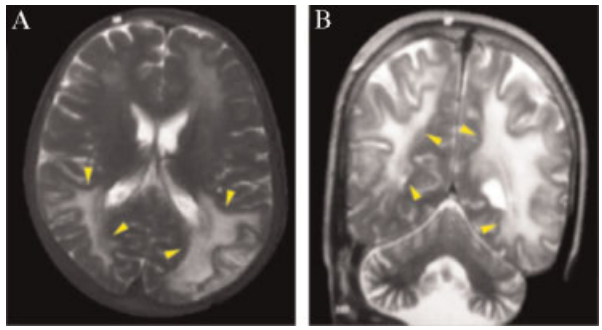

Figure 6. T2-weighted MRI images showing hyperintense lesions in white matter of the occipital and parieto-occipital lobes (arrows) in SSPE; (A) axial scan and (B) coronal scan. Reproduced with kind permission of Reference 70

The factors that turn an acute MV infection into a chronic one are as yet unknown, although various mechanisms have been postulated over the years. Many of them have focused on mutations of the viral genome, especially of gene sequences encoding for proteins that are required for viral budding and spread, such as the M protein [5,38,69,72–75]. Defects in these proteins, leading to limited viral spread or decreased budding, could lead to a less virulent species, capable of residing in its host for a prolonged period of time. The observed high antibody titers could also play an important role in the pathogenesis of SSPE, aiding viral persistence by stripping viral envelope proteins from the membrane surface [76]. In addition, *in vivo* studies in rat models demonstrated that anti-measles antibodies not only promote viral persistence [77–79] but possibly even decrease viral replication at the transcriptional level [80]. In light of these theories it is interesting that, although it seems clear that MV is the cause of SSPE, its precise site of residence and replication during the latency period between acute infection and 'relapse' has never been established [5]. Although a commonly held belief, this may well prove not to be in the CNS but somewhere else. Even in the case of active CNS disease, there is little evidence of infectious virus in the CNS itself, but more of viral 'footprints', like the inclusion bodies and intrathecal immune response described

DOI: 10.1002/rmv

earlier. At autopsy or biopsy, generally no infectious virus can be found in the CNS. Also in the acute stage of MV infection, evidence of actual CNS infection is mostly indirect [18]. However, EEG abnormalities and CSF pleiocytosis [81], occurring in about 30% of acute uncomplicated MV infections, point to the virus gaining access to the CNS during the acute phase. In this respect, and in favour of the virus itself actually entering the CNS, given the fact that measles virus infects all peripheral white blood cell lines, it is possible that the CNS is transiently infected via the normal, or altered, turnover of microglia. Then, when the virus has gained access to the CNS and has crossed the blood-brain barrier, further CNS infection could ensue. This assumption is supported by studies in rodent models which have shown that activated T cells can enter the CNS parenchyma [82] and that, additionally, B cells, secreting both virus-specific- and non-virus-specific antibodies, are recruited [83,84]. The same 'Trojan-horse' mechanism, in which infected monocytes enter the CNS upon being recruited as macrophages, has also been postulated to explain CNS involvement seen in other types of virus infections infecting cells of lymphocyte/leukocyte lineage, such as Maedi-Visna virus and HIV [85–87].

The demyelination observed in SSPE could be the result of several mechanisms. One possible mechanism involves CSF antibodies, which, as aforementioned, are produced in an unusual high amount in SSPE and have been shown capable of lysing brain cells cultured from SSPE patients *in vitro* [88]. Other theories propose that during the latency period, as MV is thought to be slowly replicating in the brain, viral products in neurons and oligodendroglia slowly increase and eventually lead to cell death and demyelination [89]. Furthermore, infiltration by CD4+ and CD8+ T cells and the release of inflammatory cytokines such as IFN-γ and TNF-α has been demonstrated, suggesting that cell-mediated damage to infected cells may play a role [90,91].

RINDERPEST VIRUS

Within the morbillivirus genus, RPV is phylogenetically most closely related to MV [1]. RPV naturally infects cattle, but, like other members of the morbillivirus genus, it has a broad host spectrum, infecting many other large ruminants, both domesticated and wild [92,93]. Nowadays largely eradicated in most developed countries, the virus remains endemic in large parts of the African continent, the Middle East and South Asia [94]. RPV exists as a single serotype, but many different strains are known [95]. These strains vary in their host affinity and are capable of exhibiting different levels and patterns of virulence within a single host species, with infections ranging from subclinical to fatal. Mortality rates of nearly 100% have been observed in cases of infection of susceptible species by a highly virulent strain of the virus such as the Saudi strain [96–98]. Thus, infection of the same host species with virus isolates of different pathogenicity leads to variations in clinical signs, the extent of morphological lesions and viral antigen distribution within the affected species [96,97]. Furthermore, host preferences have been known to change with time with disease presentation differing between hosts, as most clearly demonstrated by the African panzootic [99–101], which unambiguously demonstrated the tendency of morbilliviruses to evolve and change hosts quickly, as well as the subtleties of the interplay between host and virus. Symptoms of a classical virulent infection consist of an incubation period of 3–9 days followed by a short sharp fever, erosive stomatitis, gastroentereitis, fetid odour, dehydration and death [93] (Figure 2).

At a pathological level, primary multiplication of the virus occurs in the tonsils and pharyngeal and mandibular lymph nodes, from where further dissemination throughout the body takes place. The principal targets of RPV so far identified are epithelial cells and cells of the lymphoid system. Post-mortem findings consist mainly of lesions in lymphoid tissues, the alimentary, upper respiratory and urogenital tracts [96,102]. Demyelination and CNS involvement have never been reported in RPV infection of its natural wildlife hosts, possibly because the acute infection is either devastating, leading to a quick death, or mild or maybe even undiagnosed. The potential of RPV to cause demyelination in other host situations has been shown in experiments with infected permissive mouse strains, in which RPV indeed exhibited neurovirulence [103].

PESTE-DES-PETITS-RUMINANTS VIRUS

First considered a variant of RPV, PPRV has now long been recognised a fourth distinguishable member of the morbillivirus genus [104]. The virus

DOI: 10.1002/rmv

is most closely related to dolphin morbillivirus and to a lesser extent to rinderpest and measles [1,105,106]. PPRV, like RPV, is endemic in large parts of Africa, the Middle East and India [107–115]. It infects small ruminants, mostly sheep and goats, and causes pyrexia, ocular and nasal discharges, pneumonia, erosive stomatitis and severe diarrhoea, usually preceded by a 3–4 day incubation period [113] (Figure 2). Morbidity and mortality rates vary, but can be as high as 90–100%. In regions in which the virus is endemic these rates tend to be lower [113].

The principal pathologic findings are seen in lymphoid structures and the respiratory and digestive systems [116–118]. As in rinderpest, gastrointestinal infection is usually characterised by degeneration and necrosis of intestinal epithelium and congestion of gastrointestinal mucosa and submucosa. Pulmonary pathology includes bronchointerstitial changes and the presence of intracytoplasmic and intranuclear eosinophilic inclusions in alveolar macrophages and syncytial cells, frequently complicated by serofibrinous pneumonia. Furthermore, lymphocytolysis and syncytia formation can be seen in lymphoid tissues. PPRV antigen can be demonstrated in lymphoid, intestinal and pulmonary cells [116–120]. Neurological complications have not been reported. However, one study [117] interestingly described diffuse gliosis in the molecular layer of the cerebellum in the absence of PPRV positive staining. Like RPV, PPRV has been shown to display neurovirulence in experimentally infected mice [96].

CANINE DISTEMPER VIRUS

Neurologically, CDV is, together with MV, by far the most studied member of the morbillivirus genus. CDV has been considered an animal model of MS for years [10].

As its name implies, CDV naturally infects dogs (Figure 2). It is transmitted as an aerosol infection to the upper respiratory tract. Primary virus replication occurs in the lymphoid tissues, as in other morbillivirus infections [10,121,122]. After about 10 days, the virus starts to spread to various epithelial tissues and the CNS. The mechanisms of spread to the CNS are poorly understood but a recent publication interestingly suggests that invasion of the CNS can occur through at least two different pathways. One route is the classical haematogenous pathway through the choroid plexus and cerebral blood vessels, while the other, previously unrecognised, represents an anterograde pathway through the olfactory nerve [123]. The most serious complications of CDV infection eventually occur in the CNS, presenting a variety of clinical symptoms including optic neuritis, myelitis, ataxia, nystagmus, tremor, seizures, myoclonus, paresis and psychic changes [10,14]. While respiratory, intestinal and dermatological symptoms may occur as a result of epithelial infection, neurologic signs often occur in the absence of systemic signs [10].

Pathologically, the virus causes multifocal demyelinating lesions in the grey and white matter of the CNS. White matter demyelination generally prevails and grey matter lesions may even be totally lacking. The most frequently affected anatomical regions include the white matter of the cerebellum, the periventricular white matter, especially around the fourth ventricle, the optic pathways and the spinal cord [10]. Pathogenetically, the disease course and plaque formation are commonly divided into an acute and a chronic phase.

Acute phase

Foci of demyelination occurring in the acute phase of canine distemper encephalitis (CDE) seem to be directly virus-correlated and their development is highly predictable [10,124–128]. The most logical explanation of the onset of demyelination would be a primary infection of the myelin-producing oligodendrocytes. Therefore a large number of studies have focused on demonstrating the presence of distemper virions in oligodendrocytes. However, at the light microscope level it has been shown that the main white matter cells infected are astrocytes [129] and most studies now agree that oligodendrocyte infection is in fact extremely rare in distemper [125,130–133].

Immunocytochemical studies revealing a small number of oligodendrocytes containing CDV mRNA [10], reports infection of a small number of oligodendrocytes at the edge of lesions [128–133], and the finding of a restricted CDV infection with viral transcription but no translation in cultured oligodendrocytes [134], eventually led to the conclusion that CDV causes a restricted infection of oligodendrocytes [10]. Infection of cultures of canine oligodendrocytes superimposed on a layer of astrocytes showed degeneration, microvacuolation, loss of organelles, metabolic dysfunc-

DOI: 10.1002/rmv

tion and decrease of myelin transcription in oligodendrocytes [128,135,136]. The latter was also shown *in vivo* [128], but there is no direct evidence that these cells do indeed also undergo necrosis or apoptosis [137,138]. Moreover, infection with wild-type CDV seems to be rather non-cytolytic [10].

In summary, it is thought that, during the acute phase of CDE, infection of the white matter results in metabolic oligodendroglial changes which lead to demyelination. Whether both dysfunction and demyelination are the direct result of restricted oligodendroglial infection or of other processes remains to be shown [139–147].

Chronic phase

The chronic phase of CDE is characterised by a strong inflammatory reaction, consisting of perivascular cuffing with lymphocytes, plasma cells and monocytes [148], and leading to progression of tissue damage [133,149]. It is also characterised by a strong intrathecal antibody synthesis [148–151]. Pro-inflammatory cytokines are upregulated within the inflammatory lesions, whereas anti-inflammatory cytokines remain at normal levels [146].

A first theory suggests that tissue destruction in the chronic phase of CDE is related to the anti-viral immune response [10]. Anti-CDV antibodies binding to their target cells were found to stimulate neighbouring macrophages both *in vivo* and *in vitro*, which could, at least *in vitro*, lead to the destruction of nearby oligodendrocytes, affecting them as bystander cells [141,142,152–154).

Secondly, there is also evidence for virus-induced autoimmunity in canine distemper. Anti-myelin antibodies have been found in serum and CSF, as well as in inflammatory brain lesions [150,155], and a cell-mediated response against myelin basic protein (MBP) was found in a few dogs experimentally infected with CDV [156]. These immunological parameters, however, do not seem to correlate with the disease course [10] and, at a pathological level, distemper seems to bear little resemblance to EAE in dogs [157]. It also seems uncertain to what extent these events play an active role in the actual process of demyelination and whether an autoimmune disease would continuously progress in the absence of viral antigen [10]. With regard to the latter, interestingly, it has been shown that MHC class II expression remains upregulated in distemper even though when the number of CDV positive cells has strongly diminished [139].

A third theory postulates that the main factor leading to the chronic phase of demyelination is viral persistence [10]. Studies have shown that CDV can persist in white matter areas outside the demyelinating lesions [10,158]. Persistence of CDV would, rather than being caused by a defect in the virus itself, mostly be related to restricted infection and non-cytolytic spread, as was also postulated, in a slightly different way, for the acute phase. [10,159–161]. It is suggested that the persistent agent precipitates recurrent immune reactions, even though the infectious load may be extremely small and difficult to detect [10]. Another consideration could be the role of astrocytes, the primary target cells of CDV which readily support viral production. It is becoming more understood that astrocytes, instead of being mere 'brain glue' [162], could play a pivotal role in both normal CNS functioning and in disease states. Recently, a review [163] focused on the possible role of astrocytes in a variety of disease states, including epilepsy, amyotrophic lateral sclerosis (ALS) and stroke. Neither infections of the CNS nor MS were mentioned in this review. However, astrocytes undergo different alterations in CDE, including loss of beta-2 adrenergic receptors [164], which was also seen in MS [165,166], and an upregulation of CD44 on their cell membranes [167]. Astrocytes could play a more primary, pivotal role, rather than just a contributory one, as has occasionally been mentioned [10,138], in the development of demyelination, disrupting a balance of energy supply to other cell types or perhaps causing an upset of the immune system, thus triggering an auto-immune reaction [168-172].

PHOCINE DISTEMPER VIRUS

In 1988, the previously unknown morbillivirus PDV was responsible for a mass die-off amongst harbour seals, reducing the seal population in some regions by more than 50% [172–183] (Figure 2). Morbilliviruses were not previously known to infect aquatic mammals. By the end of the year the epidemic was practically over and the virus remained silent for more than 10 years, although initial cases of infection continued to be reported in European and also North American coastal areas [184–192]. In 2002, a second epidemic

DOI: 10.1002/rmv

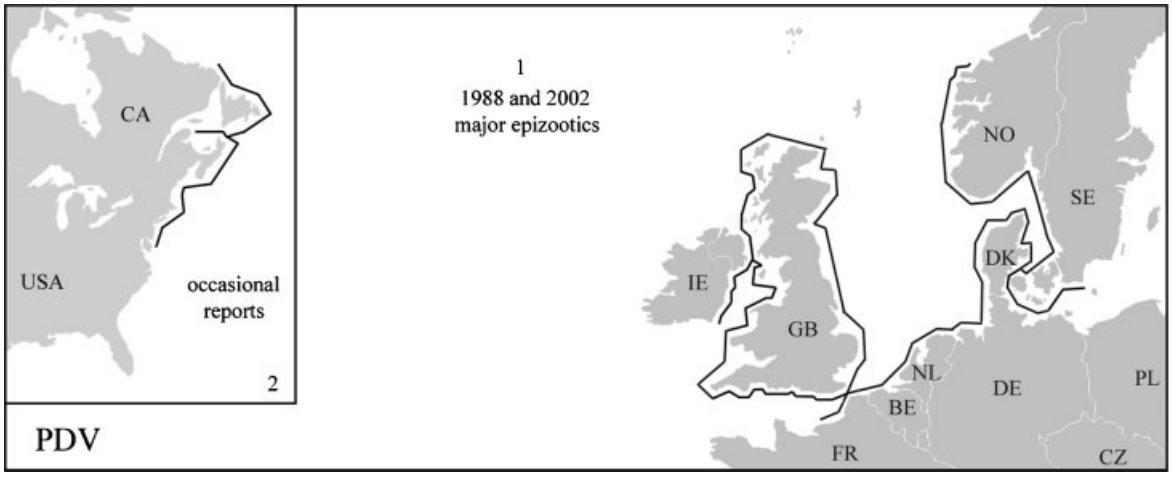

Figure 7. Map showing the different outbreaks of PDV. The names of the countries have been abbreviated: BE, Belgium; CA, Canada; CZ, Czech Republic; DE, Germany; DK, Denmark; FR, France; GB, Great Britain; IE, Ireland; NL, The Netherlands; NO, Norway; PL, Poland; SE, Sweden; USA, United States of America

occurred which largely followed the pattern of the first one [193–196]. Both epidemics occurred in northern areas, starting at the Danish island of Anholt and subsequently spreading along the whole northern European coastline, from the Wadden Sea to Norway, including the British Isles [172,177,178,181,182,194–196] (Figure 7). Why both epidemics started at Anholt and PDV was not seen until 1988 is remarkable and still remains unexplained. This possibly underlines the nature and high potential of morbilliviruses to evolve and infect new hosts [4,8] or could be due to infection following contact with another species, possibly seals from arctic populations [172,181,194,196–198]. Genetic studies have shown that PDV closely resembles CDV but is more distant from MV and RPV [1,199–211]. Clinical signs observed in PDV-infected seals include hyperthermia, dyspnoea and enteric symptoms such as diarrhoea. From clinical observations of infected animals it has become clear that PDV, like other members of the genus, causes a neurological disorder with fits, muscle twitching and an abnormal posture [172,177,194].

There has only been one large necropsy report of seals that died during these epidemics, a gross full-body screening performed on seals that died during the 1988 epidemic [11], and there have occasionally been reports describing necropsies performed on small numbers of stranded animals in isolated events [186,187]. Infection of brain tissue has been reported, characteristic of a non-suppurative demyelinating encephalitis with degeneration and necrosis of neurons, focal gliosis, perivascular cuffing and demyelination. Intracytoplasmatic and intranuclear inclusions were found in many neurons, astrocytes and ependymal cells. The other necropsy findings consisted mainly of pulmonary changes, characteristic of bronchointerstitial pneumonia, gastrointestinal lesions, lymphocytolysis and lymphoid depletion [11,186,187].

Very little is known about the pathogenesis of PDV infection and the nature of lesion development, including demyelination. There has only been one experimental study, in which seronegative seals were infected with PDV [172,212]. These animals developed clinical signs of distemper and PDV antigen was detected in a range of tissues, including the respiratory and gastrointestinal tracts, CNS and lymphoid tissues [212].

CETACEAN MORBILLIVIRUS

Remarkably, the first evidence of a morbillivirus infecting cetaceans also came in 1988, when six harbour porpoises with distemper-like lesions were found stranded on the coast of Northern Ireland [213]. At first, it was thought that this was the result of cross-species infection because these animals were found near a large colony of morbillivirus-infected harbour seals [172]. Subsequently however, harbour porpoises were also found stranded on the Dutch, English and Scottish coast-

DOI: 10.1002/rmv

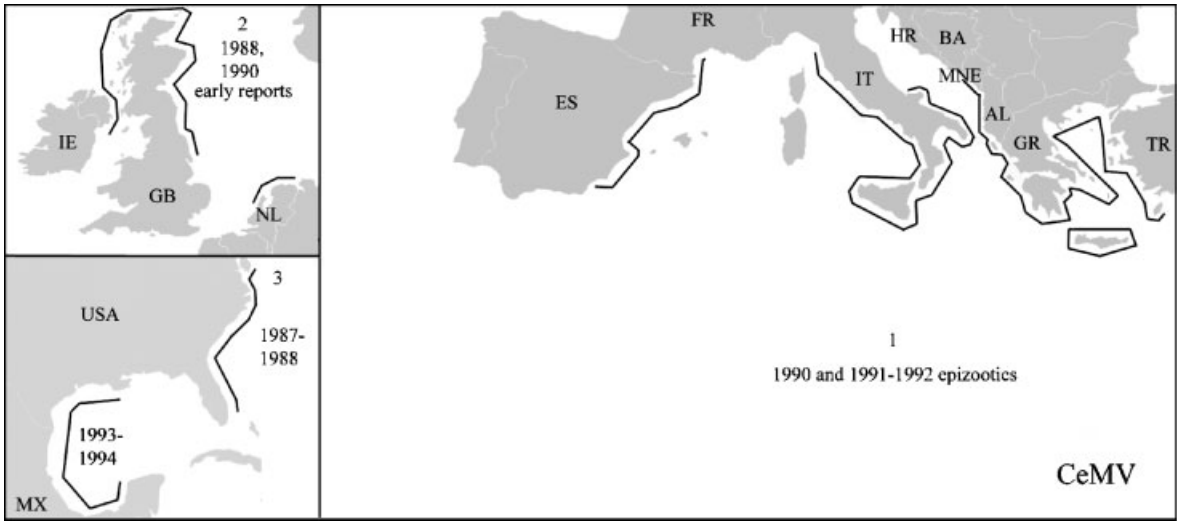

Figure 8. Map showing the different outbreaks of CeMV. The names of the countries have been abbreviated: AL, Albania; BA, Bosnia-Hercegovina; ES, Spain; FR, France; GB, Great Britain; GR, Greece; HR, Croatia; IE, Ireland; IT, Italia; MN, Republic of Montenegro; MX, Mexico; NL, The Netherlands; TR, Turkey; USA, United States of America

lines [214,215] (Figure 8). A morbillivirus was indeed recovered from these porpoises and shown to be a novel member of the genus, PMV [211,215–217], making the initial theory of cross-species infection less plausible. A few years later, in the early nineties, a mass die-off started to occur within populations of striped dolphins residing in the Mediterranean Sea, starting along the Mediterranean coast of Spain in 1990 and subsequently spreading throughout other parts of the Mediterranean over a period of 2 years before eventually subsiding in 1992 [172,178,218–220] (Figure 2). Molecular biological and antigenic studies of the virus recovered from these animals revealed another new morbillivirus, which was named DMV. PMV and DMV are so closely related (Figure 1) that they can be considered two strains of the same viral species and thus are commonly gathered under the name CeMV [172,211,215, 221–225]. Within the genus, PMV and DMV are more closely related to PPRV than to the MV-RPV or CDV–PDV branches [105,172,211,221]. After these initial cases of infection in the early nineties, DMV and PDV have, retrospectively, been held responsible for another large epidemic, occurring alongside the eastern coast of the USA between June 1987 and May 1988 [226–228], and a smaller one in the Gulf of Mexico from mid-1993 to mid-1994 [228,229]. Very few data are available with regard to the exact clinical presentation of infected animals. Neurological and behavioural changes were the only clinical features seen in striped dolphins stranded on the Spanish coast in 1990 [172,178]. Skin lesions and erosion of buccal mucosa were common [178]. Tachycardia, abnormal respiratory rates, weak sound emission and muscle tremors were also reported [172,230]. Some dolphins repeatedly struck their bodies against rocks or breakwaters, possibly due to brain damage [172].

Most of our knowledge of CeMV-induced pathology comes from full-body necropsies on animals which were found stranded. Lung lesions characteristic of bronchointerstitial pneumonia were seen, as well as gastrointestinal lesions, lymphocytolysis and lymphoid depletion [172,178,219, 220,226,227,231,232]. CNS lesions were characteristic of a non-suppurative encephalitis, with degeneration and necrosis of cortical neurons [172,178, 218,231,232].White matter changes included astrogliosis and foci of malacia, containing syncytia with two to six nuclei [232,233]. The finding of demyelination was less prominent than in PDV. Demyelination was found in two studies [219,233], one being a large study mainly focusing on neuropathology which notably described inflammatory lesions which were subacute or chronic in nature, but was not considered a prominent feature in two other studies [218,231]. These last studies were, however, performed on a much smaller number of animals. Intracytoplasmatic and intranuclear acidophilic inclusion bodies

DOI: 10.1002/rmv

were common in degenerated and necrotic neurons, glial cells and syncytia and tended to be larger and more irregular than in PDV-infected seals [172]. Large amounts of morbillivirus were found in cortical neurons, astrocytes and microglia [178]. Two studies [218,234] described encephalitis, associated with the presence of inclusion bodies and morbillivirus antigen in brain tissue, in the absence of infection or viral antigen in other organ tracts. This may indicate some sort of chronic form of infection analogous to SSPE in humans [172], but more studies are required to address this [172].

FINAL REMARKS

MS is the most common inflammatory demyelinating disease of the CNS, affecting about 2.5 million people worldwide [13,20,57]. The disease has its main onset in young to middle-aged adults between their 20 and 40th years, with a female preponderance of 1.6:1 [20]. Although MS has been studied since the late 19th century its precise aetiology to this day remains elusive [20]. Current theories postulate that the disease is an autoimmune disorder, in which an environmental, possibly viral, trigger deranges the immune system in susceptible individuals, eventually leading to demyelination [20]. Histopathologically, the disease is characterised by focal demyelination and diffuse astrogliosis [20].

In nearly 95% of all MS patients an extraordinarily high amount of intrathecally synthesised antibodies is found in the CSF, often as oligoclonal bands [20,235–237]. This finding, together with its pathological similarities to most demyelinating diseases of the CNS of known viral origin [17–19] and its specific geographical distribution [20], led to the theory that MS could be caused by a viral agent. Migration studies suggest that a viral infection in the pre-puberty could cause the eventual occurrence of the disease years later [20]. Given particularly high anti-measles antibody titers within the CSF [235–237], a morbilliform, measles-like virus was considered a likely candidate [14,15]. However, to this day no virus has been successfully recovered from the brain of MS patients.

A few points are important when evaluating the possibility of the involvement of a morbillivirus in multiple sclerosis. Morbillivirus infections frequently lead to demyelination of the CNS in a wide variety of mammals. Demyelination has long been known to occur in infections with terrestrial morbilliviruses but, as demonstrated in the previous sections, also occurs in infections with their aquatic counterparts. In this respect it is important to recognise that, even though at present virtually all demyelinating diseases of man and animals of known aetiology are of viral origin [57], the ability of a virus to induce demyelination is actually rather uncommon. In fact, many viruses infecting the CNS, such as rabies virus, are not capable of causing demyelination [57]. All morbilliviruses, at least MV, CDV and the aquatic morbilliviruses, possess specific capabilities to cause CNS demyelination, with, more importantly, forms of disease varying from acute, subacute to chronic (Figure 9). Furthermore, the genus as a whole has a wide host range, as most of its members, and viruses seem to be capable of evolving and shifting to new hosts quickly. As illustrated in this article, the occurrence of specific virus-induced CNS lesions, for example demyelination, seems to be dependent upon a complex interplay between both virus-bound and species-bound, for example immunological factors. Examples of the latter are manifold, a risk factor for SSPE being below 2 years of age, MIBE solely occurring in immunocompromised patients, and a virus as rinderpest for example even having strains of different virulence and giving different disease presentations in different hosts.

Taking these considerations together, it seems possible that a morbillivirus, possibly a yet unknown- or ancestral one (Figure 1), could play a role in the pathogenesis of the human demyelinating disease MS. Such a virus itself would not even have to be present in the CNS anymore, triggering a specific upset of the immune system eventually leading to disease: the hit-run hypothesis [238]. It seems plausible to suspect that even a virus causing devastating, acute symptoms in one species could play another, subtler role in another species, remaining subclinical, remissive or disappearing after triggering an immunological upset, according to the susceptibility of the species and species-bound factors. Secondly, one should also ask if it is plausible to suspect that the species in which a virus is first discovered because of the extreme nature of acute symptoms, is also likely to be its natural host and main 'reservoir' of infection or is itself the victim of a cross-species infection. This emphasises the need to study demyelinating

DOI: 10.1002/rmv

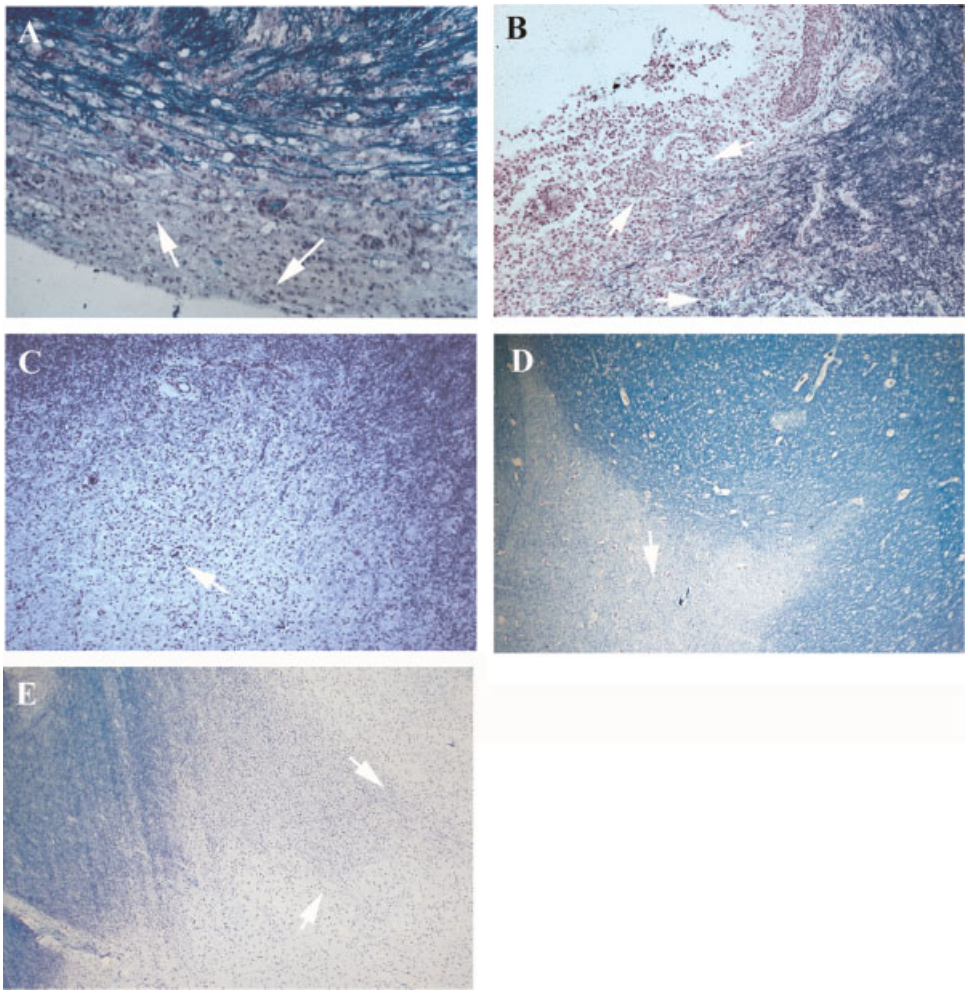

Figure 9. CNS demyelination induced by morbilliviruses (A–D) and CNS demyelination in MS (E). White arrows mark areas of demyelination. All sections are stained with Luxol Fast Blue and Cresyl Violet. (A) Acute phase of demyelination in a CDV-infected dog (pons). (B) Inflammatory demyelination in a CDV-infected dog 6 weeks post-infection. (C) Chronic phase of demyelination: demyelinated gliotic plaque in a CDV-infected dog (cerebellum). (D) Demyelination in a PDV-infected harbour seal. (E) Demyelination in MS

diseases in mammals other than humans with regard to MS, even if their presentation or prognosis in these mammals differs from MS in humans.

With regard to the specific aetiopathogenesis of the myelin destruction seen in morbillivirus infections, almost everything we know comes from studies on MV and CDV. The aquatic morbilliviruses certainly deserve specific neuropathologic attention because, when compared to MV and CDV, virtually nothing is known about the exact neuropathology and neuropathogenesis of morbillivirus-induced demyelination in aquatic mammals whereas such knowledge could be of great value. There seems to be no general consensus on the exact mechanisms by which morbilliviruses such as MV and CDV eventually elicit demyelination, especially in such differing patterns as seen in MV infection. Both viral and host factors seem to be very important and different mechanisms, such as autoimmune reactions and restrictive infection, have been postulated (Table 1).

As reviewed here, our present knowledge of morbillivirus neuropathogenesis raises challenging questions. In MV-induced encephalitis it is commonly difficult to demonstrate any virus. When the encephalitis has developed usually no virus can be discovered in ADEM or SSPE

DOI: 10.1002/rmv

Table 1. The occurrence of morbillivirus-induced demyelination in naturally infected mammals and suggested pathogenetic mechanism(s)

Virus	Naturally infected mammals	Demyelination	Suggested pathogenetic mechanism(s)
MV	Humans	+	ADEM: Auto-immune MIBE: ? SSPE: Viral persistence; Cell-mediated damage; Lysing CSF antibodies.
RPV	Large ruminants	− Neurovirulent in mice	
PPRV	Small ruminants	− Neurovirulent in mice	
CDV	Dogs	+	Acute phase: Restricted infection Chronic phase: Viral persistence; Bystander damage; Auto-immune
PDV	Seals	+	?
CeMV	Cetaceans	+	?

[5,18,38,39,46,62]. If MS is caused by a virus triggering a disease with prolonged incubation period, that is some sort of SSPE or combination of ADEM and SSPE, the interesting thought arises whether a virus causing MS should not possibly be sought in healthy persons years prior to the clinical manifestations of the disease in order to equivocally recover the causative factor of the disease. However, when looking for analogies between the neuropathology induced by viral infections of known origin and MS-neuropathology, it seems likely that viral 'signatures' can be found, based on similarities between both, which can provide more clues about the identity of a causative or triggering agent in MS. CDV raises another interesting question: virus can be demonstrated but is mostly present in the 'wrong' cells, that is astrocytes [10,125,129–133]. Whereas one would suspect a primary infection of oligodendrocytes when finding demyelination, only a small subpopulation of oligodendrocytes is infected in CDE. Furthermore, there seems to be no correlation between the amount of virus and severity of disease, especially in the chronic phase of the disease. From other examples, most strikingly HIV-encephalopathy, it is known too that a virus can infect cell types other than oligodendrocytes, in case of the latter macrophages and microglia, but yet cause demyelination [19,85,86]. The contribution of other cell types to the pathological processes leading to demyelination could play a substantial role and is certainly worth studying.

ACKNOWLEDGEMENTS

The authors would like to thank Professor Marc Vandevelde, Institute of Animal Neurology, University of Berne, Switzerland for his kind contribution of Figures 9A–9C, as well as the various other groups who kindly permitted us to use their figures in this article.

Furthermore, the authors would also like to thank Dr Paul Jepson and Robert Deaville (Zoological Society of London), Professor Thijs Kuiken and Professor Albert Osterhaus (Institute of Virology, Erasmus MC Rotterdam) and Dr Seamus Kennedy (Veterinary Sciences Division, Department of Agriculture and Rural Development for Northern Ireland, Belfast). All groups kindly provided us with brain tissue specimens of PDV-infected seals, as used in the staining shown in Figure 9D.

DOI: 10.1002/rmv

REFERENCES

1. Westover KM, Hughes AL. Molecular evolution of viral fusion and matrix protein genes and phylogenetic relationships among the *Paramyxoviridae*. *Mol Phylogenet Evol* 2001; **21**: 128–134.
2. Hall AJ. Morbilliviruses in marine mammals. *Trends Microbiol* 1995; **31**: 4–9.
3. Kennedy S. Morbillivirus infections in aquatic mammals. *J Comp Pathol* 1998; **119**: 201–225.
4. Harder TC, Osterhaus ADME. Canine distemper virus-a morbillivirus in search of new hosts? *Trends Microbiol* 1997; **5**: 120–124.
5. Rima BK, Duprex WP. Morbilliviruses and human disease. *J Pathol* 2006; **208**: 199–214.
6. Cattet MR, Duignan PJ, House CA, *et al.* Antibodies to canine distemper and phocine distemper viruses in polar bears from the Canadian arctic. *J Wildl Dis* 2004; **40**: 338–342.
7. Philippa JD, Leighton FA, Daoust PY, *et al.* Antibodies to selected pathogens in free-ranging terrestrial carnivores and marine mammals in Canada. *Vet Rec* 2004; **155**: 135–140.
8. Osterhaus A. Catastrophes after crossing species barriers. *Philos Trans R Soc Lond B Biol Sci* 2001; **356**: 791–793.
9. Cosby SL, Duprex WP, Hamill LA, *et al.* Approaches in the understanding of morbillivirus neurovirulence. *J Neurovirol* 2002; **2**: 85–90.
10. Vandevelde M, Zurbriggen A. Demyelination in canine distemper virus infection: a review. *Acta Neuropathol* 2005; **109**: 56–68.
11. Kennedy S, Smyth JA, Cush PF, *et al.* Histopathologic and immunocytochemical studies of distemper in seals. *Vet Pathol* 1989; **26**: 97–103.
12. Di Guardo G, Corradi A, Agrimi U, *et al.* Neuropathological lesions in cetaceans found stranded from 1991 to 1993 on the coasts of Italy. *Eur J Vet Pathol* 1995; **1**: 47–51.
13. Compston A, Coles A. Multiple sclerosis. *Lancet* 2002; **359**: 1221–1231.
14. Cook SD, Blumberg B, Dowling PC. Potential role of paramyxoviruses in multiple sclerosis. *Neurol Clin* 1986; **4**: 303–319.
15. Ohara Y. Multiple sclerosis and measles virus. *Jpn Infect Dis* 1999; **52**: 198–200.
16. Atkins GJ, McQuaid S, Morris-Downes MM, *et al.* Transient virus infection and multiple sclerosis. *Rev Med Virol* 2000; **10**: 291–303.
17. Cook SD, Rohowsky-Kochan C, Bansil S, *et al.* Evidence for multiple sclerosis as an infectious disease. *Acta Neurol Scand Suppl* 1995; **161**: 34–42.
18. Stohlman SA, Hinton DR. Viral induced demyelination. *Brain Pathol* 2001; **11**: 92–106.
19. Johnson RT. The virology of demyelinating diseases. *Ann Neurol* 1994; **36**: S54–S60.
20. Keegan BM, Noseworthy JH. Multiple sclerosis. *Annu Rev Med* 2002; **53**: 285–302.
21. Kandel ER, Schwartz JH, Jessel TM. *Principles of Neural Science*. McGraw-Hill: New York, 2000; 20–21.
22. Monto AS. Interrupting the transmission of respiratory tract infections: theory and practice. *Clin Infect Dis* 1999; **28**: 200–204.
23. Bryce J, Boschi-Pinto C, Shibuya K, *et al.* WHO estimates of the causes of death in children. *Lancet* 2005; **365**: 1147–1152.
24. Wild TF. Measles vaccines, new developments and immunization strategies. *Vaccine* 1999; **17**: 1726–1729.
25. Fielding AK. Measles as a potential oncolytic virus. *Rev Med Virol* 2005; **15**: 135–142.
26. Norrby E, Salmi AA, Vandvik B, *et al.* The antibody response to different measles virus antigens under various conditions of immunization. *Adv Exp Med Biol* 1972; **31**: 49–69.
27. Norrby E, Gollmar Y. Identification of measles virus-specific hemolysis-inhibiting antibodies separate from hemagglutination-inhibiting antibodies. *Infect Immun* 1975; **11**: 231–239.
28. Tyrrell DL, Ehrnst A. Transmembrane communication in cells chronically infected with measles virus. *J Cell Biol* 1979; **81**: 396–402.
29. Suryanarayana K, Baczko K, Ter Meulen V, *et al.* Transcription inhibition and other properties of matrix proteins expressed by M genes cloned from measles virus and diseased human brain tissue. *J Virol* 1994; **68**: 1532–1543.
30. Taylor MJ, Godfrey E, Baczko K, *et al.* Identification of several different lineages of measles virus. *J Gen Virol* 1991; **72**: 83–88.
31. Rima BK, Earle JA, Baczko K, *et al.* Sequence divergence of measles virus haemagluttin during natural evolution and adaptation to cell culture. *J Gen Virol* 1997; **78**: 97–106.
32. Rota JS, Hummel KB, Rota PA, *et al.* Genetic variability of the glycoprotein genes of current wild-type measles isolates. *Virology* 1994; **188**: 135–142.
33. Rota PA, Bloom AE, Vanchiere JA, *et al.* Evolution of the nucleoprotein and matrix genes of wild-type strains of measles virus isolated from recent epidemics. *Virology* 1994; **198**: 724–730.
34. Hall WC, Kovatch RM, Herman PH, *et al.* Pathology of measles in rhesus monkeys. *Vet Pathol* 1971; **8**: 307–319.
35. Kerdiles YM, Sellin CI, Druelle J, *et al.* Immunosuppression caused by measles virus: role of viral proteins. *Rev Med Virol* 2006; **16**: 49–63.
36. Kerdiles YM, Cherif B, Marie JC, *et al.* Immunomodulatory properties of morbillivirus nucleoproteins. *Viral Immunol* 2006; **19**: 324–334.

DOI: 10.1002/rmv

37. Liebert UG. Measles virus infections of the central nervous system. *Intervirology* 1997; **40**: 176–184.
38. Norrby E, Kristensson K. Measles virus in the brain. *Brain Res Bull* 1997; **44**: 213–220.
39. Menge T, Hemmer B, Nessler S, *et al.* Acute disseminated encephalomyelitis: an update. *Arch Neurol* 2005; **62**: 1673–1680.
40. Leake JA, Albani S, Kao AS, *et al.* Acute disseminated encephalomyelitis in childhood: epidemiologic, clinical and laboratory features. *Pediatr Infect Dis J* 2004; **23**: 756–764.
41. Murthy SN, Faden HS, Cohen ME, *et al.* Acute disseminated encephalomyelitis in children. *Pediatrics* 2002; **110**: e21.
42. Hynson JL, Kornberg AJ, Coleman LT, *et al.* Clinical and neuroradiologic features of acute disseminated encephalomyelitis in children. *Neurology* 2001; **56**: 1308–1312.
43. Tenembaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: a long-term follow-up study of 84 pediatric patients. *Neurology* 2002; **59**: 1224–1231.
44. Nasr JT, Andriola MR, Coyle PK. ADEM: literature review and case report of acute psychosis presentation. *Pediatr Neurol* 2000; **22**: 8–18.
45. Khong PL, Ho HK, Cheng PW, *et al.* Childhood acute disseminated encephalomyelitis: the role of brain and spinal cord MRI. *Pediatr Radiol* 2002; **32**: 59–66.
46. Gendelman HE, Wolinsky JS, Johnson RT, *et al.* Measles encephalomyelitis: lack of evidence of viral invasion of the central nervous system and quantitative study of the nature of demyelination. *Ann Neurol* 1984; **15**: 353–360.
47. Gendelman HE, Pezeshkpour GH, Pressman NJ, *et al.* A quantitation of myelin-associated glycoprotein and myelin basic protein loss in different demyelinating diseases. *Ann Neurol* 1985; **18**: 324–328.
48. Wegner C. Pathological differences in acute inflammatory demyelinating diseases of the central nervous system. *Int MS J* 2005; **12**: 13–19.
49. Aicardi J, Goutieres F, Arsenio-Nunes ML, *et al.* Acute measles encephalitis in children with immunosuppression. *Pediatrics* 1977; **59**: 232–239.
50. Hughes I, Jenney MEM, Newton RW, *et al.* Measles encephalitis during immunosuppressive treatment for acute lymphoblastic leukaemia. *Arch Dis Child* 1993; **68**: 775–778.
51. Mustafa MM, Weitman SD, Winick NJ, *et al.* Subacute measles encephalitis in the young immunocompromised host: report of two cases diagnosed by polymerase chain reaction and treated with ribavirin and review of the literature. *Clin Infect Dis* 1993; **16**: 654–660.
52. Mawhinney H, Allen IV, Beare JM, *et al.* Dysgammaglobulinaemia complicated by disseminated measles. *Br Med J* 1971; **2**: 380–381.
53. Valmari P, Lanning M, Tuokko H, *et al.* Measles virus in the cerebrospinal fluid in postvaccination immunosuppressive measles encephalopathy. *Pediatr Infect Dis* 1987; **6**: 641–649.
54. Bitnun A, Shannon P, Durward A, *et al.* Measles inclusion-body encephalitis caused by the vaccine strain of measles virus. *Clin Infect Dis* 1999; **29**: 855–861.
55. Freeman AF, Jacobsohn DA, Shulman ST, *et al.* A new complication of stem cell transplantation: measles inclusion body encephalitis. *Pediatrics* 2004; **114**: 657–660.
56. Takasu T, Mgone JM, Mgone CS, *et al.* A continuing high incidence of subacute sclerosing panencephalitis (SSPE) in the Eastern Highlands of Papua New Guinea. *Epidemiol Infect* 2003; **131**: 887–898.
57. Fazakerley JK, Walker R. Virus demyelination. *J Neurovirol* 2003; **9**: 148–164.
58. Modlin JF, Jabbour JR, Witte JJ, *et al.* Epidemiologic studies of measles; measles vaccines and subacute sclerosing panencephalitis. J Pediatrics 1977; **94**: 231–236.
59. Modlin JF, Halsey NA, Eddins DL, *et al.* Epidemiology of subacute sclerosing panencephalitis. *J Pediatrics* 1979; **94**: 231–236.
60. Jabbour JT, Duenas DA, Sever JL, *et al.* Epidemiology of subacute sclerosing panencephalitis (SSPE). A report of the SSPE registry. *J Am Med Assoc* 1972; **220**: 959–962.
61. Halsey NA, Modlin JF, Jabbour JT, *et al.* Risk factors in subacute sclerosing panencephalitis: a case-control study. *Am J Epidemiol* 1980; **111**: 415–424.
62. Garg RK. Subacute sclerosing panencephalitis. *Postgrad Med J* 2002; **78**: 63–70.
63. Connolly JH, Allen IV, Hurwitz LJ, *et al.* Measles virus antibody and antigen in subacute sclerosing panencephalitis. *Lancet* 1967; **1**: 542–544.
64. Dawson J. Cellular inclusions in cerebral lesions of lethargic encephalitis. *Am J Pathol* 1933; **9**: 7–16.
65. Perier O, Vanderhaeghen JJ, Pelc S. Subacute sclerosing panencephalitis. Electron microscopic findings in two cases with inclusion bodies. *Acta Neuropathol* 1967; **8**: 362–380.
66. McQuaid S, Kirk J, Zhou AL, *et al.* Measles virus infection of cells in perivascular infiltrates in the brain in subacte sclerosing panencephalitis: confirmation by non-radioactive *in situ* hybridization, immunocytochemistry and electron microscopy. *Acta Neuropathol* (Berlin) 1993; **85**: 154–158.
67. Kirk J, Zhou AL, McQuaid S, *et al.* Cerebral endothelial cell infection by measles virus in subacute sclerosing panencephalitis: ultrastructural and

DOI: 10.1002/rmv

in situ hybridization evidence. *Neuropathol Appl Neurobiol* 1991; **17**: 289–297.
68. Smith-Jensen T, Burgoon MP, Anthony J, *et al.* Comparison of immunoglobulin G heavy-chain sequences in MS and SSPE brains reveals an antigen-driven response. *Neurology* 2000; **54**: 1227–1232.
69. Hall WW, Choppin PW. Evidence for lack of synthesis of the M polypeptide of measles virus in brain cells in subacute sclerosing panencephalitis. *Virology* 1979; **99**: 443–447.
70. Khadilkar SV, Patil SG, Kulkarni KS. A study of SSPE: early clinical features. *J Pediatr Neurol* 2004; **2**: 73–77.
71. Simsek E, Ozturk A, Yavuz C, *et al.* Subacute sclerosing panencephalitis (SSPE) associated with congenital measles infection. *Turk J Pediatr* 2005; **47**: 58–62.
72. Hall WW, Choppin PW. Measles virus proteins in the brain tissue of patients with subacute sclerosing panencephalitis. *N Engl J Med* 1981; **304**: 1152–1155.
73. Cattaneo R, Schmid A, Spielhofer P, *et al.* Mutated and hypermutated genes of persistent measles viruses which caused lethal human brain diseases. *Virology* 1989; **173**: 415–425.
74. Billeter MA, Cattaneo R, Spielhofer P, *et al.* Generation and properties of measles virus mutations typically associated with subacute sclerosing panencephalitis. *Ann N Y Acad Sci* 1994; **724**: 367–377.
75. Cattaneo R, Schmid A, Billeter MA, *et al.* Multiple viral mutations rather than host factors cause defective measles virus gene expression in a subacute sclerosing panencephalitis cell line. *J Virol* 1988; **62**: 1388–1397.
76. Fujinami RS, Oldstone MB. Alterations in expression of measles virus polypeptides by antibody: molecular events in antibody-induced antigenic modulation. *J Immunol* 1985; **125**: 78–85.
77. Rammohan KW, McFarland HF, Bellini WJ, *et al.* Antibody-mediated modification of encephalitis induced by hamster neurotropic measles virus. *J Infect Dis* 1981; **147**: 546–549.
78. Rammohan KW, McFarland HF, McFarlin DE. Induction of subacute murine measles encephalitis by monoclonal antibody to virus haemagglutinin. *Nature* 1981; **290**: 588–589.
79. Wear DJ, Rapp F. Latent measles virus infection of the hamster central nervous system. *J Immunol* 1971; **107**: 1593–1598.
80. Liebert UG, Schneider-Schaulies SM, Baczko K, *et al.* Antibody-induced restriction of viral gene expression in measles encephalitis in rats. *J Virol* 1990; **64**: 706–713.
81. Hanninen P, Arstila P, Lang H, *et al.* Involvement of the central nervous system in acute, uncomplicated measles virus infection. *J Clin Microbiol* 1980; **11**: 610–613.
82. Hickey WF, Hsu BL, Kimura H. T lymphocyte entry into the central nervous system. *J Neurosci Res* 1990; **28**: 254.
83. Griffin DE, Levine B, Tylor W, *et al.* The role of antibody in recovery from alphavirus encephalitis. *Immunol Rev* 1997; **159**: 155–161.
84. Knopf PM, Harling-Berg CJ, Cserr HF, *et al.* Antigen-dependent intrathecal synthesis in the normal rat brain: tissue entry and local retention of antigen-specific B cells. *J Immunol* 1998; **161**: 692–701.
85. Haase AT. Pathogenesis of lentivirus infections. *Nature* 1986; **322**: 130–136.
86. Gendelman HE, Gendelman S. Neurological aspects of human immunodeficiency virus infection. In *Neuropathogenic Viruses and Immunity*, Specter S, Bendinelli M, Friedman H (eds). Plenu Press: New York, 1992; 229–254.
87. Bergsteinsdottir K, Arnadottir S, Torsteinsdottir S, *et al.* Constitutive and visna virus induced expression of class I and II major histocompatibility complex antigens in the central nervous system of sheep and their role in the pathogenesis of visna lesions. *Neuropathol Appl Neurobiol* 1998; **24**: 224–232.
88. Oldstone MBA, Boskisch VA, Dixon FJ. Subacute sclerosing panencephalitis: destruction of human brain cells by antibody and complement in an autologous system. *Clin Immunol Immunopath* 1975; **4**: 52–58.
89. Ikeda K, Abiyama H, Kondo H, *et al.* Numerous glial fibrillary tangles in oligodendroglia in cases of subacute sclerosing panencephalitis with neurofibrillary tangles. *Neurosci Lett* 1995; **194**: 133–135.
90. Hofman FM, Hinton DR, Baemayr J, *et al.* Lymphokines and immunoregulatory molecules in subacute sclerosing panencephalitis. *Clin Immunopathol* 1991; **58**: 331–342.
91. Nagano I, Nakamura S, Yoshioka M, *et al.* Expression of cytokines in brain lesions in subacute sclerosing panencephalitis (SSPE). *Neurology* 1994; **44**: 710–715.
92. Roeder PL, Taylor WP. Rinderpest. *Vet Clin North Am Food Anim Pract* 2002; **18**: 515–547.
93. Anderson J, Barrett T. Manual of the diagnosis of Rinderpest. FAO Animal Health Manual (1) 1996; 143 pp.
94. Barrett T, Rossiter PB. Rinderpest: the disease and its impact on humans and animals. *Adv Virus Res* 1999; **53**: 89–110.
95. Chamberlain RW, Wamwayi HN, Hockley E, *et al.* Evidence for different lineages of rinderpest virus reflecting their geographic isolation. *J Gen Virol* 1993; **74**: 2775–2780.

DOI: 10.1002/rmv

96. Wohlsein P, Wamwayi HM, Trautwein G, *et al.* Pathomorphological and immunohistochemical findings in cattle experimentally infected with rinderpest virus isolates of different pathogenecity. *Vet Microbiol* 1995; **44**: 141–147.
97. Rey Nores JE, McCullough KC. Rinderpest virus isolates of different virulence may vary in their capacity to infect bovine monocytes and macrophages. *J Gen Virol* 1997; **78**: 1875–1884.
98. Taylor WP. Epidemiology and control of rinderpest. *Rev Sci Tech Off Int Epiz* 1986; **5**: 407–410.
99. Wafula JS, Kariuki DP. A recent outbreak of rinderpest in East Africa. *Trop Anim Hlth Prod* 1987; **19**: 173–176.
100. Wamwayi HM, Kariuki DP, Wafula JS, *et al.* Observations on rinderpest in Kenya 1986–1989. *Rev Sci Tech Off Int Epiz* 1992; **11**: 769–784.
101. Rossiter P, Wamwayi H, Ndungu E. Rinderpest seroprevalence in wildlife in Kenya and Tanzania 1982–1993. *Prev Vet Med* 2006; **17**: 1–7.
102. Wohlsein PG, Trautwein TC, Harder B, *et al.* Viral antigen distribution in organs of cattle experimentally infected with rinderpest virus. *Vet Pathol* 1993; **30**: 544–554.
103. Galbraith SE, McQuaid S, Hamill L, *et al.* Rinderpest and peste des petits ruminants viruses exhibit neurovirulence in mice. *J Neurovirol* 2002; **8**: 45–52.
104. Gibbs EPJ, Taylor WP, Lawman MJP, *et al.* Classification of peste des petits ruminants virus as the fourth member of the genus Morbillivirus. *Intervirology* 1979; **11**: 268–274.
105. Haffar A, Libeau G, Moussa A, *et al.* The matrix protein gene sequence analysis reveals close relationship between peste des petits ruminants virus (PPRV) and dolphin morbillivirus. *Virus Res* 1999; **64**: 69–75.
106. Bailey D, Banyard A, Dash P, *et al.* Full genome sequence of peste des petits ruminants virus, a member of the morbillivirus genus. *Virus Res* 2005; **110**: 119–124.
107. Dhar P, Sreenivasa BP, Barrett T, *et al.* Recent epidemiology of peste des petits ruminants virus (PPRV). *Vet Microbiol* 2002; **88**: 153–159.
108. Lefevre PC, Diallo A. La peste des petits ruminants. *Rev Sci Tech Off Int Epiz* 1990; **9**: 935–950.
109. Shaila MS, Purushothaman V, Bhavasar D, *et al.* Peste des petits ruminants virus of sheep in India. *Vet Rec* 1989; **125**: 602.
110. Taylor WP, Diallo A, Gopalkrishna S, *et al.* Peste des petits ruminants has been widely present in southern India since, if not before, the late 1980s. *Prev Vet Med* 2002; **52**: 1–8.
111. Shaila MS, Shamaki D, Forsyth MA, *et al.* Geographical distribution and epidemiology of peste des petits ruminants viruses. *Virus Res* 1996; **43**: 149–153.
112. Nanda YP, Chatterjee A, Purohit AK, *et al.* The isolation of peste des petits ruminants virus from northern India. *Vet Microbiol* 1996; **51**: 207–216.
113. Roeder PL, Obi TU. Recognizing peste des petits ruminants: a field manual. FAO Animal Health Manual (5) 1999; 28 pp.
114. Wamwayi HM, Rossiter PB, Kariuki DP, *et al.* Peste des petits ruminants antibodies in east Africa. *Vet Rec* 1995; **136**: 199–200.
115. Roeder PL, Abraham G, Kenfe G, *et al.* Peste des petits ruminants in Ethiopian goats. *Trop Anim Hlth Prod* 1994; **26**: 69–73.
116. Kumar P, Tripathi BN, Sharma AK, *et al.* Pathological and immunohistochemical study of experimental peste des petits ruminants virus infection in goats. *J Vet Med B Infect Dis Vet Public Health* 2004; **51**: 153–159.
117. Toplu N. Characteristic and non-characteristic pathological findings in peste des petits ruminants (PPR) of sheep in the Ege District of Turkey. *J Comp Path* 2004; **131**: 135–141.
118. Aruni AW, Lalitha PS, Mohan AC, *et al.* Histopathological study of a natural outbreak of peste des petits ruminants in goats of Tamilnadu. *Small Rumin Res* 1998; **28**: 233–240.
119. Brown CC, Mariner JC, Olander HJ. An immunohistochemical study of the pneumonia caused by peste des petits ruminants virus. *Vet Pathol* 1991; **28**: 166–170.
120. Bundza A, Afshar A, Dukes WD, *et al.* Experimental peste des petits ruminants (goat plaque) in goats and sheep. *Can J Vet Res* 1988; **52**: 46–52.
121. Appel MJ. Pathogenesis of canine distemper. *Am J Vet Res* 1969; **30**: 1167–1182.
122. Krakowka S, Higgins RJ, Koestner A. Canine distemper virus: review of structural and functional modulations in lymphoid tissues. *Am J Vet Res* 1980; **41**: 284–292.
123. Rudd PA, Cattaneo R, Von Messling V. Canine distemper virus uses both the anterograde and hematogenous pathway for neuroinvasion. *J Virol* 2006; **80**: 9361–9370.
124. Higgins RJ, Krakowka SG, Metzler A, *et al.* Primary demyelination in experimental canine distemper virus induced encephalomyelitis in gnotobiotic dogs. Sequential immunologic and morphologic findings. *Acta Neuropathol* 1982; **58**: 1–8.
125. Higgins RJ, Krakowka SG, Metzler AE, *et al.* Experimental canine distemper encephalomyelitis in neonatal gnotobiotic dogs. A sequential ultrastructural study. *Acta Neuropathol* 1982; **57**: 287–295.
126. Summers BA, Greisen HA, Appel MJ. Early events in canine distemper demyelinating encephalomyelitis. *Acta Neuropathol* 1979; **46**: 1–10.

DOI: 10.1002/rmv

127. Vandevelde M, Zurbriggen A, Higgins RJ, *et al.* Spread and distribution of viral antigen in nervous canine distemper. *Acta Neuropathol* 1985; **67**: 211–218.
128. Zurbriggen A, Schmid I, Graber H, *et al.* Oligodendroglial pathology in canine distemper. *Acta Neuropathol* 1998; **95**: 71–77.
129. Mutinelli F, Vandevelde M, Griot C, *et al.* Astrocytic infection in canine distemper virus-induced demyelination. *Acta Neuropathol* 1989; **77**: 333–335.
130. Blakemore WF, Summers BA, Appel MG. Evidence of oligodendrocyte infection and degeneration in canine distemper encephalomyelitis. *Acta Neuropathol* 1989; **77**: 550–553.
131. Raine CS. On the development of CNS lesions in natural canine distemper encephalomyelitis. *J Neurol Sci* 1976; **30**: 13–28.
132. Summers BA, Appel MJ. Demyelination in canine distemper encephalomyelitis: an ultrastructural analysis. *J Neurocytol* 1987; **16**: 871–881.
133. Wisniewski H, Raine CS, Kay WJ. Observations on viral demyelinating encephalomyelitis. Canine distemper. *Lab Invest* 1972; **26**: 589–599.
134. Zurbriggen A, Yamawaki M, Vandevelde M. Restricted canine distemper virus infection of oligodendrocytes. *Lab Invest* 1993; **68**: 277–284.
135. Glaus TC, Griot C, Richard A, *et al.* Ultrastructural and biochemical findings in brain cell cultures infected with canine distemper virus. *Acta Neuropathol* 1990; **80**: 59–67.
136. Graber H, Müller C, Vandevelde A, *et al.* Restricted infection with canine distemper virus leads to down-regulation of myelin gene transcription in cultured oligodendrocytes. *Acta Neuropathol* 1995; **90**: 312–318.
137. Schobesberger M, Zurbriggen A, Summerfield A, *et al.* Oligodendroglial degeneration in distemper: apoptosis or necrosis? *Acta Neuropathol* 1999; **97**: 179–187.
138. Schobesberger M, Zurbriggen A, Doherr MG, *et al.* Demyelination precedes oligodendrocyte loss in canine distemper virus-induced encephalitis. *Acta Neuropathol* 2002; **103**: 11–19.
139. Alldinger S, Wunschmann A, Baumgärtner W, *et al.* Up-regulation of major histocompatibility complex class II antigen expression in the central nervous system of dogs with spontaneous canine distemper encephalitis. *Acta Neuropathol* 1996; **92**: 273–280.
140. Brügger M, Jungi TW, Zurbriggen A, *et al.* Canine distemper virus increases procoagulant activity of macrophages. *Virology* 1992; **190**: 616–623.
141. Botteron C, Zurbriggen A, Griot C, *et al.* Canine distemper virus-immune complexes induce bystander degeneration of oligodendrocytes. *Acta Neuropathol* 1992; **83**: 402–407.
142. Griot-Wenk M, Griot C, Pfister H, *et al.* Antibody-dependent cellular cytotoxicity in antimyelin antibody-induced olgodendroglial damage *in vitro*. *J Neuroimmunol* 1991; **33**: 145–155.
143. Tipold A, Moore P, Zurbriggen A, *et al.* Early T-cell response in the central nervous system in canine distemper virus infection. *Acta Neuropathol* 1999; **97**: 45–56.
144. Barben G, Stettler M, Jaggy A, *et al.* Detection of IgM antibodies against the nucleocapsid protein of canine distemper virus in dog sera using a dot-blot-assay. *J Vet Med A* 1999; **46**: 115–121.
145. Miao Q, Baumgartner W, Failing K, *et al.* Phase-dependent expression of matrix metalloproteinases and their inhibitors in demyelinating canine distemper encephalitis. *Acta Neuropathol* 2003; **106**: 468–494.
146. Markus S, Failing K, Baumgartner W. Increased expression of pro-inflammatory cytokines and lack of up-regulation of anti-inflammatory cytokines in early distemper lesions. *J Neuroimmunol* 2002; **125**: 30–41.
147. Gröne A, Fonfara S, Baumgartner W. Cell type-dependent cytokine expression after canine distemper virus infection. *Viral Immunol* 2002; **15**: 493–505.
148. Vandevelde M, Fankhauser R, Kristensen F, *et al.* Immunoglobulins in demyelinating lesions in canine distemper encephalitis. An immunohistological study. *Acta Neuropathol* 1981; **54**: 31–41.
149. Vandevelde M, Kristensen F, Kristensen B, *et al.* Immunological and pathological findings in demyelinating encephalitis associated with canine distemper virus infection. *Acta Neuropathol* 1982; **56**: 1–8.
150. Vandevelde M, Zurbriggen A, Steck A, *et al.* Studies on the intrathecal humoral immune response in canine distemper encephalitis. *J Neuroimmunol* 1986; **11**: 41–51.
151. Wunschmann A, Alldinger S, Kremmer E, *et al.* Identification of CD4+ and CD8+ T cell subsets and b cells in the brain of dogs with acute-, subacute- and chronic-demyelinating distemper encephalitis. *Vet Immunol Immunopathol* 1999; **67**: 101–116.
152. Bürge T, Griot C, Vandevelde M, *et al.* Antiviral antibodies stimulate production of reactive oxygen species in cultured canine brain cells infected with canine distemper. *J Virol* 1989; **63**: 2790–2797.
153. Griot C, Bürge T, Vandevelde M, *et al.* Antibody-induced generation of reactive oxygen radicals by brain macrophages in canine distemper encephalitis: a mechanism for bystander demyelination. *Acta Neuropathol* 1989; **78**: 396–403.
154. Griot C, Bürge T, Vandevelde M, *et al.* Bystander demyelination through antibody induced macro-

DOI: 10.1002/rmv

phage activation in canine distemper virus infection. Schweiz Arch Neurol Psychiatr 1989; **140**: 39–41.
155. Krakowka S, McCullough B, Koestner A, *et al.* Myelin-specific autoantibodies associated with central nervous system demyelination in canine distemper virus infection. *Infect Immun* 1973; **8**: 819–827.
156. Cerruti Sola S, Kristensen F, Vandevelde M, *et al.* Lymphocyte responsiveness to lectin and myelin antigens in canine distemper infection in relation to the development of demyelinating lesions. *J Neuroimmunol* 1983 4: 77–90.
157. Summers BA, Greisen HA, Appel MJ. Canine distemper and experimental allergic encephalomyelitis in the dog: comparative patterns of demyelination. *J Comp Pathol* 1984; **94**: 575–589.
158. Bollo E, Zurbriggen A, Vandevelde M, *et al.* Canine distemper virus clearance in chronic inflammatory demyelination. *Acta Neuropathol* 1986; **72**: 69–73.
159. Müller C, Fatzer R, Beck K, *et al.* Studies on canine distemper virus persistence in the nervous system. *Acta Neuropathol* 1995; **89**: 438–445.
160. Zurbriggen A, Grabber H, Wagner A, *et al.* Canine distemper persistence in the nervous system is associated with noncytolytic virus spread. *J Virol* 1995; **69**: 1678–1686.
161. Meertens N, Stoffel MH, Cherpillod P, *et al.* Mechanism of reduction of virus release and cell-cell fusion in persistent canine distemper virus infection. *Acta Neuropathol* 2003; **106**: 486–494.
162. Volterra A, Meldolesi J. Astrocytes, from brain glue to communication elements: the revolution continues. *Nature Rev Neurosci* 2005; **6**: 626–640.
163. Seifert G, Schilling K, Steinhäuser C. Astrocyte dysfunction in neurological disorders: a molecular perspective. 2006; **7**: 194–206.
164. De Keyser J, Wilczak N, Walter JH *et al*. Disappearance of beta2-adrenergic receptors on astrocytes in canine distemper encephalitis: possible implications for the pathogenesis of multiple sclerosis. *Neuroreport* 2001; **12**: 191–194.
165. De Keyser J, Wilczak N, Leta R, *et al*. Astrocytes in multiple sclerosis lack beta-2 adrenergic receptors. Neurology 1999; **53**:1628–1633.
166. Zeinstra E, Te Riele P, Langlois X, *et al*. Aminergic receptors in astrogliotic plaques from patients with multiple sclerosis. *Neurosci Lett* 2002; **331**: 87–90.
167. Alldinger S, Fonfara S, Kremmer E, *et al*. Up-regulation of the hyalonurate receptor CD44 in canine distemper demyelinated plaques. *Acta Neuropathol* 2000; **99**:138–146.
168. Zeinstra E, Wilczak N, Streefland C, *et al*. Astrocytes in chronic active multiple sclerosis plaques express MHC class II molecules. *Neuroreport* 2000; **11**:89–91.
169. De Keyser J, Zeinstra E, Frohman E. Are astrocytes central players in the pathophysiology of multiple sclerosis? *Arch Neurol* 2003; **60**:132–136.
170. De Keyser J, Zeinstra E, Wilczak N. Astrocytic β2-adrenergic receptors and multiple sclerosis. *Neurobiol Dis* 2003; **15**:331–339.
171. De Keyser J, Zeinstra E, Mostert J, *et al*. β2-Adrenoreceptor involvement in inflammatory demyelination and axonal degradation in multiple sclerosis. *Trends Pharmacol Sci* 2004; **25**:67–71.
172. Kennedy S. Morbillivirus infections in aquatic mammals. *J Comp Pathol* 2005; **119**: 201–225.
173. Osterhaus AD, Vedder EJ. Identification of virus causing recent seal deaths. *Nature* 1988; **335**: 20.
174. Osterhaus A. A morbillivirus causing recent seal deaths. *Vaccine* 1989; **7**: 483–484.
175. Kennedy S, Smyth JA, McCullough SJ, *et al*. Confirmation of cause of recent seal deaths. *Nature* 1988; **335**: 404.
176. Have P, Nielsen J, Botner A. The seal deaths in Danish waters 1998 2. Virological studies. *Acta Vet Scand* 1991; **32**: 211–219.
177. Kennedy S. A review of the 1988 European seal morbillivirus epizootic. *Vet Rec* 1990; **127**: 563–567.
178. Di Guardo G, Marruchella G, Agrimi U, *et al.* Morbillivirus infections in aquatic mammals: a brief overview. *J Vet Med* 2005; **52**: 88–93.
179. Rima BK, Curran MD, Kennedy S. Phocine distemper virus, the agent responsible for the 1988 mass mortality of seals. *Sci Total Environ* 1992; **115**: 45–55.
180. Hall AJ, Pomeroy PP, Harwood J. The descriptive epizootiology of phocine distemper in the UK during 1988/1989. *Sci Total Environ* 1992; **115**: 31–44.
181. Hall AJ. Morbilliviruses in marine mammals. *Trends Microbiol* 1995; **31**: 4–9.
182. Heide-Jorgensen MP, Harkonen T, Dietz R, *et al.* Retrospective of the 1988 European seal epizootic. *Dis Aquat Organ* 1992; **13**: 37–62.
183. Krogsrud J, Evensen O, Holt G, *et al.* Seal distemper in Norway in 1988 and 1989. *Vet Rec* 1990; **126**: 460–461.
184. Jauniaux T, Boseret G, Desmecht M, *et al.* Morbillivirus in common seals stranded on the coast of Belgium and northern France. *Vet Rec* 2001; **148**: 587–591.
185. Visser IK, Vedder EJ, Vos HW, *et al.* Continued presence of phocine distemper virus in the Dutch wadden sea seal population, *Vet Rec* 1993; **133**: 320–322.
186. Duignan PJ, Sadove S, Saliki JT, *et al.* Phocine distemper in harbour seals (Phoca vitulina) from Long Island, New York. *J Wildl Dis* 1993; **29**: 465–469.
187. Daoust PY, Haines DM, Thorsen J, *et al*. Phocine distemper in a harp seal (Phoca groenlandica) from the Gulf of St. Lawrence, Canada. *J Wildl Dis* 1993; **29**: 114–117.

DOI: 10.1002/rmv

188. Ross PS, Visser IK, Broeders HW, *et al.* Antibodies to phocine distemper virus in Canadian seals. *Vet Rec* 1992; **127**: 563–567.
189. Henderson G, Trudgett A, Lyons C, *et al.* Demonstration of antibodies in archival sera from Canadian seals reactive with a European isolate of phocine distemper virus. *Sci Total Environ* 1992; **115**: 93–98.
190. De Swart RL, Harder TC, Ross PS, *et al.* Morbillivirus and morbillivirus diseases of marine mammals. *Infect Agents Dis* 1995; **4**: 125–130.
191. Duignan PJ, Nielsen O, House C, *et al.* Epizootiology of morbillivirus infection in harp, hooded and ringed seals from the Canadia Arctic and western Atlantic. *J Wildl Dis* 1997; **33**: 7–19.
192. Duignan PJ, Saliki JT, St Aubin DJ, *et al.* Epizootiology of morbillivirus infection in North American harbour seals (Phoca vitulina) and gray seals (Halichoerus grypus). *J Wildl Dis* 1995; **31**: 491–501.
193. Jensen T, van de Bildt M, Dietz HH, *et al.* Another phocine distemper outbreak in Europe. *Science* 2002; **297**: 209.
194. Müller G, Wohlsein P, Beineke A, *et al.* Phocine distemper in German seals 2002. *Infect Dis* 2004; **10**: 723–725.
195. Rijks JM, van De Bildt MW, Jensen T, *et al.* Phocine distemper outbreak, The Netherlands, 2002. *Emerg Infect Dis* 2005; **11**: 1945–1948.
196. Harkonen T, Dietz R, Reijnders P, *et al.* The 1988 and 2002 phocine distemper virus epidemics in European harbour seals. *Dis Aquat Organ* 2006; **68**: 115–130.
197. De Koeijer A, Diekmann O, Reijnders P. Modelling the spread of phocine distemper virus among harbour seals. *Bull Math Biol* 1998; **60**: 585–596.
198. Harkonen T, Dietz R, Reijnders P, *et al.* The 1988 and 2002 phocine distemper virus epidemics in European harbour seals. *Dis Aquat Organ* 2006; **68**: 115–130.
199. Cosby SL, McQuaid S, Duffy N, *et al.* Characterization of a seal morbillivirus. *Nature* 1988; **336**: 115–116.
200. Orvell C, Sheshberadaran H. Phocine distemper virus is phylogenetically related to canine distemper virus. *Vet Rec* 1991; **129**: 267–269.
201. Harder TC, Moennig V, Greiserwilke I, *et al.* Analysis of antigenic differences between 16 phocine distemper virus isolates and other morbilliviruses. *Arch Virol* 1991; **118**: 261–268.
202. Blixenkrone-Moller M, Svansson V, Appel M, *et al.* Antigenic relationships between field isolates of morbilliviruses from different carnivores. *Arch Virol* 1992; **123**: 279–294.
203. Blixenkrone-Moller M, Sharma B, Varsanyi TM, *et al.* Sequence analysis of the genes encoding the nucleocapsid protein and phosphoprotein (P) of phocid distemper virus, and editing of the P gene transcript. *J Gen Virol* 1992; **73**: 885–893.
204. Curran MD, Rima BK. The genes encoding the phosphoproteins and matrix proteins of phocine distemper virus. *J Gen Virol* 1992; **73**: 1587–1591.
205. Curran MD, O'Lean D, Kennedy S, *et al*. Molecular characterization of phocine distemper virus-gene order and sequence of the gene encoding the attachment (H) protein. *J Gen Virol* 1992; **73**: 1189–1194.
206. Curran MD, Lu YJ, Rima BK. The fusion protein gene of phocine distemper virus-nucleotide and deduced amino acid sequences and a comparison of morbillivirus fusion proteins. *Arch Virol* 1992; **126**: 159–169.
207. Rima BK, Curran MD, Kennedy S. Phocine distemper virus, the agent responsible for the 1988 mass mortality of seals. *Sci Total Environ* 1992; **115**: 45–55.
208. Sharma B, Norrby E, Blixenkrone-Moller M, *et al.* The nucleotide and deduced amino acid sequence of the M gene of phocid distemper virus (PDV)—the most conserved protein of morbilliviruses shows a uniquely close relationship between PDV and canine distemper virus. *Virus Res* 1992; **13**: 13–25.
209. Kovamees J, Blixenkrone-Moller M, Sharma B, *et al.* The nucleotide sequence and deduced amino acid composition of the haemagglutin and fusion proteins of the morbillivirus phocid distemper virus. *J Gen Virol* 1991; **72**: 2959–2966.
210. Visser IK, van der Heijden RW, van de Bildt MW, *et al.* Fusion protein gene nucleotide sequence similarities, shared antigenic sites and phylogenetic analysis suggest that phocid distemper virus type 2 and canine distemper virus belong to the same virus entity. *J Gen Virol* 1993; **74**: 1989–1994.
211. Barrett T, Visser IK, Mamaev L, *et al.* Dolphin and porpoise morbilliviruses are genetically distinct from phocine distemper virus. *Virology* 1993; **193**: 1010–1012.
212. Harder T, Willhaus T, Frey HR, *et al.* Morbillivirus infections of seals during the 1988 epidemic in the Bay of Heligoland III. Transmission studies of cell culture-propagated phocine distemper virus in harbour seals (Phoca vitulina) and a gray seal (Halichoerus grypus)-clinical, virological and serological results. *J Vet Med Ser B* 1990; **37**: 641–650.
213. Kennedy S, Smyth JA, Cush PF, *et al.* Viral distemper now found in porpoises. *Nature* 1988; **336**: 21.
214. Kennedy S, Kuiken T, Ross HM, *et al.* Morbillivirus infection in two common porpoises (Phocoena phocoena) from the coasts of England and Scotland. *Vet Rec* 1992; **131**: 286–290.
215. Visser IKG, van Bressem MF, de Swart RL, *et al.* Characterization of morbilliviruses isolated from

DOI: 10.1002/rmv

dolphins and porpoises in Europe. *J Gen Virol* 1993; **74**: 631–641.
216. McCullough SJ, McNeilly F, Allan GM, *et al.* Isolation and characterization of a porpoise morbillivirus. *Arch Virol* 1991; **118**: 247–252.
217. Welsh MJ, Lyons C, Trudgett A, *et al.* Characteristics of a cetacean morbillivirus isolated from a porpoise (Phocoena phocoena). *Arch Virol* 1992; **125**: 305–311.
218. Domingo M, Ferrer L, Pumarola M, *et al.* Morbillivirus in dolphins. *Nature* 1990; **348**: 21.
219. Duignan PJ, Geraci JR, Raga JA, *et al.* Pathology of morbillivirus infection in striped dolphins (Stenella coeruleoalba) from Valencia and Murcia, Spain. *Can J Vet Res* 1992; **56**: 242–248.
220. Di Guardo GU, Agrimi D, Amaddeo M, *et al.* Morbillivirus infection in a striped dolphin (Stenella coeruleoalba) from the coast of Italy. *Vet Rec* 1992; **130**: 579–580.
221. Blixenkrone-Moller M, Bolt G, Gottschalck E, *et al.* Comparative analysis of the gene encoding the nucleocapsid protein of dolphin morbillivirus reveals its distant evolutionary relationship to measles virus and ruminant morbillivirus. *J Gen Virol* 1994; **75**: 2829–2834.
222. Bolt G, Blixenkrone-Moller M. Nucleic acid hybridization analyses confirm the presence of a hitherto unknown morbillivirus in Mediterranean dolphins. *Vet Microbiol* 1994; **41**: 363–372.
223. Bolt G, Blixenkrone-Moller M, Gottschalck E, *et al.* Nucleotide and deduced amino acid sequences of the matrix (M) and fusion (F) protein genes of cetacean morbilliviruses isolated from a porpoise and a dolphin. *Virus Res* 1994; **34**: 291–294.
224. Rima BK, Wishaupt RGA, Welsh MJ, *et al.* The evolution of morbilliviruses—a comparison of nucleocapsid gene sequences including a porpoise morbillivirus. *Vet Microbiol* 1995; **44**: 127–134.
225. van Bressem MF, Visser IKG, De Swart RL, *et al.* Dolphin morbillivirus infection in different parts of the Mediterranean Sea. *Arch Virol* 1995; **129**: 235–242.
226. Lipscomb TP, Schulman FY, Moffett D, *et al.* Morbilliviral disease in atlantic bottlenose dolphins (Tursiops truncatus) from the 1987–1988 Epizootic. *J Wildl Dis* 1994; **30**: 567–571.
227. Schulman FY, Lipscomb TP, Moffett D, *et al.* Histologic, immunohistochemical and polymerase chain reaction studies of bottlenose dolphins from the 1987–1988 United States Atlantic Coast Epizootic. *Vet Pathol* 1997; **34**: 288–295.
228. Krafft A, Lichy JH, Lipscomb TP, *et al.* Post mortem diagnosis of morbillivirus infection in bottle-nosed dolphins (Tursiops truncates) in the Atlantic and Gulf of Mexico epizootics by polymerase chain reaction-based assay. *J Wildl Dis* 1995; **31**: 779–785.
229. Taubenberger JK, Tsai M, Krafft AE, *et al.* Two morbilliviruses implicated in bottlenose dolphin epizootics. *Emerg Infect Dis* 1996; **2**: 213–216.
230. Piza J. Striped dolphin mortality in the Mediterranean. In *Proceedings of the Mediterranean Striped Dolphin Mortality International Workshop*, Pastor X, Simmonds S (eds). Greenpeace Mediterranean Sea Project: Palma de Mallorca Spain, 1991; 93–103.
231. Kennedy S, Smyth JA, Cush PF, *et al.* Histopathological and immunocytochemical studies of distemper in harbor porpoises. *Vet Pathol* 1991; **28**: 1–7.
232. Di Guardo G, Agrimi U, Morelli L, *et al.* Post mortem investigations on cetaceans found stranded on the coasts of Italy between 1990 and 1993. *Vet Rec* 1995; **136**: 439–442.
233. Di Guardo G, Corradi A, Agrimi U, *et al.* Neuropathological lesions in cetaceans found stranded from 1991 to 1993 on the coasts of Italy. *Eur J Vet Pathol* 1995; **1**: 47–51.
234. Tsur I, Goffmann O, Yakobsen B, *et al.* Morbillivirus infection in a bottlenose dolphin (Tursiops truncates) from the Mediterranean sea. *Eur J Vet Pathol* 1997; **2**: 83–85.
235. Sindic CJM, Monteyne P, Laterre EC. The intrathecal synthesis of virus-specific oligoclonal IgG in multiple sclerosis. *J Neuroimmunol* 1994; **54**: 75–80.
236. Correale J, de los Milagros Bassani Molinas M. Oligoclonal bands and antibody responses in multiple sclerosis. *J Neurol* 2002; **249**: 375–389.
237. Reiber H, Ungefehr S, Jacobi C. The intrathecal, polyspecific and oligoclonal immune response in multiple sclerosis. *Mult Scler* 1998; **4**: 111–117.
238. Scarisbrick IA, Rodrigues M. Hit–Hit and Hit–Run: viruses in the playing field of multiple sclerosis. *Curr Neurol Neurosci Rep* 2003; **3**: 265–271.
239. Mckinley M, O'Loughlin V. Human anatomy. McGraw-Hill: New York ; 2006.

DOI: 10.1002/rmv