REVIEW ARTICLE

Animal herpesviruses and their zoonotic potential for cross-species infection

Grzegorz Woźniakowski[1], Elżbieta Samorek-Salamonowicz[1]

[1] Department of Poultry Viral Diseases, National Veterinary Research Institute, Pulawy, Poland

▌Abstract

Herpesviruses of humans and animals cause severe diseases that influence not only the health and epidemiological status but are also economically important in the context of food production. The members of *Herpesviridae* are host specific agents that also share many properties that potentially make them capable of crossing the species barriers. The objective of presented review paper was to summarize the relationship between herpesviruses of animals and humans and their zoonotic potential. In humans, the most epidemiologically important herpesviruses are represented by Human herepesvirus-1 and Human herpesvirus-2, which are commonly known as herpes simplex virus type 1 and 2, varicella-zooster virus (VZV), Epstein-Barr virus (EBV), Kaposi's Sarcoma-associated herpesvirus (KSHV), cytomegalovirus (CMV), as well as Human herpesviruses: HHV-6A, HHV-6B, and HHV-7. However, in terms of the potential to cross the species barrier, there are a few herpesviruses, including B virus disease (CeHV-1), Marek's disease virus (MDV), Equid herpesvirus-1 (EHV-1) or pseudorabies virus (PRV), which are potentially able to infect different hosts. To summarize, in advantageous conditions the host specific herpesviruses may pose a threat for public health but also may exert a negative impact on the economical aspects of animal production. The most probable of these are zoonotic infections caused by B virus disease; however, close contact between infected animal hosts and humans may lead to transmission and replication of other *Herpesviridae* members.

▌Key words

herpesviruses, B-virus disease, Marek's disease virus (MDV), Equid herpesvirus-1 (EHV-1), pseudorabies virus (PRV)

INTRODUCTION

Herpesvirales is a huge order that includes numerous viruses which can potentially infect humans and almost all animal species, including insects, fish, molluscs, reptiles, birds, and finally mammals. It is known that the word 'herpes' has been used in human medicine for at least 2,600 years due to early description of the disease causing eczema and cancer of the skin [1]. Other sources used this word to describe different types of disease comprised of zoster, labial and genital herpes. The family *Herpesviridae* is divided into three subfamilies of *Alpha-*, *Beta-* and *Gammaherpesvirinae*. The most reliable classification is based on analysis of double-stranded DNA (dsDNA) of herpesviruses, but all of them share common features as well as structures of some proteins [2, 3]. The most unique feature of herpesviruses is associated with the latency stage in the affected host and then the subsequent reactivation to recurrent infection. Their oncogenic potential and viral integration into the host chromosomes also makes them unique among viruses. Thy have a rather narrow host range, but due to a common origin of evolution they also share a potential to infect new hosts [4, 5, 6, 7, 8, 9, 10]. In general, at least one of the most important diseases of domestic animals is caused by herpesvirus, and some of them are potentially epizootic and may be transferred between distantly-related species [11, 12, 13, 14, 15]. The most important human diseases caused by herpesviruses include Human herepesvirus-1 (HHV-1) and Human herpesvirus-2 (HHV-2) also named herpes simplex virus 1 and 2 (HSV-1, HSV-2), varicella-

zooster virus (VZV), Epstein-Barr virus (EBV), Kaposi's Sarcoma-associated herpesvirus (KSHV), cytomegalovirus (CMV), Human herepesvirus-6A, 6B, and 7 [5,10,15–18]. The most important diseases of animals caused by herpesviruses include bovine rhinotracheitis, Marek's disease, infectious laryngotracheitis and pseudorabies. These viruses are rather host-specific, with the exception of pseudorabies virus (Suid herpesvirus-1) which infects not only swine, but also sheep, cattle, dogs, cats and raccoons [2, 6, 9, 16, 17, 19, 20, 21, 22, 23, 24, 25]. It is known that transmission of RNA viruses between species is more likely in comparison to DNA viruses which are in general host specific. On the other hand, currently due to the close contact of farmers, veterinarians but also travelers and owners of household animals, the possibility and probability of virus transmission between non-related hosts becomes more feasible [13,19, 20,26, 27, 28].

Objective. The presented review paper is intended to show and summarize the relationship between herpesviruses of animals and humans and their zoonotic potential. Such cross-species infections are generally rare but still unpredictable and possible.

State of knowledge – Herpes-simplex virus. Herpes-simplex virus type 1 and 2 (*Human herpesvirus-1 and 2*) remain one of the most important concerns for human health. In spite of the mild character of the infection and long-life latency, it also may have a more severe impact on human health leading to rather rare encephalitis and death [2, 15]. It can also be an anthropozoonotic agent. A few cases of fatal HHV-1 infection cases have been described in New World Primates, among maromosets (*Callithrix jacchus*). The infection may also have fatal consequences for night monkeys (*Simia trivigrata*) or gibbons (*Hylobates lar*) [8, 12, 21, 23, 29, 30]. The virus

Address for correspondence: Grzegorz Woźniakowski, National Veterinary Research Institute, Department of Poultry Viral Diseases, Partyzantów 57, 24-100 Pulawy, Poland
E-mail: grzegorz.wozniakowski@piwet.pulawy.pl

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was also successfully transferred to rabbits. Rare cases of encephalitis occurred after transmission of HHV-1 from rabbit owner to rabbit. The study conducted so far showed a serological relationship between HHV-1 and B-virus that is present among Macaques [4, 6, 11].

Epstein-Barr virus and other related members of *Gammaherpesvirinae*. Human herpesvirus-4, which belongs to *Lymphocryptovirus* of *Gammaherpesvirinae,* causes infectious mononucleosis or glandular fever [2, 5, 6]. Other closely related viruses include *Herpesvirus saimiri* (Saimiriine herpesvirus-2 SaHV-2) infecting squirrel monkeys (*Saimiri sciureus*) and *Herpesvirus ateles* isolated from Spider monkeys (*Ateles spp.*) [4, 8, 12, 24, 29]. These viruses cause subclinical infections and replicate in T lymphocytes [31]. In natural hosts, infection is completely asymptomatic. The virus may also infect human T lymphocytes; however, to-date, no human cases have been described [31]. SaHV-2 has been used as a genetic vector but it may be dangerous due to its close relationship with *Human herpesvirus 8* which causes Kaposi sarcoma (KSHV-1) in humans [11, 32].

B virus disease of macaques. The B virus, also called cercopithecine herpesvirus-1 (CeHV-1), occurs frequently among macaques. The virus shares a similar infection scheme to human herpesvirus-1. B virus is infectious for all macaques (Macaca spp.), among others, M. Japanese, M. rhesus, M. cynmolgus and M. pigtail [9]. The seroprevalence of CeHV-1 reaches from 5.3% – 97% in Indonesia [2, 9, 22]. In macaques, the infection is rather asymptomatic; however, B virus presents a real zoonotic threat for the humans. A few fatal cases in humans have been described [4, 9, 33], from a total 24 cases described, 19 were fatal. The symptoms include paralysis and severe encephalitis. Infection may be transmitted through the saliva of monkeys or after being bitten by the animal. Therefore, animal handlers or veterinarians working in animal parks are prone to be infected with this virus. However, the transmission is also possible in laboratory conditions by the workers processing central nervous tissue or other internal organs of monkeys, especially kidneys. The virus stage of infection is also similar to human herpes simplex with life-long latency in ganglia. After the latency stage during the external stress or temporal immunosuppression of animals, the virus enters into the reactivation stage and produces infection in the salivary glands and genital fluids. In the case of human infection, the incubation period lasts from 2–5 weeks. The clinical signs include formation of small vessels under the skin and hyperesthesia around the scratch or bite. Further signs include paralysis and encephalitis that lead to death [15, 34]. Most of the described cases of human infection were caused by inappropriate handling or breeding of the animals; therefore, a specialized regulation should be adhered to by animal handlers, traders or even by owners of macaques.

Pseudorabies virus (Aujeszky's disease virus or Suid herpesvirus-1). Pseudorabies virus (*Suid herpesvirus-1* SuHV-1) primarily infects swine; however, there are a number of secondary hosts such as cattle, horses, dogs and cats [17]. The virus may be also transmitted to other species causing clinical signs, for example, in mink or panther [10, 16]. In many countries, SuHV-1 has been eradicated from domestic swine. However, the virus remains enzootic in free-ranging

animals which may exert an influence on swine production. In the primary host – swine, the clinical signs may be not present but the infected animals shed the virus via saliva and nasal discharges to other susceptible swine, predominantly piglets younger than 3 months and sows. The mortality in infected piglets may reach 100% while in sows infection may result in 50% abortion [17]. Vaccination of swine with the accessible live-attenuated, inactivated and recombinant DNA, remarkably reduces mortality. However, this does not prevent infection with the wild-type virus. Of more serious importance is the transmission of SuHV-1 to secondary hosts, including horses, dogs and cats. The disease is manifested as severe neurological signs that frequently lead to death of the infected animal. In spite of few described cases of SuHV-1 infection in humans, similar SuHV-1 and HHV-1 host receptors which use viral penetration, a recently conducted study has shown that both viruses use different protein interactions that lead to envelopment [13, 14, 15]. SuHV-1 in particular conditions may infect humans although the risk remains low.

Equine herpesvirus-1. Equine herpesvirus-1 (EHV-1) is a major viral agent affecting horses [15, 25]. The virus causes abortion as well as encephalomyelitis and respiratory disease. Most cases of EHV-1 caused abortion during gestation. The virus causes encephalomyelitis as a result of infection of the endothelial cell lining aerterioles of the brain and spinal cord. EHV-1 investigated *in vitro* has shown a potential to infect a wide spectrum of cells from different hosts; it is therefore considered to potentially infect different hosts. To-date, no positive serological results have been shown in samples from humans working with horses infected with EHV-1; therefore, such infection remains only theoretical.

Marek's disease virus. Marek's disease virus (MDV) belongs to *Alphaherpesvirinae* subfamily and shares molecular properties with other herpesviruses causing lymphomas, including Epstein-Barr virus or Kaposi-sarcoma associated virus. MDV causes lymphoproliferative disease in chickens, turkeys and Japanese quail [3, 5, 20]. Among susceptible birds, the virus causes lymphomas with subsequent infection of CD4^{+} T lymphocytes [3, 28]. The virus integrates with host DNA within the 2nd and 4th chromosomes by telomeric sequences [28]. This analogy is also observed in human herpesvirus-6 causing lymphomas [35]. The only possible prevention method is vaccination of 1-day-old nestlings with live-attenuated vaccines. Vaccination does not protect birds from being infected with virulent field MDV strains, but prevents the disease onset. Thus, vaccinated birds are potential carriers of virulent MDV and shed the virus into environment within particles of dust and fine skin scrapings [19]. Therefore, not only birds are prone to inhalation of the virus particles but also animal holders and veterinarians [19, 26, 27, 28, 36]. The exact influence of the close contact of human with MDV is unknown. However, taking into account the high degree of homology between MDV, HHV-1, EBV or KSHV, it is possible that the virus may also replicate in human beings and are a potential threat. The MDV-genome structure represented by unique long (U_L) and short regions (U_S) flanked by internal (IR_S, IR_L) and terminal (TR_S, TR_L) repeats are identical with HHV-1, which is common among the human population as previously mentioned [15].

A study carried out between 1970–1980 showed a higher incidence of Hodgkin's disease and non-Hodgkin lymphoma,

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as well as multiple myeloma among farmers and veterinarians working with poultry [28, 37]. This phenomenon was explained as non-specific immunosuppression by cancerogenic physical, chemical and biological factors. However, subsequent papers describing the serological study on the prevalence of antibodies against turkey herpesvirus (HVT) in sera collected from farmers, bird holders and veterinarians, showed a 71% prevalence of these antibodies in farmers in contrast to 20.8% antibodies among white-collar workers [38]. These results were comparable with data obtained after examination of the sera for EBV-specific antibody. The EBV antibodies were then found among 76.4% of farmers and 32.0% of white-collars. Interestingly, the same study conducted on a set of sera from the apes showed negative results. A similar study conducted on apes infected with MDV field strains was performed by Sharma et al. [3]. However, no sero-conversion was found nor any clinical signs observed. The study was conducted on 113 people from different social groups dealing with poultry on farms or with MDV in laboratory conditions. The respondents, students and 25 persons affected by Burkitt's lymphomas, showed no significant results by sero-neutralisation and immunofluorescence assay. A similar study conducted using ELISA was performed in Poland and France [28]. These results showed high titers among people dealing with poultry. However, in the examined MDV positive sera the presence of antibodies specific for human cytomegalovirus (CMV) and HHV-1 were found. The only dependency observed was related with the gender of the examined patients subjected to serological examination. The higher MDV titers and percentage of positive results were found among women. This ideally reflects the higher susceptibility of hens to MDV [28]. So far, the conducted study using molecular biology methods, including polymerase chain reaction (PCR), have shown a 20% incidence of specific MDV genome sequence within human sera [39]. However, the obtained results were independent from the group of the examined people comprised of farmers, veterinarians, and white collars; therefore, they are questionable. Moreover, further attempts to repeat this study were unsuccessful and should be investigated in the future [40, 41].

Purchase and Witter [18], after a set of virological studies, did not find any relationships in the epidemiology of MDV and human herpesviruses leading to cancer development. However, it is not evident that infection of the human with MDV is impossible. It is worth mentioning the possible relationhip of MDV with the etiology of sclerosis multiplex (SM) or neurolymphomatosis among humans [27, 36, 41, 42]. The conducted study showed 91% incidence of anti-MDV antibodies in people affected by SM. However, these sera were also positive for EBV antibodies, which makes these results non-convincing. Summarizing the role of MD as zoonosis, it is still too early to draw a final conclusion.

CONCLUSIONS

Herpesviruses cause different diseases of humans and animals. Due to their specific features on entering into the latency stage, they may persist as a subclinical infection without development of the clinical form of the disease. In spite of their narrow host range and due to the kind of the encoded nucleic acid in particular conditions, transmission of herpesviruses to other species is possible. Although for their natural hosts their presence is manifested by mild symptoms, or is asymptomatic, their transmission to other species may lead to severe disease and death.

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