Epidemiology of EHV-1 and EHV-4 infections: A review
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Abstract
This review mainly focuses on the epidemiological characteristics of respiratory diseases, abortions, perinatal mortalities and neurological diseases in horses caused by EHV-1 and EHV-4. There are several sources of EHV-1 and EHV-4 which are transmitted by different routes. The latency and reactivation of EHV-1 and EHV-4 play an important role in the persistence of infection with these viruses in the equine population. These viruses are major agents in respiratory diseases in horses. Mares and their foals play an important role in the circulation of these viruses on farms. Abortion and perinatal mortality can take the sporadic or epizootic form. Neurological disease is caused primarily by neuropathogenic EHV-1. Combined epizootics of neurological diseases and abortions are common.

Abbreviations
EHV: Equine Herpesvirus; DNA: Deoxyribonucleic Acid; EIV: Equine Influenza Virus; IURD: Infectious Upper Respiratory Tract Disease; EMPF: Equine Multinodular Pulmonary Fibrosis; PCR: Polymerase Chain Reaction; SNP: Single Nucleotide Polymorphism; ORF: Open Reading Frame; EHM: Equine Herpesvirus Myeloencephalopathy

Introduction
The order *Herpesvirales* comprises three families since viruses infecting mammals, birds and reptiles are grouped together in the family *Herpesviridae* which is divided into three subfamilies, *Alpha*, *Beta* and *Gammaherpesvirinae* [1]. EHV-1 and EHV-4 are classified in the *Alphaherpesvirinae* subfamily, all belonging to the genus *Varicellovirus* [1,2]. Among equine herpesviruses, EHV-1 and EHV-4 are the most clinically, economically and epidemiologically relevant pathogens [3].

The herpesvirus is a linear double-stranded DNA virus with an icosahedral capsid surrounded by a structured integument and an envelope containing spikes of viral glycoproteins on the surface, and due to the varying size of the envelope, these viruses can range from 120 to 250 nm in diameter [4]. The identity between EHV-1 and EHV-4 at the DNA level has been estimated to be 55 to 84% [5].

The animal can be clinically affected several times during its life and the resulting disease tends to be less severe [6]. Resistance to reinfection can be achieved after repeated infections [7]. EHV-1 and EHV-4 are very close antigenically since cross-reacting neutralizing antibodies can develop following multiple exposures to these viruses [5].

This review concerns EHV-1 and EHV-4 and mainly focuses on the persistence and spread of these viruses, and their epidemiology in sporadic and epizootic cases of respiratory disease, abortion, perinatal mortality and neurological disease.

Persistence and spread of viruses
Transmission of most EHV infections between horses occurs directly as a result of direct exposure to exudates and aerosols and indirectly from air, water and environmental contaminants...
The most common route of transmission is the respiratory tract [5]. Infection can also occur by ingesting contaminated material through a runny nose [10]. Respiratory secretions from horses, foals, fetal and placental tissue, and aborted placental fluids are common sources of the virus [10,11]. Environmental factors have varying effects on the environmental persistence of EHV-1, which decreases over time and poses a risk of transmission [12]. EHV-1 can survive at room temperature on horsehair or burlap (35 days) and even on paper, wood or rope (one week) [13].

Horses and foals are contagious by the respiratory route in the active stage of the disease and probably during the later periods of viral reactivation and dissemination in latent infected horses because the latent period is unknown but is thought to be lifelong [6]. Most horses stop shedding the virus around 1 to 2 weeks after infection [14]. Nasal excretion after recrudescence of latent EHV-1 is short (2 days) [15]. EHV-1 can be excreted in the semen of infected stallions [16]. Transmission of EHV-1 through semen has been suggested during mating or by artificial insemination [17]. EHV-1 and EHV-4 can be excreted in the nasal secretions of vaccinated mares and their unweaned and unvaccinated foals [18]. Usually, EHV-4 is excreted by male foals and foals with respiratory disease [19].

After infection, EHV-1 and EHV-4 localize in many neuronal and lymphoid tissues (lymphoreticular system, circulating CD8+ T cells, lymph nodes and trigeminal ganglion neurons) and become latent [20,21]. It is estimated that >50% of the horse population is latent infected with EHV-1, and as a hypothesis, reactivation in latent infected horses is the major biological source of infectious virus [22]. Also, it is suggested that transmission of EHV-1 after reactivation of latent infection is due to stress of parturition, estrus activity or lactation [23]. Experimentally, EHV-1 can be reactivated by administration of high doses of glucocorticoids [24]. Clinical disease may result from this recrudescence [15]. In contrast, experimental reactivation of EHV-4 was performed with some difficulty and may not have mimicked natural reactivation [20].

Abortion or neurological disease can occur months or years after latent respiratory infection with EHV-1 [25]. Latency leads to the occurrence of sporadic cases of abortions and neurological diseases in horses reared in closed areas away from an external source of EHV-1 [26].

Infections of foals and respiratory diseases

EHV-1, EHV-4, Equine Influenza Virus (EIV) and Streptococcus equi subs. equi are the main pathogens responsible for Infectious Upper Respiratory Tract Disease (IURD) [27]. EHV-4 is the most common pathogen detected in horses showing clinical signs of IURD [27]. EHV-4 is usually isolated from foals with profuse serous or mucopurulent nasal discharge [19].

In Germany, an outbreak of EHV-4, respiratory disease affected 41 horses (20 foals, 10 stallions and 11 mares) and 73% of infected mares and their foals shed the virus at the same time. Several factors were involved in the onset of this outbreak such as stress caused by seasonal changes, management practices, routine equestrian activities and exercise [28]. Also, suppression of the ability to neutralize the virus in the nasal mucosa may occur after transport and may contribute to susceptibility to EHV-1 [29]. In China, a virological investigation of the agents causing an outbreak of respiratory disease showed the involvement of EHV-4 [30].

Seroepidemiological studies have demonstrated infection of 30-day-old foals with EHV-1 [31]. In addition, a seroepidemiological investigation showed positive results of EHV-1 and EHV-4 infection in vaccinated mares and their 5-week-old foals [18]. It was reported in another study that the seroprevalence of EHV-4 in all mares and foals tested was 99%, and that of EHV-1 was 26.2% and 11.4% in mares and foals respectively [23].

The mare population is a source of virus for unweaned foals [23]. The mare and foal populations are considered to be a reservoir responsible for new infections in the foal population before and after weaning [31]. EHV-1 and EHV-4 can even circulate within the population of vaccinated mares and their unweaned foals [18]. Also in another study, it was reported that EHV-1 and EHV-4 circulate widely in mare and foal populations but EHV-4 was not the cause of the respiratory disease which affects all foals [32].

In addition, both gammaherpesviruses EHV-2 and EHV-5 are classified in the group of less characterized respiratory viruses associated with IURD [33]. EHV-2 and EHV-5 have been detected in horses with mild respiratory disease [34], pneumonia [35] and multinodular pulmonary fibrosis (EMPF) [36,37], and even in immunocompetent hosts, apparently healthy and without clinical signs of the disease [38,39]. Also, EHV-2 plays a role in the transactivation of EHV-1 and EHV-4 [40].

Several authors have reported co-infection with several EHV in apparently healthy equines. In Korea, in a virological investigation of equine herpesviruses in clinically healthy horses, EHV-2 and EHV-5 were detected in 41.7% and 21.7% of blood samples, respectively, and in 13.4% and 18.7% of lung tissue, respectively. Also, EHV-1, EHV-2 and EHV-5 were detected in 12.0%, 5.5% and 11.2% of nasal swabs, respectively. Co-infection with EHV-2 and EHV-5 was detected in 11.6% of blood samples and 6.4% of lung tissue, and co-infection with EHV-1, EHV-2 and EHV-5 was detected in 0.8% of nasal swabs [41]. In Egypt, a virological and serological investigation on four equine herpesviruses (EHV-1, EHV-2, EHV-4 and EHV-5) in different populations of Arabian horses and donkeys showed that these viruses are endemic and constitute a continuing threat to horses [42]. In China, study of the prevalence of EHV-2, EHV-4 and EHV-5 by virological analysis of 453 nasal swabs from clinically healthy foals (36/453, 7.9%) and horses (417/453, 92.1%), showed that 9.9% of samples were positive for EHV-5 and 1.5% were positive for EHV-2, but all were negative for EHV-4 [30].

Abortions and perinatal mortalities

Abortion due to EHV can take the form of sporadic events or disease outbreaks (epizootics) [43,44]. Abortions occur more
frequently in the last three months of gestation and almost none before 4 months [45,46]. Also, perinatal mortality of foals can take the sporadic form or the form of epizootics [47]. Foals can be stillborn, alive but weak and die quickly or healthy at birth, become sick and die within 3 days of birth [47].

In a population of pregnant mares in Germany, the percentage of abortions reached 6.5%, 25% of these abortions were of infectious origin, of which 40% were due to EHV-1, or 10% of all abortions [48]. In France, fetoplacental infections represented 63.7% of abortion cases since, for infectious causes, the vast majority of abortion cases were caused by bacteria (79.9%), followed by viruses (15.1%) including EHV-1 and EHV-4, and fungi (1.8%) [46]. In another study carried out in France, covering the period 2002–2005 and aimed to assess the contribution of five different EHVs to equine abortion using consensus PCR on 407 fetuses, stillborn foals, premature foals, EHV-1 has been identified as the major cause of abortions in mares (59/407 cases, 14.5%). Detection of EHV-2 and EHV-5 DNA in abortion cases has inferred a role for these viruses in abortion [49]. In UK, during an epizootic associated with EHV-1, 11 of 18 unvaccinated mares (Welsh ponies) aborted [50].

In Hungary, out of 93 aborted equine fetuses and 8 weak foals, 15 (14.9%) were found infected with EHV-1 by immunohistochemistry and 13 (12.9%) by virological analysis [51]. In Great Britain, equine herpesvirus infections of fetuses or newborn foals were estimated at 6.5% of final diagnoses since 95% of these infections were caused by EHV-1 and 5% by EHV-4 [45]. In the Netherlands, out of 254 fetal and neonatal isolates, 244 (96%) were typed as EHV-1 and 10 (4%) as EHV-4 [52]. In Australia, 33 of 44 mares aborted or lost foals within the first day of birth, and 6 foals were infected with EHV-1 [43].

Neuropathogenic strains and neurological diseases

Recent research has increasingly focused on neuropathogenic (neurotropic or neurovirulent) strains of EHV-1. It was believed that these neuropathogenic and non-neuropathogenic strains could be distinguished via a single nucleotide polymorphism (SNP) in the ORF30 open reading frame of the gene encoding viral DNA polymerase with a single nucleotide substitution of adenine (A) at the guanine (G) at nucleotide 2254 causing the change from asparagine (N) to aspartic acid (D) at amino acid 752 [53]. Neurological disease appears to have a stronger association with the ORF30 G2254 genotype while the non-neuropathogenic biovariant (ORF30 A2254 genotype) has been linked primarily to non–neurological disease since 78% of neuropathogenic isolates encoded A2254 (acid amino acid 752), while 42% (86%) of the neuropathogenic isolates encoded G2254 (amino acid D752) [53]. Currently, there are RT–PCR tests using allelic discrimination for detection and differentiation between these strains, neuropathogenic EHV-1 (G2254) and non-neuropathogenic EHV-1 (A2254) [54,55].

In Serbia, Bosnia and Herzegovina, 142 tissue and nasal swab samples from apparently healthy unvaccinated horses were examined and the results showed that the detection of EHV-1 by PCR and its isolation was in 81% and 45.1% of the analyzed samples, respectively, and 82.1% of the strains were neuropathogenic [56]. In South Korea, 12 EHV-1 isolates were isolated and characterized as non–neuropathogenic [57].

In central Kentucky, out of 426 archived EHV-1 isolates (1951–2006) collected from abortions, the percentage of isolates with a neuropathogenic genotype ranged from 3.3% in the 1960s to 14.4% in the 1990s [58]. In Germany, for 32 EHV-1 isolated from 06 abortion epizootics and 34 archived EHV-1 (1987–2009) isolated from sporadic cases, 89.4% (59/66) of EHV-1 isolates from abortions were of neuropathogenic genotype (G2254/N752) and 10.6% (7/66) were of neuropathogenic genotype (G2254/D752) [59].

Epizootics of neurological diseases with simultaneous abortions have been reported. During a storm of abortions or perinatal deaths in Austria caused by EHV-1, 10 mares died with neurological disorders and 17 mares suffered from lameness and paralysis of varying degrees with 22 cases of abortion, stillbirths and premature foals [60]. Another combined epizootic of neurological diseases and abortions has occurred in Australia as out of 10 pregnant and lactating mares, 5 developed a neurological disease of which 3 died, one mare aborted and the other gave birth to an atactic and incontinent foal [32]. In a neuropathogenic EHV-1 (G2254/D752) epidemic affecting 61 horses in Germany, 8 horses developed EHM, 6 pregnant mares aborted of which 3 had EHM [61]. Also, in Brazil, EHV-1 was isolated from a fatal case of equine myeloencephalopathy in a mare and this strain is suggested to be neurovirulent [62].

There are factors that contribute to the onset of EHM since it has been reported that 24% of EHV-1 isolated from horses with neurological disease are strains containing the opposite allele (ORF30 A2254) [63]. In Germany, during a severe abortion epizootic caused by EHV-1 (ORF30 G2254), 16 pregnant mares vaccinated regularly with an inactivated vaccine aborted, two gave birth to weak non–viable foals and no neurological disease has been reported which suggests that vaccination of pregnant mares did not influence the occurrence of abortions but prevented the development of neurological diseases [44].

Conclusion

Due to the pathological importance of EHV-1 and EHV-4 in veterinary medicine, these viruses become an objective to be studied. These viruses are major pathogens that spread among susceptible horses during periods of latency and reactivation as they cause respiratory diseases, abortions, perinatal mortalities and neurological diseases. Latency and reactivation allow these viruses to persist and spread in the equine population. Infection with these viruses results in the appearance of different clinical forms of diseases either as sporadic cases or epizootics. There are epidemiological differences according to the concerned countries and the pathogenicity of the viral strains involved in the infection.

References


