GETAH VIRUS

SUMMARY

Etiology

- Getah virus (GETV) is an enveloped RNA virus belonging to the genus *Alphavirus* in the family *Togaviridae*.
- Many strains of GETV are known to exist. The GETV genome undergoes frequent mutation.

Cleaning and Disinfection

- GETV survives in cold environments.
- Alphaviruses, such as GETV, are inactivated within minutes at temperatures of 58˚C or higher. They are killed by UV light, radiation, and acidic conditions.
- Effective denaturing agents include formaldehyde, beta-propiolactone, detergents, and lipid solvents.

Epidemiology

- Although only pigs and horses show signs of disease, anti-GETV antibodies have been found in many other species.
- GETV may be a cause of febrile illness in humans.
- GETV is found in many parts of the world, including Eurasia, South- and Far East Asia, Australia, and New Zealand.
- Little is known about morbidity in swine; death due to GETV is negligible. In horses, morbidity of up to 40% has been observed.

Transmission

- GETV is transmitted via mosquitoes. Vectors include *Culex tritaeniorhynchus* and *Aedes vexans nipponii*. GETV is also capable of replicating in other mosquito species, many of which are found in the United States.
- Direct contact and aerosol transmission are suspected in horses.
- Vertical transmission has been observed in experimentally infected mice and hamsters.
- Similar to Japanese encephalitis virus (JEV), pigs appear to be amplifying hoses involved in GETV transmission.

Infection in Swine/Pathogenesis

- GETV causes CNS signs, diarrhea, and death in piglets, as well as reproductive failure in sows and gilts. Infection in adult animals is often subclinical.

Diagnosis

- Virus isolation is possible. Tests to detect antigen include reverse transcriptase polymerase chain reaction (RT-PCR). A multiplex assay that detects six major swine RNA viruses (porcine reproductive and respiratory syndrome virus, JEV, porcine epidemic diarrhea virus, porcine rotavirus, transmissible gastroenteritis virus, and GETV) has been developed.
- Antibodies can be detected via enzyme-linked immunosorbent assay (ELISA), serum neutralization (SN), hemagglutination inhibition (HI), and complement fixation (CF). CF can distinguish GETV from the closely related Sagiyama virus (SAGV), though SN is thought to be most specific in distinguishing GETV from other antigenically related alphaviruses.
- A new strain of GETV has recently been identified via the random amplified polymorphic DNA (RAPD) technique.

Immunity

- A live-attenuated trivalent vaccine (GETV, JEV, and porcine parvovirus) has been available for swine in Japan since 1993; however, it may not provide protection against new GETV strains in circulation.

Prevention and Control

- Control of mosquito vectors is critical to prevent GETV infection. Insecticides can be used to reduce the mosquito population. Mosquito breeding sites (e.g., stagnant water) should be eliminated.
- Pigs should be housed indoors. Mosquito access to pigs should be decreased via screening of barns and use of fans inside buildings.

Gaps in Preparedness

- GETV primarily affects horses. More research is needed to understand the nature of clinical disease in swine and humans, as well as resulting morbidity and mortality.
- Vaccine research is needed to determine the efficacy of current formulations compared to recently circulating GETV strains.
- Mosquito surveillance would be helpful to determine if and where possible vector species are found in the United States.

OVERVIEW

Getah virus (GETV) is an enveloped RNA virus belonging to the genus *Alphavirus* in the family *Togaviridae*. GETV is a member of the Old World cluster of alphaviruses, along with Chikungunya virus (CHIKV), Ross River virus (RRV), O'nyong nyong virus (ONNV), and Sindbis virus (SINV), among others. Clinical disease has been observed only in horses and pigs. However, anti-GETV antibodies have been discovered in a wide range of animals, including birds, reptiles, marsupials, cattle, water buffaloes, and goats. Pathogenicity of GETV in humans has not been clearly established.

GETV exhibits a wide geographic distribution throughout Asia and the Pacific Islands, from tropical climates up to northern tundra. The GETV genome has shown a propensity to mutate with time, and viral strains isolated in the same year, regardless of geographic location, tend to show greater similarity. This may be related to the seasonal reintroduction of the virus by its mosquito vectors from warmer to colder climates each year, rather than local clustering of isolated viral strains. There is also discussion of the inclusion of Sagiyama virus (SAGV), found in Japan and Taiwan, as a subtype of either GETV or RRV, though a consensus has not been reached.

GETV relies on mosquito-borne transmission, and the virus has been identified in many mosquito species. Common vectors include *Culex tritaeniorhynchus* and *Aedes vexans nipponii*, and outbreaks in vertebrate hosts tend to coincide with seasonal peaks in the presence of regional arthropod vectors. Wild boars and domestic pigs may act as amplifying hosts in the GETV transmission cycle, exhibiting high levels of transient viremia. A 2014 outbreak in racehorses in Japan coincided with a similar epizootic in pigs in the same part of the country known for its extensive swine production. Anti-GETV antibodies have been discovered in a variety of other vertebrate species that could also act as reservoir hosts, though none have been specifically implicated in the spread of the virus.

GETV is best known for causing sporadic outbreaks of a mild febrile illness in horses, though it can also cause reproductive failure in swine and death in newborn piglets. Although some strains are more virulent than others, the severity of infection appears to be age-dependent in swine, and infection in adult animals is typically subclinical.

The virus can be successfully isolated using a variety of cell lines or suckling mice. Plasma of infected individuals, as well as lymph nodes, placenta, amniotic fluid, and organs of dead fetuses are adequate samples for virus isolation. Feces, urine, nasal swabs, and saliva have also been sampled for diagnosis in horses and swine, but appear to be less reliable. Reverse transcription polymerase chain reaction (RT-PCR) assays are used to detect viral RNA, while enzyme-linked immunosorbent assay (ELISA), serum neutralization (SN), hemagglutination inhibition (HI), and complement fixation (CF) are used for detection of anti-GETV antibodies. Only the CF test can distinguish GETV from closely related SAGV, though SN is thought to be most specific in distinguishing GETV from other antigenically related alphaviruses. Multiplex PCR assays for simultaneous detection of multiple swine diseases, including GETV, are also available. Amplification of random DNA segments, known as random amplified polymorphic DNA (RAPD), for detection and discovery of new viral strains has successfully identified a previously unknown GETV isolate.

An inactivated vaccine for horses has been produced in Japan since 1979, following the first known GETV outbreak there. Another recent Japanese outbreak in horses in 2014 has raised questions about the efficacy of vaccination programs and existing vaccines against current strains of the virus. A live-attenuated trivalent vaccine for protection against GETV, Japanese encephalitis virus (JEV), and porcine parvovirus (PPV) has been available for swine in Japan since 1993; it is unknown if this particular vaccine offers complete protection against new strains.

GETV is not currently a major threat due to its low morbidity and mortality, infrequent outbreaks, and unproven zoonotic potential. However, its existence in a variety of climates and mosquito vectors, frequent mutation rate, relation to known human pathogens, and ability to cause reproductive failure in swine make it deserving of continued surveillance. As much of the literature and knowledge of GETV is based on outbreaks in previous decades, current research on prevalence and pathogenesis in swine, other potential host species, and development of vaccines for new strains would be beneficial if the disease is introduced in the United States.

LITERATURE REVIEW

1. Etiology

1.1 Key Characteristics
Getah virus (GETV) is a mosquito-borne virus belonging to the genus *Alphavirus* in the family Togaviridae. It is an enveloped, single-stranded RNA virus within the Semliki Forest serocomplex of alphaviruses,[1] closely related to Ross River virus (RRV), Bebaru virus (BEBV), and Sagiyama virus (SAGV). GETV is a member of the Old World cluster of alphaviruses, generally known to cause rash, polyarthritis, and febrile illness that is rarely fatal. In contrast, New World alphaviruses are more of a public health concern, causing encephalitis and neurological disease with potential for human fatalities.[4]

1.2 Strain Variability
The GETV genome can undergo frequent mutation, as indicated by oligonucleotide fingerprint analysis.[5] Biological differences among some strains have been demonstrated in the laboratory with cross-neutralization tests.[6] Greater similarity is observed among isolates obtained in the same year,[5] though not necessarily from the same geographic location. Point mutations continue to occur over time, but there does not appear to be a geographic clustering of viral strains. This trend may be a result of the mode of transmission of GETV. Due to the transient nature of infection among vertebrates and seasonal disappearance of mosquito vectors in colder areas, it is possible that the virus is reintroduced to temperate climates from southern regions every year.[7]

Mosquito surveillance near the location of a 1978 Japanese outbreak in horses identified 18 strains of GETV in just six months during the following year.[5] Until a recent reemergence of the virus in 2014, no new strains of GETV had been isolated in Japan for more than two decades.[8] Isolates have also been identified in Malaysia and South Korea, in addition to at least ten GETV strains in China and fifteen in Russia and Mongolia.[9]

Sequence analysis of Chinese and Korean GETV isolates and an SAGV isolate in Japan revealed a high level of identity, and it has been suggested that SAGV should be classified as a strain of GETV.[9] The *NSP1* genes of GETV and SAGV share a high nucleotide identity with a completely identical amino acid sequence.[7,10,11] Similarly, amino acid sequences of the *E1* gene are highly homologous,[11,12] and the 3' untranslated regions share a 94% identity with identical arrangement of three repeated sequence elements. Biological and serological similarities between GETV and SAGV further support this theory.[10] Still, there appears to be a lack of agreement on appropriate classification, as the International Committee on Taxonomy of Viruses has considered SAGV to be a subtype of RRV, not GETV, since 2000.[13]

2. Cleaning and Disinfection

2.1 Survival
GETV isolates have been identified in Russia and Mongolia reaching the northern tundra, the lone alphavirus known to exist in these harsh environmental conditions.[9] Peak infection in host species may be associated with seasonality of specific mosquito vectors, as observed in the 1978 epizootic in Japan. The greatest number of infected horses coincided with peak numbers of the known regional vector, *Ae. vexans nipponii*, seen in early October.[5]

2.2 Disinfection
Alphaviruses are inactivated within minutes at temperatures of 58˚C or higher, and also lose infectivity when exposed to UV light, radiation,[14] and acidic conditions. Their ideal pH range is 7–8.[15] Effective denaturing agents include formaldehyde, beta-propiolactone, detergents, and lipid solvents.[14]

3. Epidemiology

3.1 Species Affected

Only horses and pigs are known to show clinical signs of disease; however, anti-GETV antibodies have been discovered in a wide range of animals, including birds, reptiles, marsupials,[1] cattle, water buffaloes,[5] and goats.[16] Mice, hamsters, guinea pigs, and rabbits have been infected experimentally.[1] In addition to domestic pigs, wild boars can also be vertebrate hosts.

3.2 Zoonotic Potential

Antibodies to GETV have been identified in humans and monkeys,[5] though disease manifestation, if any, appears to be limited to fever.[17] Seroepidemiological studies on Hainan Island in China have implicated the M-1 strain of GETV, or a closely related virus, in a febrile illness in humans. Prevalence of antibody to the M-1 strain was significantly higher in people with fever than in those with no disease symptoms.[16] However, no clinical signs were reported among horse handlers present during a 1978 GETV epizootic at a large racehorse training facility in Japan.[5] While the virus has not been irrefutably linked to human illness, there is sporadic evidence to suggest that GETV infection may be responsible for occasional undiagnosed fever.[18] RRV, one of the closest phylogenetic relatives of GETV, is a known human pathogen.[9]

3.3 Geographic Distribution

GETV has a wide range of distribution in Eurasia, Southeast and Far East Asia, Pacific islands, and Australasia.[17] It has not been reported in the Americas or Caribbean. GETV exists in a diverse variety of ecosystems from tropical climates to northern tundra.[19] It was first isolated from the *Culex gelidus* mosquito in Malaysia in 1955.[2]

3.4 Morbidity and Mortality

Clinical disease occurs infrequently as a result of GETV infection. Seropositivity in equine populations may be widespread in endemic areas, but observed clinical cases are generally limited. During outbreaks in horses, morbidity of up to 40% has been observed.[1] Specific data on morbidity in swine is not available. Though abortion and death of newborn piglets has occasionally been reported, mortality in species susceptible to GETV infection is thought to be negligible.[1]

4. Transmission

Transmission is primarily vector-borne. Mosquito vectors include *Cx. tritaeniorhynchus* and *Aedes vexans nipponii.*[1] The M-1 strain of GETV is capable of replicating in *Ae. aegypti* and *Cx. fatigans* mosquitoes.[16] Susceptibility to GETV infection has also been reported in *Cx. gelidus, Cx. fuscocephala, Ae. nigripes, Ae. communis, Ae. excrucians,*[19] *Ae. japonicus, Ae. albopictus, Cx. pipiens pallens, Cx. pseudo-vishnui, Cx. bitaeniorhynchus, Anopheles amictus, Armigeres subalbatus,* and *Tripteroides bambusa,* species, though their potential role in maintenance of natural transmission cycles is unclear.[21] *Ae. aegypti, Ae. albopictus, Ae. japonicus, Ae. vexans, Ae. communis, Ae. excrucians,* and *Cx. pipiens* have all been identified in the United States.[22]

Some evidence suggests the virus may also spread by direct contact through nasal discharge during outbreaks in horses.[1] Horses experimentally infected with GETV can exhibit high levels of the virus in their nasal secretions,[20] and aerosol transmission has been achieved experimentally.[5] Horse-to-horse spread has been implicated in an epizootic in horses India in 1990,[20] though aerosol transmission is generally believed to be uncommon in natural infection.[5] Gnotobiotic piglets inoculated intramuscularly at five days of age develop severe disease, while oronasal inoculation results in only mild clinical signs, further supporting the theory of natural infection by mosquito vector.[3] Similarly, attempts to isolate closely related SAGV from oral or nasal samples of experimentally infected pigs have been unsuccessful,

suggesting that transmission by contact or aerosol is unlikely.[11] Vertical transmission through milk[1] and transplacental infection in inoculated mice and hamsters has also been observed.[5]

Similar to Japanese encephalitis virus (JEV), GETV appears to be maintained in a transmission cycle in which pigs are amplifying hosts.[2] Epizootiological studies in Japan revealed an outbreak in pigs in two major swine production regions in 2014, leading up to a nearby outbreak in racehorses at a large training facility that same year.[23] Other vertebrates may also act as natural reservoirs or amplifying hosts, though infection in wildlife species is believed to be subclinical.[20]

5. Infection in Swine/Pathogenesis

5.1 Clinical Signs
Infection in swine appears to be dependent on age, typically subclinical in adults and potentially fatal in fetuses and newborns.[3] Infected newborn piglets are known to exhibit tremors, depression, and yellow-brown diarrhea.[15] Piglets inoculated experimentally at five days old have also exhibited anorexia, red discoloration of the skin, trembling of the tongue, and loss of coordination in the pelvic limbs at 20 hours post-infection. Some piglets died within 60–70 hours after inoculation with the virus, others were near death within two to three days; recovery in a single piglet, showing no clinical signs by two days post-infection, has also been observed.[3]

Both experimentally and naturally infected sows may farrow dead fetuses, especially when exposure to the virus is before 26–28 days of gestation.[15] Dead fetuses from a naturally infected sow can potentially be stunted, congested and discolored, or in some cases show no gross pathological lesions.[24]
Four- and five-month-old piglets, without antibodies to GETV, inoculated intramuscularly with the Kanagawa strain of the virus, showed no clinical signs.[3] In contrast, a mixed group of four week and eight month old pigs inoculated either intravenously or intramuscularly with GETV (MIP-99 or MI-110 strain) all developed transient fever and anorexia immediately following infection. Depression and diarrhea were also observed in the piglets inoculated with the MIP-99 strain.[25]

Symptoms in horses include fever, urticarial rash, and hind leg edema, but the disease is not life-threatening.[17]

5.2 Postmortem Lesions
Perivascular dermatitis, cuffing of cerebral blood vessels, and hyperplastic lymphoid tissue may be observed in experimentally inoculated animals euthanized during the period of clinical infection. The disease is not usually fatal,[1] except in fetuses and newborn piglets.[15]

6. Diagnosis

6.1 Clinical History
GETV was first reported in swine in 1987, and subsequent experimental inoculation in piglets has induced fever, anorexia, depression, and diarrhea. The virus is associated with diarrhea and high mortality in newborn piglets, and has also been found in late-term dead fetuses.[15]

The disease is better known for causing outbreaks in racehorses, with epizootics occurring in Japan in 1978, 1979, and 1983, in India in 1990,[23] and again in Japan in 2014.[23] Most horses make a full recovery within one week, and abortion is not a feature of the disease in horses.[20]

6.2 Tests to Detect Nucleic Acids, Virus, or Antigens

Virus isolation can be achieved using rabbit kidney (RK-13), African green monkey kidney (Vero)[15], swine kidney (SK-L), hamster lung (HmLu-1),[6] and pig kidney (CPK) cell lines,[24] or by intracerebral inoculation of suckling mice.[5] Reverse transcription polymerase chain reaction (RT-PCR) assays for detection of viral RNA are also available.[15]

A triplex RT-PCR assay has been described for the simultaneous detection of GETV, JEV, and Tahyna virus (TAHV). While primers and probes have been designed for all three viruses, only JEV-positive clinical samples were tested experimentally.[26] Multiplex RT-PCR has been developed for the simultaneous detection of six major swine RNA viruses – porcine reproductive and respiratory syndrome virus (PRRSV), JEV, porcine epidemic diarrhea virus (PEDV), porcine rotavirus A (PoRV-A), transmissible gastroenteritis virus (TGEV), and GETV. Primers were designed to target the nonstructural NSP1 protein of GETV, and the test was able to detect GETV propagated in Vero cell culture. Sensitivity of the assay to detect GETV from the mixture of viruses was actually higher than from a GETV solution alone.[27]

A new method for the discovery of unknown virus strains has been demonstrated with the successful identification of a novel GETV isolate. Random amplified polymorphic DNA (RAPD) involves the amplification of random DNA segments, and thus does not necessitate prior knowledge of the genome of the target organism. Virus discovery cDNA RAPD (VIDISCR) requires complete isolation of the viral genome without contamination of cellular RNA and DNA, followed by comparison of cloned and sequenced fragments with known viral genomes. This technique allows for rapid detection and potential identification of unknown or unexpected viruses in disease outbreaks.[18]

6.3 Tests to Detect Antibody

Serological tests include enzyme-linked immunosorbent assay (ELISA) and hemagglutination inhibition (HI) using paired sera.[15] Side-by-side comparison of these tests indicates that ELISA values correlate well with HI titers, though ELISA values may begin to rise several days before HI titers.[28] Anti-GETV antibodies can also be detected by complement fixation (CF) and serum neutralization (SN). The SN test is thought to be more specific in distinguishing GETV from other antigenically related alphaviruses,[5,20] however, only CF tests are able to separate GETV from closely related SAGV based on immunological differences.[7] This appears to be a result of the slight variation in capsid amino acid sequences, as capsid protein is a major CF antigen in some arboviruses.[7,9] HI and SN tests recognize envelope proteins.[7]

6.4 Samples

6.4.1 Preferred Samples

GETV has been isolated from spleen and lymph nodes, as well as placenta, amniotic fluid, and organs of dead fetuses.[15] Liver,[24] brain, lungs, kidneys, tonsils, and intestines have been used.[6] GETV has been recovered from the fecal sample of an experimentally inoculated piglet;[3] however attempted virus isolation from fecal or urine samples of horses has not been successful.[5] Plasma can also be used for virus isolation, [20] though viremia is short-lived and samples for detection of GETV should be collected at, or soon after, the onset of fever.[5] Ideally, any serological tests should include paired samples to demonstrate a rise in titer from acute to convalescent phases of disease.[20]

6.4.2 Oral Fluids

Recovery of the virus from oral swabs of piglets inoculated oronasally has been reported at two days post-infection,[3] but there is apparently no data available on oral sampling in naturally occurring infection in swine. Nasal swabs and saliva of acutely infected individuals have been used for diagnosis in horses with varying degrees of success.[20]

7. Immunity

7.1 Post-exposure
Development of serum neutralizing anti-GETV antibodies has been reported at six days post-infection in pigs, with maximum titers observed at day 14.[25] Following natural infection in horses, individuals with a serum neutralizing titer greater than 1:4 are considered to be resistant to GETV challenge.[1] In serological studies of closely related SAGV, the serum neutralizing antibody titer was much higher in naturally infected pigs than in experimentally infected pigs, likely resulting from repeated reinfection by mosquito vectors.[11]

7.2 Vaccines
A live-attenuated trivalent vaccine for protection against GETV, JEV, and porcine parvovirus (PPV) has been available in Japan since 1993; however, a recently sequenced Japanese strain of GETV is not the same as that of the vaccine.[8] It is unknown whether this particular vaccine offers complete protection against new strains of the virus. Mention of regular GETV vaccination of sows has appeared in unrelated studies,[29] though exact information on the administered vaccine is unavailable.

An inactivated vaccine for GETV has been available since 1979, and a bivalent inactivated vaccine for GETV and JEV has been available since 1997, both for use in horses in Japan.[30] Vaccination programs at racehorse training facilities appeared to be effective for many years, despite serological evidence of continued circulation of the virus. No GETV outbreaks were reported until just recently, in 2014, prompting reinvestigation of vaccine efficacy and epidemiology of the virus.[23]

7.3 Cross-protection
All mosquito-borne alphaviruses are antigenically related, but most are distinguishable by cross-reactivity tests.[4] They are divided into eight antigenic complexes based on their serological cross-reactivity. Conservation among the viral C proteins and E1 glycoproteins facilitates cross-reactivity within the serogroups, while antibodies against the E2 proteins tend to be virus specific[9] and contain most neutralizing epitopes.[15]

8. Prevention and Control
There are currently no effective antiviral remedies available for the treatment of alphaviruses, only palliative care with analgesics and anti-inflammatory drugs.[31] Prevention and control in endemic areas centers on control of mosquito vectors by limiting breeding sites, applying insecticides, and reducing exposure by housing susceptible animals indoors at night. Certain at-risk horse populations in Japan receive yearly GETV vaccinations, seemingly limiting the number of outbreaks.[20] No data is available on the prevalence and efficacy of vaccination practices in swine.

9. World Organization for Animal Health (OIE) Terrestrial Animal Health Code
GETV is not covered in the 2015 OIE Terrestrial Animal Health Code. There are no recommendations for importation of horses or swine from countries or zones infected with GETV.

10. Gaps in Preparedness
GETV is primarily an equine disease known for several sporadic, concentrated, nonfatal outbreaks at large horse boarding facilities over the past four decades. It is generally underrepresented in current literature, and even less is known about the nature of clinical disease in swine and humans and the exact prevalence among these populations.

Despite the zoonotic potential and global distribution of alphaviruses, the pathogenesis of alphavirus infection in humans is not clearly understood, and licensed human vaccines and targeted anti-viral

therapies are lacking.[31] Evaluation of the efficacy of previously developed swine and horse vaccines against current GETV strains is also warranted, along with development of new methods of vaccination available for use in the United States.

The environmentally diverse range of GETV, its ability to mutate rapidly, and its potential to be transmitted by a wide variety of mosquito vector species, is certainly cause for further research and surveillance. Investigation into additional host species and local mosquito vectors could lead to a better understanding of risk to livestock and humans and a more targeted response if the virus reaches North America.

ACKNOWLEDGEMENTS

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