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Uncommon and Neglected Venezuelan Viral Diseases: Etiologic Agents, Physiopathological, Clinical and Epidemiological Characteristics (Enfermedades virales venezolanas infrecuentes y olvidadas: agentes etiológicos, características fisiopatológicas, clínicas y epidemiológicas)

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[ARTÍCULO DE REVISIÓN]

Abstract (english)

Viral infectious diseases are common in Venezuela, influenza, dengue, yellow fever, HIV infection, viral Hepatitis, chikungunya fever and many others represent public health problems in the country and therefore, have been well documented. However, other rarer and even unique or lethal viral illnesses present in Venezuela are usually poorly understood or even unknown. This review described Venezuelan Hemorrhagic Fever, Venezuelan Equine Encephalitis, Hantavirus Infections and Mayaro fever, named as neglected diseases, emphasizing the etiologic agents and their most relevant pathogenic mechanisms, clinical and epidemiological characteristics. Although there is not an official report about the re-emergence of these diseases, falling living standards and unsanitary conditions, together with limited accessibility to hygiene products and medical supplies, put us on alert about the re-emergence of these neglected diseases.

Keywords (english)

Viral disease, Venezuela, Guanarito, Arenavirus, Encephalitis, Togavirus, Alphavirus, Hantavirus, Mayaro, Neglected diseases.

Resumen (español)

Las enfermedades infecciosas virales son comunes en Venezuela, influenza, dengue, fiebre amarilla, infección por VIH, hepatitis viral, fiebre chikungunya y muchas otras representan problemas de salud pública en el país y por lo tanto, han sido bien documentadas. Sin embargo, otras enfermedades virales más raras e incluso únicas y letales presentes en Venezuela son generalmente poco estudiadas y hasta desconocidas. Esta revisión describe alguna de estas enfermedades olvidadas tales como la fiebre hemorrágica venezolana, la encefalitis equina venezolana, las infecciones por hantavirus y la fiebre de Mayaro, haciendo hincapié en los agentes etiológicos y en sus mecanismos patogénicos más relevantes, características clínicas y epidemiológicas. Aunque no hay informes oficiales sobre el resurgimiento de estas enfermedades, la caída de los niveles de vida y las condiciones insalubres, junto con el acceso limitado a los productos de higiene y suministros médicos, debe alertar sobre el resurgimiento de estas enfermedades olvidadas.

Palabras clave (español)

Enfermedad viral, Venezuela, Guanarito, Arenavirus, Encefalitis, Togavirus, Alfavirus, Hantavirus, Mayaro, Enfermedades olvidadas.

Introduction

Viral infectious diseases represent an important public health problem in Latin America and Venezuela, many of them are endemic and affect

thousands of people every year. Dengue virus for example, has expanded in the whole American continent, mainly because the incredible spreading out that its vector has experimented during the last decade (1), indeed, it has been reported that only in 2014 there had been more than 30000 cases of

dengue in Venezuela (2). Moreover, several hepatitis virus have been described in different regions and in geographically isolated populations around the country (1), until July, 561 cases of hepatitis A and B, had been reported in 2014, similar data is presented with many other viral diseases such as HIV/AIDS (1362 cases reported in 2014), or influenza (4269 cases reported in 2014) (2). Other diseases such as yellow fever are endemic in several regions around the country (3), or represent new risks to the population, as chikungunya fever (2).

These diseases have a clear public health impact and are widely known among health professionals, nevertheless, others are uncommon and poorly understood, therefore they are unnoticed or grossly underreported because in the absence of laboratory confirmation, are recorded as much more common diseases like dengue or malaria.

The aim of this review is to gather updated information about Venezuelan Hemorrhagic Fever, Venezuelan Equine Encephalitis, Hantavirus Infections and Mayaro fever, which are neglected viral infections, still latent in our population.

Viral Infection: an overview

The etiologic agents of Venezuelan Hemorrhagic Fever, Venezuelan Equine Encephalitis, Hantavirus Infections and Mayaro fever, are ribonucleic acid (RNA) viruses, which spread is facilitated by environmental polluting, unhealthy conditions, and growth of rodent and mosquitoes populations(4). Some RNA viruses have re-emerged and are currently producing pandemics, although is not the case of the diseases treated in this review.

In the environment, viruses remain infectious for several weeks depending on different factors such as humidity, temperature, and association with protective proteins (5). A full genomic characterization of 199 RNA viruses belonging to virus families Arenaviridae, Bunyaviridae, Filoviridae, Flaviviridae, and Togaviridae, has been done (6) (figure 1). All these viruses are widely spread around the world, transmission to humans occurs via inhalation of aerosolized rodent urine, saliva, and feces, rarely by rodent bites, and can cause severe and often fatal zoonotic diseases (5). In addition, at least 38 viral species are transmitted by ticks.

Tick-borne viruses are found in six different virus families (Asfarviridae, Reoviridae, Rhabdoviridae, Orthomyxoviridae, Bunyaviridae, Flaviviridae) and at least 9 genera. Some tick-borne viruses pose a

significant threat to the health of humans (Tick-borne encephalitis virus, Crimean-Congo haemorrhagic fever virus) or livestock (African swine fever virus, Nairobi sheep disease virus) (7).

All stages of their replication cycle depend on support by host-encoded factors (8). During their replication cycle, viruses hijack and reprogram the host cellular pathways to facilitate their propagation, thus they must penetrate its target cell, and start its life cycle; which usually includes internalization, genome expression, replication, synthesis of components and finally morphogenesis and budding (9).

Most viruses usually go through a limited replication process in the cells through which they initially penetrated the host, to eventually advance to specific tissues for which they present particular tropism and usually clinical manifestations of viral diseases are consequence of the cellular damage that follows the virus' replication and budding. Throughout this process, the virus must also disseminate to different hosts, usually through body fluids. Finally, either resolution or death may occur, depending greatly of the host genetic susceptibility and immunological state (10).

Venezuelan Hemorrhagic Fever (VHF)

Arenaviruses include multiple human pathogens ranging from the low-risk lymphocytic choriomeningitis virus (LCMV) to highly virulent hemorrhagic fever (HF) causing viruses such as Lassa (LASV), Junin (JUNV), Machupo (MACV), Lujo (LUJV), Sabia (SABV), Guanarito (GTOV), and Chapare (CHPV), for which there are limited preventative and therapeutic measures (11). VHF has been associated with Guanarito Virus infection, which was first isolated in spleen from a deceased patient in 1989 (12, 13). GTOV belongs to the Arenavirus genus of the Arenaviridae family (14) and belongs to the New World arenaviruses (figure 1a), also known as Tacaribe Complex (15, 16), that includes several viruses such as JUNV, MACV and SABV, which are also known etiologic agents of hemorrhagic fevers in Argentina, Bolivia and Brazil, respectively (16, 17). The other group, known as Old World arenaviruses, includes Lassa virus (responsible of hemorrhagic fevers in Africa) and the Lymphocytic Choriomeningitis Virus, which provokes aseptic meningitis (16). Even though they are phylogenetically related, these viruses appear to have evolved independently for a very long time, leading to a different host range, geographical distribution and pathogenic potential (17).

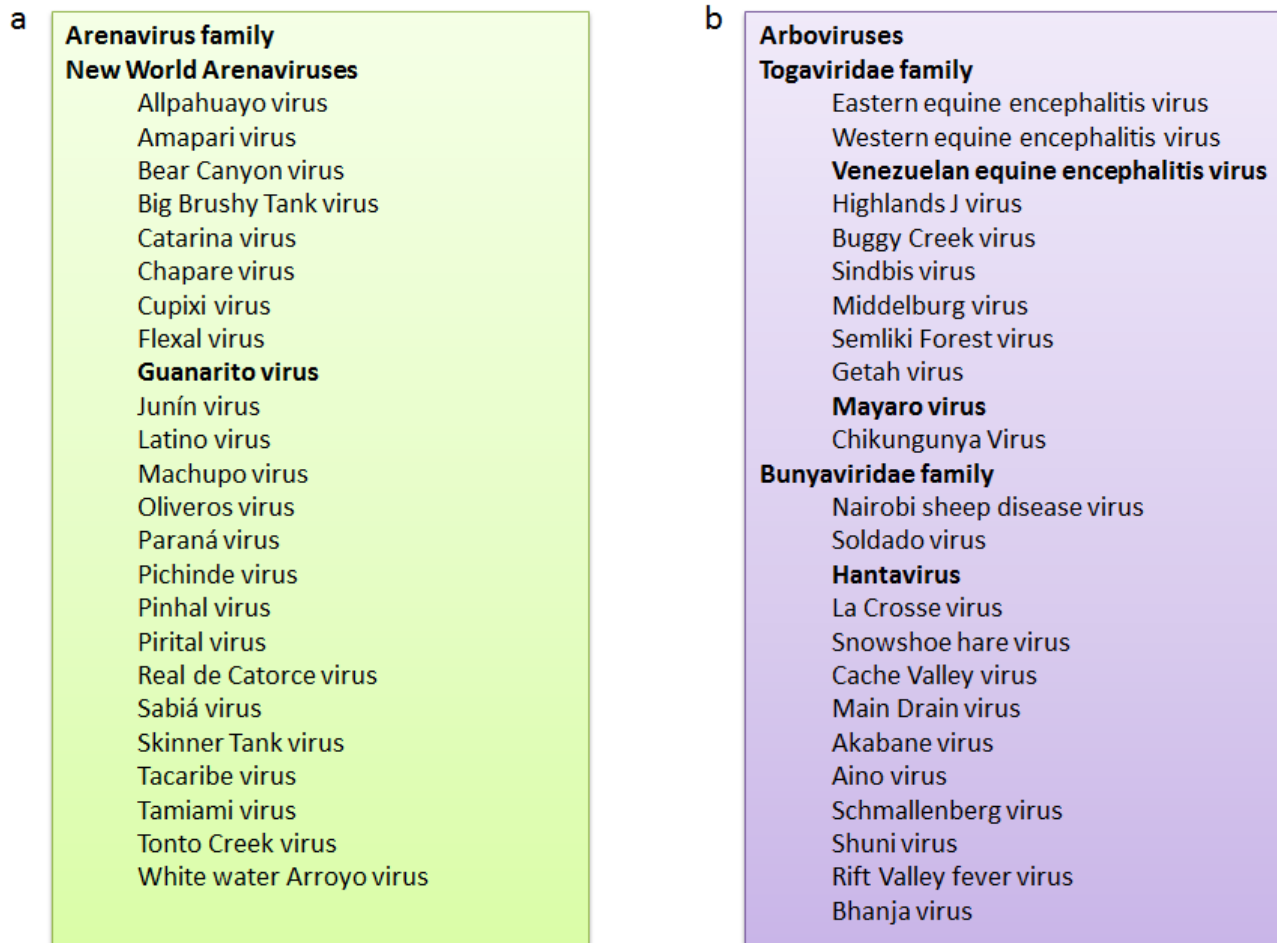


Figure 1. Phylogenetic classification of virus involved in some neglected diseases in Venezuela. Arenavirus family **1a**, Togaviridae and Bunyaviridae families **1b**. While Guanarito virus does not require an arthropod vector to be transmitted to humans, Venezuelan Equine Encephalitis, and Mayaro virus are arboviruses. While the whole Bunyaviridae is also transmitted by arthropods, mainly mosquitoes; Hantavirus represent the only exception.

Characteristics and Lifecycle

As other members of this group, GTOV genetic information is encoded in two single strand RNA molecules that are classified as L (large, 7,3 kb) and S (small 3,5 kb). Even though they have been usually classified as negative sensed viruses, both RNA chains of arenaviruses use an ambisense coding strategy that allows them to translate two different proteins separated by a noncoding region, in opposite directions (18). The S molecule codifies the Nucleoprotein (NP) which plays a crucial role in the genome replication and has also shown capacity to interfere with the normal activity of IFN-I-type molecules; it also includes the gene of the viral glycoprotein precursor (GPC) that is eventually processed by the molecular apparatus of the infected

cell to produce the two mature structural glycoproteins of the virus (GP-1 and GP-2, required for the internalization process). The L RNA molecule codifies the viral RNA polymerase (L protein) and a small RING finger protein (known as Z Protein) which apparently could interact with some eukaryotic translation initiator factors (15).

Interactions between the GP complex and the Human Transferrin Receptor 1 (hTfR1), that is regulated by the cytosolic level of iron, allows the complex internalization and deliver to the acidic endosome via the clathrin-mediated pathway (11, 12, 15, 19), it is then released into the cytoplasm through a pH-dependent membrane fusion step that is accomplished by the transmembrane portion of the viral glycoprotein GP2 (20). Under low iron dietary

condition in some endemic areas, Tfr1 gene expression can be upregulated, resulting in a suspected worse disease prognosis (21), currently, specific antibodies of the hTfr1 have been used to effectively inhibit viral replication (19).

After reaching the cytoplasm, the viral L polymerase is released and starts viral RNA replication; during the process short mRNA molecules are generated, which encode both the NP protein and the L polymerase itself. These two proteins later attach to the RNA molecules forming the active transcription unit, which eventually transcribes the GPC and Z proteins. After the GPC is cleaved by cellular enzymes into the Gp-1 and GP-2 proteins, Z apparently inhibits the RNA replication process, favoring instead the packaging of these molecules inside the viral capsid and allowing the formation of the virions which finally burst out from host cells in portions of the membrane enriched with both GP's and Z proteins, incorporating this membrane regions to its own structure (12, 15).

Epidemiology

Guanarito virus infects rodents, that act as its natural reservoir, specifically *Zygodontomys brevicauda*, located mostly in the central and western Venezuelan Llanos, mainly in Portuguesa, Barinas and Guarico, states that represent the circulation area of the virus, and are considered endemic regions; other nearby states such as Apure and Cojedes are considered areas at risk (22, 23). *Sigmodon alstoni* was also proposed as a natural reservoir for Guanarito virus, however, these rodents were eventually identified as reservoirs of a different, non-pathogenic arenavirus known as Pirital, also isolated in Portuguesa in 1997 (23-25). Guanarito virus also has been isolated in feces and urine from rodents, and infects humans when the aerolized particles are inhaled (12). However, the virus can also be transmitted to humans by a biting from the infected animal or by contact between the excretions and a skin injury (22) (figure 2a).

Rodents are commonly found near roads and cultivated fields but rarely inside the houses or nearby areas (22, 26). This indicates that patients get infected outdoors, which is why it affects mainly male farmers, between the ages of 15 and 49 who work in contaminated areas with the rodent's excretions (22). This also explains why most part of the cases (53, 3%) are reported during November and January, months of intense agricultural activity (26). The virus is endemically present in the affected region, especially

the Guanarito Municipality in the south of Portuguesa, where it was first isolated, however outbreaks have occurred, mainly during 1989, 1992 and 2002 (12). Until 2010, 728 confirmed cases had been reported and 171 were fatal (22). On July 26th, 8 cases had been confirmed only in 2014 (2).

Clinical Presentation and Pathogenesis

VHF was described in 1989 after a group of farmers from Portuguesa, Venezuela, became ill. The clinical onset of this disease is similar to that of other South American hemorrhagic fevers (12, 19). Characteristically, after a two weeks incubation period, undifferentiated fever, accompanied by malaises, headaches, arthralgia, sore throat and other nonspecific symptoms, are present. This is very common with patients infected with Guanarito virus are frequently misdiagnosed. The patients usually get worse, developing vomits and diarrhea which may lead to dehydration. Eventually, the hemorrhagic signs such as epistaxis, bleeding gums, and melena tend to appear; hemoptysis, hematemesis, hematuria and menorrhagia have also been described. Other symptoms include Central Nervous System (CNS) manifestations such as tremors and convulsion, being these, a sign of poor prognosis (12, 26). Laboratory findings such as leukopenia and thrombocytopenia are also common (22). Mortality rate has been described to round the 30 %, increasing to 70% when seizures are present (26) (see table 1).

VHF diagnosis must always be confirmed by identifying the L polymerase and GP1 genes from patient's samples using a reverse transcriptase PCR (RT-PCR) assay. Recently, JUNV infection has been confirmed by ELISA, using NP-specific antibodies, and this technique could probably be used to identify Guanarito Virus proteins as well. (12).

The pathogenic mechanism through which Guanarito causes these symptoms is not yet fully understood, however active replication has been described in lymphoid cells, this could create a direct cytopathic effect, activating several plasmatic and inflammatory factors which eventually conduct to capillary damage and increased permeability, this is consisting with the high interferon levels found in these patients (22). Autopsies show pulmonary congestion and edema associated with hemorrhagic findings, which were also present in liver and kidneys. Blood has also been found in the gastrointestinal tract and other hollow viscera (12).

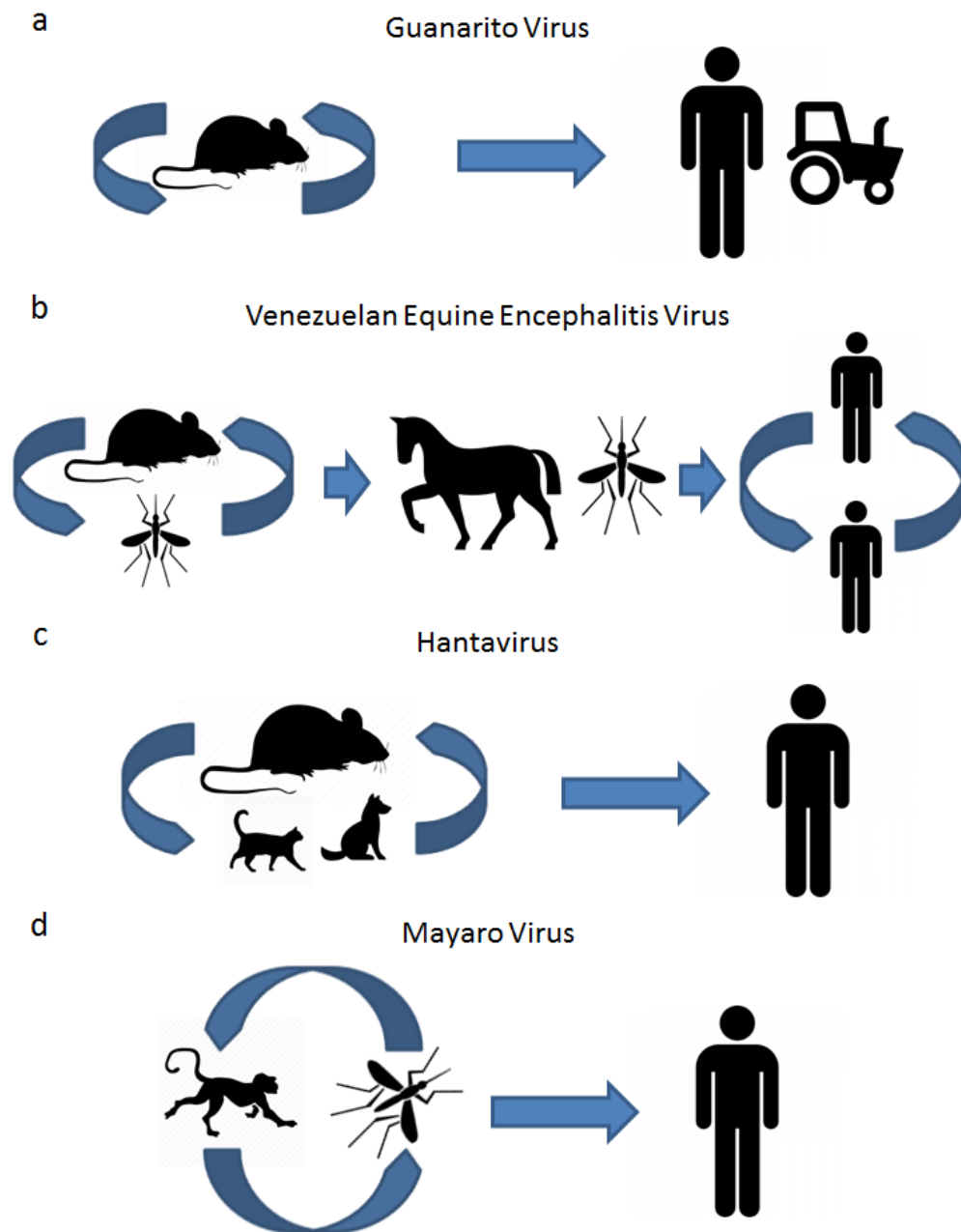


Figure 2. Vectors and reservoirs of some neglected diseases in Venezuela. Guanarito Virus **2a**: Chronic infections of hosts by excretions and bitings. Humans become infected by feces aerolized by agricultural activity. Venezuelan Equine Encephalitis Virus (VEEV) **2b**: Enzootic cycle is maintained in small mammals by vectors such as *Culex spp.* One of these vectors can infect an equine, which acts as amplification host. The VEEV can then be transmitted to humans, starting an epizootic cycle by *Aedes spp.* or *Psophora spp.* Hantavirus **2c**: Rats are the main animal reservoir but dogs, cats, cattle and other mammals can also be infected. Humans who get in close contact with feces, saliva, urine or other excretions of infected animals, become infected. Mayaro Virus **2d**: Marmosets and small primates are the main reservoir, it is both sustained in these populations and transmitted to humans by mosquitoes from genus *Haemagogus*, its main vector.

Altered endothelial barrier functions are implicated as the cause of hemorrhagic disease following. hTfR1, is highly expressed on vascular endothelial cells (EC) (27) and high levels of productive infection are observed in vitro in presence of

arenavirus (28). In vitro assays in presence of JUNV show that a productive infection of EC induced expression of cell adhesion molecules (ICAM-1) and, to a lesser extent, VCAM-1 (29). ICAM up-regulation is involved in EC activation resulted in reduced

expression and secretion of coagulation factors, such as the prothrombic von Willebrand factor (VWF). Interestingly, infection of EC with JUNV, markedly induced the production of the vasoactive mediator nitric oxide (NO) and prostaglandin PGI₂ (29), providing a possible link between viral infection and increased vascular permeability observed in fatal Argentine haemorrhagic fever cases (28)

Venezuelan Equine Encephalitis (VEE)

This disease is produced by the Venezuelan Equine Encephalitis Viruses (VEEV) members of the *Togaviridae* family and the *Alphavirus* genus, first isolated from the brain of dead horses in Yaracuy, Venezuela, in 1938 (30) (figure 1b). Human and animal disease take place when VEEV undergoes an amplification cycle where equids (horses, donkeys and mules) become infected and develop high titer viremia, facilitating transmission by *Aedes* and *Psorophora spp.* mosquitoes to susceptible equids or people (31). Six serotypes have been described: I to VI, along as 13 different subtypes, all of them with serological differences. Subtypes IAB and IC are the most commonly found in Venezuela (32) associated with human and equine infections, being described as epizootic (figure 2b) strains; the other 11 subtypes usually infect small mammals instead, but can also infect humans and even cause death, being known as enzootic strains (30, 33). The epizootic strains appear to be able to develop from enzootic viruses that suffer mutations that expand their host range (34). The enzootic transmission cycle of VEEV is maintained among rodents and other vertebrates (e.g., cotton rats, spiny rats, bats, and opossums) as reservoirs and mosquitoes in the subgenus *Culex (Melanoconion)* as primary vectors (figure 2b) (35). During epizootic or epidemic cycles, equids are efficient amplification hosts with high-titered viremia for mosquito transmission. Therefore, infections from horses will be transmitted to humans during epizootic events. In addition to humans, dogs, pigs, cats, cattle, goats, bats, and birds can be infected during an epizootic event. They develop viremia that can be a source of mosquito infections (30, 35).

Characteristics and Lifecycle

Togaviruses, including VEEV, are icosahedral, enveloped, single strand positive sensed RNA viruses, with a genome of approximately 11400 nucleotides in length, which encodes four nonstructural proteins (nsP1, 2, 3 and 4) required for the viral replication and

protein processing (30), and three structural ones, known as Capsid Protein (CP), and envelope proteins 1 and 2 (E1 and E2) (33). Recently a third envelope protein (E3) has been identified in the viral capsid (34).

It has been shown that E2 is involved in targeting and binding to the host cell, using laminin binding protein as a receptor for receptor-mediated endocytosis (30, 34). However, other proteins must be involved in the process, explaining the restricted host range of the different strains (30). Once the virus reaches the endosome and in presence of a low pH environment, E1 protein promotes membrane fusion and release of virions in the cytoplasm (30). At this point translation of the nonstructural proteins takes place, allowing the beginning of the replication process, eventually large negative strands of RNA are produced and serve as a template to form the small positive strands and sub genomic chains that encode the structural polypeptides that are finally cleaved by cellular mechanisms, forming the mature structural proteins (30, 34). Finally, multiple copies of the CP interact with the newly replicated RNA to form the viral nucleocapsid. At the same time, trimmers of E1 and E2 organize in the cellular membrane and are incorporated to the viral nucleocapsid before the new virions leave the cell (30, 34).

Epidemiology

All VEEV are arboviruses and are mainly transmitted by mosquitoes from the genus *Aedes*, *Culex* and *Ochlerotatus*, nevertheless other arthropods such as tick (*Amblyomma* and *Hyalomma* genus) and some species of flies, are also capable of transmitting the epizootic strains, although in an inefficient way (30). The viruses first infect the epithelial cells of the arthropod's gut and eventually move to secondary tissues such as the salivary glands, from where they can pass to the mammal's bloodstream after the vector's biting. The enzootic strains mostly infect small mammals. Epizootic viruses, on the other hand infect horses, donkeys and other equines, in which they suffer replication and from which are eventually transmitted to humans. Even though outbreaks of VEEV have never occurred in absence of horse populations, urban transmission is potentially possible through *A. aegypti* due to its capability of getting infected after biting a human (30).

The VEEV are present in the whole American continent, having been isolated in Texas, Mexico, Guatemala, El Salvador, Nicaragua, Panama, Colombia, Ecuador, Peru, Venezuela, and Trinidad (33, 36). The first outbreaks reported occurred in 1935 in Colombia, since then the virus quickly spread to northern

Venezuela and Peru between 1936 and 1940, reaching Trinidad in 1943. During this period of time, the role of horses in the transmission had not been established yet. After major outbreaks in Colombia during the 60's and Central America, México and Texas during the 70's, reports dropped until 1992 when several cases appeared, first in Trujillo and the western coast of Lake Maracaibo (Venezuela). One of the major Venezuelan outbreaks took place in 1995, with cases in Falcon, Carabobo, Yaracuy, Zulia, and the Guajira Peninsula, affecting an estimated of 75.000 to 100.000 people. Is remarkable the fact that this event was preceded by unusually heavy rainfalls which favored the reproduction of the transmitter mosquitoes (30). In 2010 the 62, 2% of 111 equines studied using ELISA tests in Lara, Venezuela resulted positives for VEEV(37).

Clinical Presentation and Pathogenesis

Even though the VEE is extremely lethal for horses and many other equines (reaching up to 80% of mortality). In humans, disease is presented in a wide spectrum of severity going from an unapparent infection or subtle febrile disease in some cases, or an active encephalitis and even death (33). In humans,

the mortality rate usually varies from 4% to 14%; affecting every age group, nevertheless, neurological disease and sequels are more common in children. The virus can also affect the fetus if acquired by the mother during the pregnancy, leading to malformations and spontaneous abortions (30). In the apparent cases, the disease usually develops after a 2-5 days incubation period, the most usually observed signs and symptoms include myalgia, mainly in the lumbar area, headaches, nausea, vomits, diarrhea, fever, tachycardia, leukopenia and retro ocular pain; the neurological symptoms, generally less common, include convulsions, confusion, somnolence and photophobia. Must part of the cases usually remit after 4 to 6 days, however in some patients, stupor, coma and eventually death may occur. In these last cases is also common to find hemorrhagic damage in brain, lungs and gastrointestinal tract (38).

VEE is usually confirmed by ELISA, using monoclonal murine antibodies, specific to E1, E2 and CP (39). More recently, recombinant human anti-VEEV single-chain variable fragments (scFv) have proved capacity to use complete and active virus particles as antigens (40). The confirmation of VEE infection consists of detection of IgM antibody in the

Table 1. Clinical Presentation of some neglected viral diseases in Venezuela.

Clinical Manifestations	Guanarito Virus	Venezuelan Equine Encephalitis	Hantavirus	Mayaro Virus
General	+++ (initial stages)	+	+ + (initial stages)	+++
Osteo-muscular	+ (initial stages)	+	+ +	
Hemorrhagic	+++	+ (associated to CNS damage)	++ +++	+
Gastrointestinal	++	+	+ +	
CNS	+	+++ (generally only in children)		
Respiratory	+		+++	
Leukopenia	+	+		
Thrombocytopenia	++		++ +++	+
Others		Congenital malformations and spontaneous abortions are common in infections during pregnancy	Signs of renal failure such as oliguria, hematuria, proteinuria, hyperazoemia	Photophobia, chills, jaundice and polyuria have been described

CNS: Central Nervous System. Hantavirus Pulmonary Syndrome (HPS): red. Hantavirus Fever with Renal Syndrome (HFRS): blue

cerebrospinal fluid (CSF) or serum or virus detection by PCR (38).

A murine model that mimics human and equine disease, proved that lethal disease starts with productive infection of lymphoid tissue and ends in the destruction of the CNS. At the later phase of encephalitis development, infectious virus is low to undetectable in peripheral organs and blood, but high virus levels are found in the brain and death occurs 5–7 days after infection. Conventional T-cells are critical to the host defense against alphavirus infection and also repairing neural damage (41). The inflammatory response, mainly represented by the activation of effector populations of NK cells, seems to play a key role in pathogenesis. Even though early production of type-I IFN has shown a positive effect on the control of infection, high production of several cytokines, especially IL-2, has been associated with lethal encephalitis. Interestingly, NK depletion has been related to minimal but statistically significant suppression of viral replication in mice; which clearly indicates that the cytotoxicity mediated by these cells plays an important, yet poorly understood role on the pathogenesis of encephalitis (42). Apoptosis also seems to play an important role in the development of the disease, since its reduction following treatment with melatonin has decreased the mortality in infected mice (43).

Hantavirus Infection

Hantavirus is a genus of viruses that belong to the Bunyaviridae family (figure 1b), very common in South America, where more than 18 species have been described, most part of them causing subclinical infections, nevertheless, some can produce severe conditions with a mortality rate of nearly 60% (44). These diseases are classified in two major groups: the hemorrhagic fever with renal syndrome (HFRS), common in Africa and Asia, and the hantavirus cardiopulmonary syndrome” (HPS) in the Americas with case fatality rates of up to 35–50%(45). HPS was first described in the southwestern United States in 1993 after several patients developed febrile conditions accompanied by severe pulmonary edema and hypotension (46). Some of the species related to the development of cardiopulmonary symptomatology found in South America are: Andes, Anajatuba, Araraquara, Paranoá, Bermejo, Castelo dos Sonhos, Juquitiba, Araucária, Laguna Negra, Lechiguana, Maripa, Oran, Rio Mamore and Tunari (47). On the other hand HFRS is mainly associated with the

Hantaan, Seoul, Dobrava and Puumala species, among others (48, 49).

Characteristics and Lifecycle

Hantaviruses are spherical and enveloped, its genome consists of three single strand, negative sensed RNA molecules, designated as L (Large), M (Medium) and S (Small), which respectively codify the nucleocapsid protein (NP), the glycoproteins 1 and 2 (GP1, GP2) and an RNA dependent RNA polymerase (50). Hantaviruses seem to enter their host cells through interactions with the β integrin receptors (51), being endothelial cells their main targets (mainly in kidneys and lungs), and secondarily infecting leukocytes (52, 53). After internalization, a pH-dependent membrane fusion, releases the nucleocapsid in the cytoplasm, where the NP and the RNA polymerase are first translated in free ribosomes. Eventually, the rest of the proteins are translated in the endoplasmic reticulum and suffer glycosylation in the Golgi complex. Hantavirions are thought to form in this organelle’s membrane before migrating to the plasmatic membrane in secretory vesicles and finally leaving the cell through exocytosis (50).

Epidemiology

Most Hantaviruses have their natural reservoirs in many species of rodents and even though others mammals like cats and cattle have been infected it is not known if this is an incidental event or such animals might also act as reservoirs (54, 55). Human infection occurs accidentally when saliva, feces or urine of infected animals is aerosolized and inhaled by the patient, explaining why hantavirus infection is mainly associated with people who get in close contact with these animals (56, 57) (figure 2c).

In Venezuela, Hantavirus infection has been described as an uncommon but widely distributed disease (58). Even though Venezuelan patients have shown the presence of specific antibodies in their bloodstream, the viruses have never been isolated from their samples (48). In 1997 a new species of Hantavirus was isolated in several rodent species (*Oryzomys bicolor*, *Rattus rattus*, *Zygodontomys brevicauda* and mainly *Sigmodon alstoni*) for the first time in Portuguesa, Venezuela, being named Caño Delgado Virus (59). Even though symptomatic infection has not been described with this virus, its’ vector’s wide distribution and the sub registration of cases, strongly demand further investigation (60).

As described above, close contact with the rodent’s excretions is required for humans to get infected, for this reason the viruses commonly affect

farmers in rural areas, describing different patterns during the different seasons. Nevertheless, other professionals such as veterinarians, pest control workers, and zoologist, might get infected in urban areas, where Hantaviruses species can be present in black rats (*Rattus rattus*) (44, 61).

Clinical Presentation and Pathogenesis of HPS and HFRS

The pathogenesis of hantavirus disease is characterized by changes in blood coagulation, vasodilatation and disturbances in the barrier function of the capillaries, resulting in extravasation of blood and inflammatory processes in the affected organs (62). HPS develops as a febrile undifferentiated condition characterized by headaches, nausea, vomiting and myalgia. Abdominal pain, diarrhea, chills, malaise, dizziness and pulmonary symptoms such as productive cough and shortness of breath are common; initially no hemorrhagic symptoms are evident. Tachycardia and tachypnea are also regular findings. As the infection advances, most patients will present alveolar and interstitial infiltrates; in most part of fatal cases pulmonary edema and hypotension appear shortly after, with death occurring between the 7th and 8th day after the onset of the condition (46). A case was reported in El Tigre, Anzoátegui, Venezuela, in July 1999, Hantavirus-specific IgM and IgG antibodies were detected in the patient (48).

HFRS is characterized by a similar symptomatology; however, petechiae, hematuria, brain, gastrointestinal, and conjunctival hemorrhages are usual. Signs of renal damage such as oliguria, proteinuria, elevation of blood urea and creatinine are also common (63). Although this condition is usually observed in Africa and Asia, a case was reported in Portuguesa, Venezuela, in 1993, and eventually confirmed serologically (48).

Hantavirus infection is generally confirmed using ELISA to identify specific IgM and IgG antibodies. However, recently these antibodies have been detected with more rapid immunochromatographic tests using recombinant hantavirus antigens (64, 65).

EC infection could lead to viremia, which has been postulated to play an important role in the vascular dysfunction, Hantaviruses bind and inactivate $\alpha\beta3$ integrin that normally form complexes with VEGF receptors, and thus Hantaviruses similarly disengage the normal regulation of VEGF-induced permeability. Hantaviruses that cause HFRS or HPS were found to commonly use $\alpha\beta3$ integrins to enter primary human EC (66). These findings define EC receptors as targets of dysregulated VEGF-directed permeability responses

and potential mechanisms by which hantaviruses inactivate platelets and contribute to thrombocytopenia. (67). Elevated production of TNF- α , IL-2, IL-6, IFN- γ and IFN- α from infected dendritic cells might also play an important role in the disease (49, 52). High or too low counts of specific TCD8⁺ cells have both been related with poor prognosis. In a similar way impaired function of regulatory T-cells have also shown a role in pathogenesis of both HCPS and HFRS, making evident that cytotoxic response plays a key role in the physiopathology of the Hantavirus infection (44, 49, 68).

Mayaro Fever

Mayaro fever is produced by the Mayaro Virus (MAYV), part of the Alphavirus genus and Togaviridae family, being closely related to Chikungunya, O'nyong-nyong, Ross River, Barmah Forest, and Sindbis viruses, all of them belonging to the Semliki Forest Virus Group (SFV) (69, 70) (figure 1b). The virus takes its name from the community where it was first isolated in Trinidad and Tobago in 1954 (69). Two different genotypes of MAYV have been identified and denominated L and D (71), Venezuelan isolate grouped within genotype D and was most closely related to isolates from Trinidad (32).

Characteristics and Lifecycle

As other alphaviruses, MAYV's genome consists of a single strand, positive sensed, 11 kb RNA molecule divided in a genomic region, that codifies four nonstructural proteins (nsP1, nsP2, nsP3 and nsP4) and a subgenomic region containing structural proteins (E1, E2, E3, C and 6K) (69). These viruses' genome shows a high rate of mutation, especially in the structural region, which allows them to present an incredibly high host range (72). E2 has a crucial role during the internalization process, interacting with a specific receptor in the host cell's surface, favoring endocytosis of the virus. Once in the endosome and at a low pH, nucleocapsid is released in the cytoplasm and after being degraded exposes the RNA, allowing the beginning of transcription and replication processes. Some nonstructural proteins such as nsP2 apparently can inhibit transcription of the cellular genome, favoring viral transcription and replication instead (69).

Epidemiology

The MAYV is endemic in many South American tropical forests, having as main natural

reservoir marmosets and many other primates. It is transmitted between these primates to humans through mosquitoes from the genus *Haemagogus*, which represent its main vector (73) (figure 2d). A remarkable fact is that MAYV can infect a wide range of vertebrates, having been isolated also in migratory birds and lizards (69, 74). Although vector-dependent transmission is typical, airborne transmission has been described under laboratory conditions (75).

Although having enzootic cycles in most part of South America, small outbreaks of Mayaro fever have been described in Bolivia, Brazil and Peru (69, 70). A case was reported in France during 2010, in a patient who had recently returned from the Brazilian Amazon (76). In Venezuela, the first cases of Mayaro disease were described in January 2000, in four patients that had camped in a rural zone of Miranda (69, 70). The most recent outbreak of this disease in Venezuelan territory occurred between February and March 2010 in Ospino, Portuguesa with 72 cases. Both, vectors and reservoirs of MAYV are known to inhabit in this region (69). As these cases indicate, Mayaro fever is rare and usually affects people who have recently visited tropical forests where the enzootic cycle of the virus takes place (70).

Clinical Presentation and Pathogenesis of Mayaro Fever

Mayaro disease is an undifferentiated disease, similar to dengue and other febrile illnesses (70). Common symptoms include headaches, myalgia, arthralgia, retro ocular pain, dizziness, nausea, photophobia, rash and chills. Hemorrhagic manifestations, jaundice and polyuria have also been described (69, 73, 75). This febrile condition usually lasts 3-5 days with eventual recovery (71). The only lethal case recorded so far occurred in 2001 in Mexico in a patient who developed encephalopathy 30 days after infection (77). Diagnostic of this disease is confirmed by identification of anti-MAYV IgM antibodies with ELISA (78).

Pathogenesis of Mayaro Fever is unknown, however necrosis of skeletal muscle, and periosteum has been demonstrated in animals and might explain some of the symptoms (79). In other related infections such as Chikungunya fever, a persistent infection of synovial macrophages has also been described (80).

General Therapeutic Measures

Although as with most part of viral conditions, treatment is mainly supportive, antibody therapy consisting of transfusion of plasma from convalescent patients, and antiviral therapy with internalization inhibitors have shown positive results in both treatment of New World arenavirus and hantavirus infection, experimental vaccines against hantaviruses have been proved in mice and hamsters, showing also positive results (12, 81).

A vaccine called TC-83 was developed in 1961 using mutations in the E2 glycoprotein and an untranslated genome region to produce an attenuated form of the VEEV and although it was effectively used in equines and laboratory personal to protect them against the virus, it showed poor cross neutralization of the different serotypes and regression to the pathogenic, wild-type phenotype(82); more recently, vaccines using replicon particles from VEEV, WEEV and EEEV, as also attenuated forms of VEEV IE which promoters have been substituted by Internal Ribosome Entry Sites (IRES) from other viruses, have produced antibodies in mice and macaques(83, 84) antibody therapy has prevented disease but not infection of VEEV in treated mice (30, 85).

Mayaro's fever treatment relies mostly on non-steroidal anti-inflammatory analgesics (86). However, a vaccine candidate developed from attenuated serotypes of MAYV produced by substituting the virus promoters with picornavirus' IRES has proved both reduced pathogenicity and an increased production of neutralizing antibodies in mice (87).

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