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Sección Especial

LOS MAMÍFEROS COMO HOSPEDADORES DE PARÁSITOS

Artículo

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JABORÁ ORTHOHANTAVIRUS IN RODENTS OF ALTO PARANA ATLANTIC FOREST: FIRST DESCRIPTION IN ARGENTINA

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ABSTRACT. The genus *Orthohantavirus* groups rodent-borne hantaviruses, including non-pathogenic and pathogenic viruses. The latter include agents that cause hantavirus pulmonary syndrome (HPS), a severe disease endemic to the Americas. In northeastern Argentina, the first HPS cases were reported in the province of Misiones in 2003. The viruses Lechiguanas and Juquitiba were characterized from blood samples of HPS cases, but only the latter was found in rodents in the area. In neighboring areas of the Atlantic Forest in Brazil and Paraguay, Juquitiba and Jaborá viruses (JABV) were found associated with *Oligoryzomys nigripes* and *Akodon montensis,* respectively. We collected rodent samples from 2017 to 2020 and analyzed them for IgG antibodies against hantavirus by ELISA. For the positive rodents, we extracted total RNA and performed reverse transcription-polymerase chain reaction (RT-PCR) followed by a nested PCR. The phylogenetic analysis included 35 nucleotide sequences from the GenBank public repository. Of 746 captured rodents, IgG was detected in 14 A. montensis (28%, n = 50). The viral genome amplification revealed a new orthohantavirus to Argentina. The genotype in consistent with the JABV found in neighboring countries. This paper reports JABV as a new orthohantavirus variant in Argentina, expanding the known range of this variant. This finding has public health relevance because prevention is the main tool to avoid human infection.

RESUMEN. JABORÁ ORTHOHANTAVIRUS EN ROEDORES DEL BOSQUE ATLÁNTICO DEL ALTO PARANA: PRIMERA DESCRIPCIÓN EN ARGENTINA. El género *Orthohantavirus* agrupa los hantavirus transmitidos por roedores, incluidos los virus patógenos y no patógenos. Entre estos últimos se encuentran los agentes causantes del síndrome pulmonar por hantavirus (SPH), una enfermedad grave endémica de las Américas. En el noreste de Argentina, los primeros casos de SPH se registraron en 2003. Se caracterizaron los hantavirus Lechiguanas y Juquitiba a partir de los casos de SPH, pero solo el último se encontró en roedores de la zona. Los virus Juquitiba y Jaborá (JABV) fueron encontrados posteriormente en áreas cercanas de la

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Mata Atlántica en Brasil y Paraguay, asociados a *Oligoryzomys nigripes* y *Akodon montensis*, respectivamente. Aquí analizamos muestras de roedores obtenidas entre 2017 y 2020 y detectamos anticuerpos IgG contra orthohantavirus mediante la técnica ELISA. Para los roedores positivos, se extrajo el ARN total y se sometió a la transcripción inversa-reacción en cadena de la polimerasa (RT-PCR) seguida de una PCR anidada. Para el análisis filogenético se incluyeron 35 secuencias de nucleótidos del repositorio público GenBank. De 746 roedores capturados, se detectó IgG en 14 *A. montensis* (28%, n=50). La amplificación del genoma viral reveló un nuevo orthohantavirus para Argentina, cuyo genotipo es consistente con el JABV encontrado en países limítrofes. Este estudio informa al JABV como una nueva variante de orthohantavirus para Argentina, y expande así el rango conocido de esta variante. Este hallazgo es de relevancia en salud pública, en relación a una patología donde la prevención es la principal herramienta para evitar la infección a humanos.

Key words: Andes virus, emerging infectious diseases, Hantavirus Pulmonary Syndrome, orthohantavirus, viral zoonoses.

Palabras clave: Andes virus, enfermedades infecciosas emergentes, orthohantavirus, Síndrome Pulmonar por Hantavirus, zoonosis virales.

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INTRODUCTION

In the last decades, an increasing number of small mammals have been identified as reservoir hosts of newly recognized hantaviruses in nature. Some of them were associated with severe human diseases. Hantaviruses are three-segmented negative-stranded RNA viruses that were recently reclassified in the family *Hantaviridae* (Laenen et al. 2019; Abudurexiti et al. 2019). The genus *Orthohantavirus* groups rodent-borne hantaviruses, including non-pathogenic and pathogenic viruses. The latter includes agents that cause Hantavirus Pulmonary Syndrome (HPS), which was first described in North America in 1993 (Chapman et al. 1994). Since then, several viruses have been identified in the Americas, among which there are 14 recognized species by the International Committee on Taxonomy of Viruses. In South America, five viral species, *Andes, Caño Delgadito, Laguna Negra, Maporal*, and *Necocli orthohantavirus*, group 23 viruses, seven of which are still not associated with human disease. The Andes virus (ANDV) is the best-known etiologic agent of HPS from South America, causing a high fatality rate (up to 50%) (Wells et al. 1997). However, in Argentina, several closely related viruses are more prevalent. To date, orthohantaviruses are distributed in four regions of the country (Martinez et al. 2010; Alonso et al. 2019). In the Central region, mostly comprised of Humid Pampas and Parana Flooded Savanna, there is circulation of the Plata virus and Lechiguanas virus (LECV), harbored mainly by *Oligoryzomys flavescens*, and in two localities by *O. nigripes* (Vadell et al. 2011; Colombo et al. 2019) as well as the Buenos Aires virus, which is supposed to be hosted by the same rodent species (Levis et al. 1998). In addition, Maciel and Pergamino viruses are also present in the area but are not associated with human diseases to date. These are harbored by *Necromys benefactus* and *Akodon azarae*, respectively (Bohlman et al. 2002). In Northwestern Argentina, mostly in the Yungas Forest, Orán and Bermejo viruses are prevalent in *O. chacoensis* and *O. occidentalis* (Bohlman et al. 2002; Gonzalez Della Valle et al. 2002; Rivera et al. 2018). In the Patagonian Forests (Andean Patagonia) ANDV is mostly associated with *O. longicaudatus, Abrotrhix olivaceous*, and *A. hirta*. In Northeastern Argentina, the first HPS cases were reported in the province of Misiones in 2003. The LECV and Juquitiba (JUQV) viruses were characterized by the HPS cases, but only the latter was found in rodents in the area (Padula et al. 2007). However, in neighboring areas of the Atlantic Forest of Brazil and Paraguay, JUQV and Jaborá (JABV) viruses are widely distributed and are associated with *O. nigripes* and *A. montensis*, respectively (De Oliveira et al. 2009, 2011; Raboni et al. 2012; Guterres et al. 2014; Chu et al. 2011). Both rodent species are widespread in Northeastern Argentina and have a high abundance in several environments in Misiones (Lanzone et al. 2018; Teta et al. 2018; Galliari & Pardiñas 2021). These species have a high tolerance to habitat fragmentation and

can often be found in anthropized environments (Galliari & Pardiñas 2021; Burgos et al. 2021).

The maximum area in which a virus can be endemic is determined by the geographical distribution of its hosts. Other factors such as contact rates, sex ratio, and the age of individuals also influence the dynamics of rodents and virus spread. Crossing events of virus variants between different species are expected when rodent species share an ecosystem and have high levels of contact between individuals, as has been documented for LECV, for which there is evidence of host-switching from *O. flavescens* to *O. nigripes* (Vadell et al. 2011). These events could be particularly important in the Atlantic Forest, where the richness of wild species is one of the highest in Argentina. Potentially, spill-over events could lead to a spread of pathogenic orthohantaviruses to new host species, increasing viral exposure to humans. Understanding hantavirus distribution, viral dynamics, and the interrelationship among orthohantavirus hosts in sympatry is important for assessing the potential emergence of new viruses affecting humans. This knowledge is particularly important as anthropogenic changes to wildlife habitats increasingly contribute to the emergence and re-emergence of zoonoses.

For these reasons, the aim of this work was to describe and characterize for the first time the finding of JABV in *Akodon montensis* in the Atlantic Forest of the province of Province, Northeast Argentina, an endemic area for HPS.

MATERIALS AND METHODS

We analyzed samples from rodents that were collected from 2017 to 2020 in Northeast Argentina. Rodent trapping was carried out every three months in four areas: urban, periurban, rural, and natural protected areas (Reserva Indígena Iryapú and Reserva Nacional Iguazú) located in the department of Iguazú (-26.022; -54.612), in the north of the province of Misiones, Argentina. Traps were active for three consecutive nights during each session and baited with a mixture of peanut butter, fat, and rolled oats. The species were identified based on external morphology (the metrics recorded were used to double-check the identification done on the field, whenever necessary) (Burgos et al. 2021). During each live-trapping session, blood samples were collected. IgG antibodies against hantavirus were detected in blood samples by ELISA as previously described (Padula et al. 2007). Briefly, recombinant ANDV nucleoprotein was used as a specific antigen, the blood samples were diluted 1:100, then incubated with peroxidase-labeled goat anti-*Peromyscus leucopus* IgG secondary antibody (Kirkegaard and Perry Laboratories); ABTS (2.2'-azinodi [3-ethyl-benzthiazoline sulfonate]) was used as the substrate for peroxidase, and absorbance was measured at 405 nm. Seropositive individuals were detected in two sites, a periurban area, called Reserva Indígena Iryapú, and a natural protected area, called Reserva Nacional Iguazú (Burgos et al. 2021).

Because these seropositive animals were found in protected areas, only a few individuals could be taken for tissue collection. Viral RNA detection was performed on these lung tissues (n = 2). Total RNA was extracted using Trizol, following the recommendations of the manufacturer, and subjected to a reverse transcription-polymerase chain reaction (RT-PCR) followed by a nested PCR; for the amplification, a conserved region of the orthohantavirus genome was selected. Specific primers were used to amplify a 952nts fragment from the S-segment (nucleotides 22 to 974) and a 663nts fragment from the M-segment (nucleotides 2249 to 2912). All fragments were numbered in the antigenome-sense sequence relative to ANDV S and M segments corresponding to GenBank accession numbers AF324902 and AF324901, respectively. The amplicons were sequenced using BigDye Terminator™ v3.1 Cycle Sequencing Kit and for purification, the BigDye® X-Terminator Purification Kit (Applied Biosystems, Foster City, CA, USA), according to the recommendations of the manufacturer.

The sequences obtained were aligned with those of previously published sequences of hantaviruses by ClustalW in MEGA 10 software. For the phylogenetic analysis, 35 partial and complete nucleotide sequences from the GeneBank public repository were included. The phylogenetic analyses based on S-segment sequences were conducted using Bayesian inference. Estimates of clade confidence were based on bootstrap analyses and posterior probabilities using a Bayesian Markov Chain Monte Carlo (MCMC) method implemented in Beast v1.10.1 (Rambaut et al. 2018), using the GTR + G model of nucleotide substitution. MCMC settings consisted of a run for 10 million generations and sampled every 100th generation, yielding 10 000 trees. After eliminating 10% of the samples as burn-in, a consensus tree was built. The statistical support of the clades was measured by the Bayesian posterior probabilities. The best-fit evolutionary model was determined using jModelTest version 0.1 (Posada 2008). For analyses, sequences of the Old World Hantaan virus (NC005218) and the Seoul virus (AY027040) were used as outgroup species.

Rodents were handled according to the National Animal Care Law 14.346, and following the INMeT Safety Standards established in the "Biosafety Guidelines for Working with Small and Medium-sized Mammals" (Carroll et al. 2016).

RESULTS

From 746 captured rodents, hantavirus-specific IgG was detected in 14 individuals, all of which were *A. montensis*. This represents an overall seroprevalence of 1.9% (14/746) and of 28% for *A. montensis* (14/50). All seropositive individuals were collected in natural protected areas: 12 in the Reserva Nacional Iguazú and two in the Reserva Indígena Iryapú (**Fig**. 1). Viral genome amplification was successful in one of the two seropositive *A. montensis* captured in the Reserva Indígena Iryapú *A. montensis* #391, captured at (-26.022; -54.612). Two sequences of 854 bp and 663 bp were obtained from the S- and M-segments, respectively. As a result of pairwise comparisons, the highest nucleotide identity (92.9%) was found with a

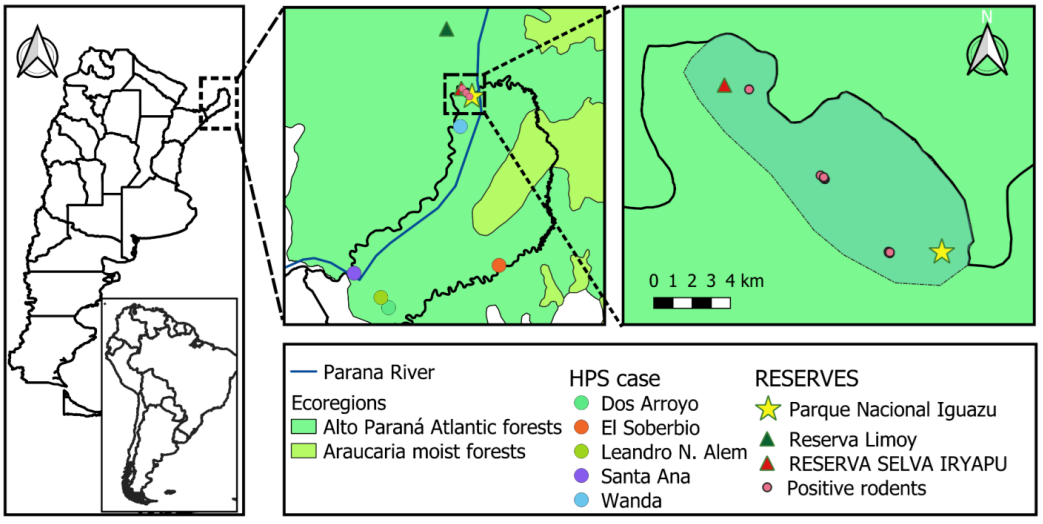

Fig. 1. Rodents captured from 2017 to 2020 and Hantavirus Pulmonary Syndrome (HPS) cases reported from 2003 to 2020, in the province of Misiones, Argentina. The first amplified figure shows the origin towns from the HPS cases (colored dots) and the location of the nature reserves where the rodents were collected (the star and triangles). The second amplified figure shows the Parque Nacional Iguazú and Reserva Iryapu, and the georeferencing sites of IgG positive rodents (pink dots).

viral sequence recovered from an *A. cursor* rodent in Paraguay in 2003, and both clustered together with JABV (GenBank Acc. Num. EU373732) (**Fig**. 2). At the amino acid level, the identities were 100% with the same sequences (GenBank Acc. Num. ABY76313).

DISCUSSION

In recent years, several novel hantaviruses with unknown pathogenic potential were identified throughout the world in a variety of mammals. More than 90 species of rodents (order Rodentia) and an increasing number of bats (order Chiroptera) and shrews (family Soricidae) are recognized as hosts, and at least 47 rodent species are known to host pathogenic orthohantaviruses (Holmes & Zhang 2015; Milholland et al. 2018). The diversity of orthohantavirus hosts is a key factor in the emergence of human diseases because viruses could evolve at faster rates in genetically diverse well-mixed host populations than in homogeneous host populations (González et al. 2019). Argentina presents a high diversity of orthohantaviruses, mainly in the central endemic region. Here we describe the presence of the JABV in Argentina, a relevant finding that contributes to the knowledge of the hantavirus variability in the northeast region of the country. In agreement with reports previously published (De Oliveira et al. 2011; Chu et al. 2009; Rosa et al. 2005; Chu et al. 2011), this study represents additional evidence that *A. montensis* is the reservoir for JABV. This rodent species predominates in this forest ecosystem assemblage and has a wide distribution, ranging Argentina, Brazil, Paraguay, and Uruguay. The presence of hantavirus in this species has been described in nearby areas of Brazil and Paraguay.

In nearby areas of Paraguay and Brazil where infected *A. montensis* were previously reported, this host coexists sympatrically with other rodent species hosting pathogenic hantaviruses. The province of Misiones is not an exception, as the presence of *O. nigripes* (JUQV reservoir) and cases of HPS caused by JUQV and LECV have been previously reported (Padula et al. 2007). Considering that hantaviruses establish life-long infections, infected individuals can shed viral particles for extended periods through excretions and/or secretions into the environment, facilitating virus transmission among genetically similar host species (González et al. 2019; Forbes et al. 2018; Voutilainen et al. 2015) and phylogenetic evidence supports host-switching events (Holmes & Zhang 2015; Nemirov et al. 2002; Rivera et al. 2015). Transmission rates to humans could rise if a pathogenic hantavirus successfully infects a new host with a wider geographic distribution. Phylogenetic studies suggested reassortment and host-switching in the evolution of South American hantaviruses (Chu et al. 2009, 2011; Rivera et al. 2015). The plasticity of JABV to switch to other phyloge-

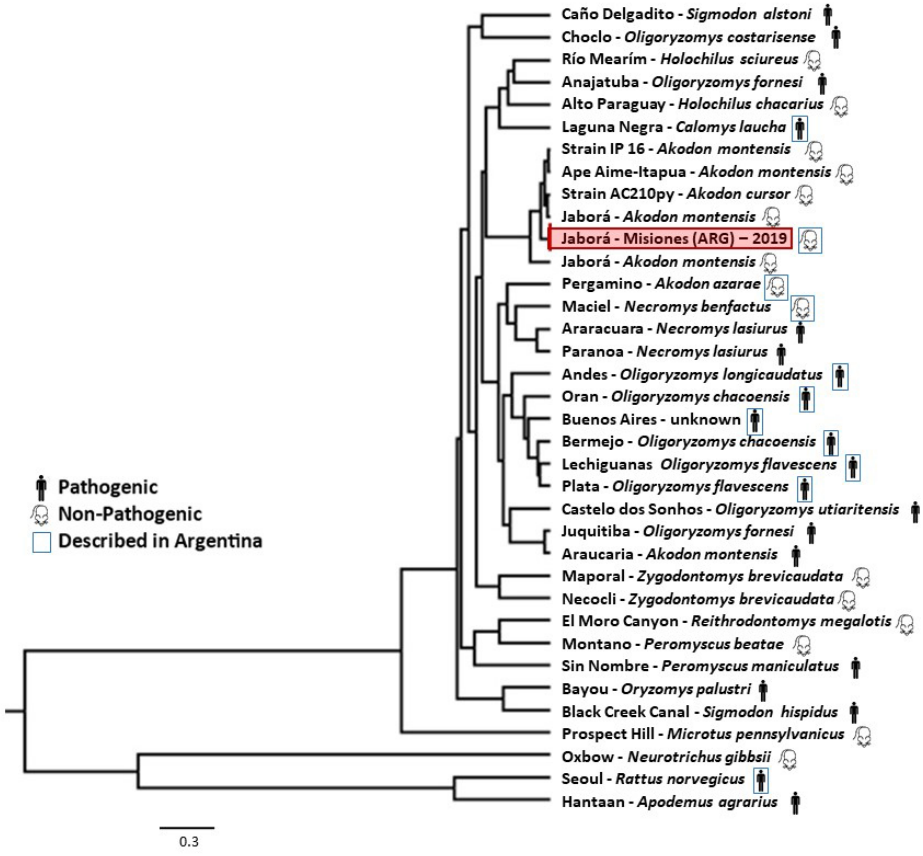

Fig. 2. Phylogenetic relationships among hantaviruses based on a Bayesian analysis. Bayesian phylogenetic analysis of the partial S-segment sequence of the rodent captured in Parque Nacional Iguazú, Misiones. For comparison, a set of representative hantavirus sequences from South America, North America, and Eurasia were included in the analysis. Alignment used in the analysis included 952nt (nucleotides 22 to 974 of the S segment, with regard to ANDV strain AF324302) fragments and complete S-segment sequences. Hantaan (HTNV) and Seoul (SEOV) sequences were used as outgroup species. The scale bars indicate an evolutionary distance of 0.3 substitutions per position in the sequence. Posterior probabilities (pp) are depicted above the nodes. GenBank accession nos.: Alto Paraguay DQ345762; Anajatuba JX443690; Andes AF324902; Ape Aime-Itapua GU205340; Araraquara EF571895; Araucaria AY740629; Bayou NC 038298; Bermejo AF482713; Black Creek Canal L39949; Cano Delgadito DQ285566; Castelo dos Sonhos AF307324; Choclo DQ285046; El Moro Canyon NC 038423; Hantaan MK636801; AC210py EU373732; IP16 DQ345764; Paranoa EF576661; Jabora EF492471; Jabora GU205335; Juquitiba GU213198; Laguna Negra JX443681; Lechiguanas AF482714; Maciel virus AF482716; Maporal AB689164; Montano AB620084; Necocli NC 043409; Oran AF482715; Oxbow NC 043174; Pergamino AF482717; Prospect Hill M34011 X55128; Rio Mearim virus DQ451828; Seoul GU592951; Sin Nombre KF537003; Buenos Aires-Hu39694 AF482711 and Plata.

netically related hosts has already been described, adding *A. paranaensis* and *A. serrensis* as possible hosts (Teixeira et al. 2014). Additionally, although the JABV virus has not been associated with human illness, other viruses previously considered non-pathogenic were finally associated with disease in humans. The Alto Paraguay virus, for example, was identified only in *Holochilus chacarius* several years before it was characterized in an HPS case (Bellomo et al. 2021). Another example is the Tula virus, an Old World orthohantavirus previously considered non-pathogenic in Europe but which was also finally associated with human disease (Schultze et al. 2002).

The emergence and re-emergence of viruses have been causing serious threats to public health. Since there is still no safe and effective vaccine or specific antiviral treatment against American orthohantaviruses, monitoring their prevalence in wild rodents becomes relevant. This finding contributes to the knowledge of hantavirus distribution in the

region, which might facilitate monitoring and prevention of future viral emergencies.

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Author's contribution: CB wrote the manuscript with support from VM. EB and MVV performed the rodent sample collection. RC and SK performed serological analysis. DA contributed to sample molecular processing. CB processed the molecular data and performed the phylogenetic analysis. VM and IGV designed and directed the Project. SK, CB and NP developed the figures. CB, VM and IGV contributed to the interpretation of the results. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

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