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Hantavirus pulmonary syndrome: encephalitis caused by virus Andes

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Abstract Hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome (HPS) are rodent-borne emerging diseases caused by members of the genus *Hantavirus*, family *Bunyaviridae*. Some species of hantavirus may cause encephalitis, but this is the first report in Andes virus associated to HPS.

Keywords Hantavirus pulmonary syndrome · Hantavirus · Neurologic manifestations · Encephalitis · Andes virus

Introduction

Hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) are rodent-borne emerging diseases caused by members of the genus *Hantavirus*, family *Bunyaviridae* (Elliott et al. 2000). The incidence of encephalitis in HFRS is around 1% (Bergmann et al. 2002). Transverse myelitis and acute disseminated encephalomyelitis (ADEM)-like syndrome have been previously attributed to complications following HPS in USA (Huisa et al. 2009). This is the first report that describes a case of encephalitis in Andes virus (ANDV) associated to HPS.

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Case report

The patient is a 24-year-old male, a construction worker, and living in an urban area (Villa Governador Galvez) near Rosario, one of the most important cities of Argentina. He lives near a vacant lot inhabited by rodents. On the onset of symptoms, he presented headache, myalgia, arthralgia, and significant fatigue. Three days after that he also presented fever, vomiting, dry cough, and dyspnea at rest. The patient showed no signs of petechiae or ecchymosis.

He was admitted to the intensive care unit (ICU) 5 days post-onset of symptoms. He had an Apache II score of 18 and SOFA score of 10. He presented septic shock with a mean arterial pressure <60 mmHg, central venous pressure of 0 mmHg, and heart rate of 170/min. Initial resuscitation with crystalloids was performed with no hemodynamic improvement. However, generalized edema developed which was interpreted as capillary leak syndrome, so we continued the resuscitation with colloids and began hemodynamic support with dopamine (13 μg/kg/min).

He also showed respiratory distress with a respiratory rate of 40/min, hypoventilation in both lung bases and diffuse bilateral subcrepitant rales, and supraclavicular and intercostal retractions. Chest X-ray showed bilateral diffuse pulmonary infiltrates and effacement of both costophrenic sinuses. The arterial PO_2/fraction of inspired oxygen (FiO_2) ratio was equal to 128. He was connected to mechanical ventilation, in volume control mode, with positive end expiratory pressure of 16 cmH_2O, tidal volume of 0.400 L, and FiO_2 of 0.80 and was ventilated with lung protective strategy. Liquid handling was restrictively performed in terms of crystalloid, and human albumin 20% was indicated 50 ml/8 h with furosemide.

Laboratory showed typical abnormalities for HPS such as hemoconcentration, thrombocytopenia, leukocytosis,

normal erythrocyte sedimentation rate, prolonged clotting times, mild renal insufficiency, hypoalbuminemia, and increased lactate dehydrogenase (Table 1). As the report of this case was conducted retrospectively, we could not confirm the presence of immunoblasts because we had no peripheral blood smear on admission.

Blood cultures were negative. Empiric antibiotic therapy was begun with ampicillin/sulbactam (1.5 g/6 h) and clarithromycin (500 mg/12 h).

To assess the humoral immune response of the patient, ANDV recombinant antigen was used for the enzyme-linked immunosorbent assay as described before (Padula et al. 2000). Capture-IgM and IgG antibodies were detected 5 days post-onset of symptoms in serum sample. Serological tests for virus dengue, leptospirosis, and Argentine hemorrhagic fever were negative.

Thirteen days post-onset of symptoms, the patient showed clinical improvement. Sedation and mechanical ventilation were removed. After that, he presented confusional syndrome, psychomotor excitation, and tonic–clonic seizure. Neck stiffness was noted. No focal neurologic signs were observed. Kernig, Brudzinski, and Babinski signs were negative. Diphenylhydantoin was administrated.

CT scan without contrast (Fig. 1), MRI of the central nervous system (CNS) (Fig. 2a–c), and lumbar puncture were performed. Cytological and physicochemical analysis of cerebrospinal fluid (CSF) reports include: appearance crystal; glycorrhachia 0.64 g/l; detection of globulins (Pandy reaction) ++; proteinorrachia 1.39 g/l and leukocytes 10/mm^3. CSF culture was negative.

Table 1 Laboratory tests on admission

Blood	Value
Hematocrit	56.20%
Hemoglobin	18.7 g/dL
Leukocytes	31.3×10^3/mm^3
Neutrophils	78%
Lymphocytes	16%
Platelets	44×10^3/mm^3
Prothrombine time	18.3 s
Partial-thromboplastin time, activated	44 s
Erythrocyte sedimentation rate	4 mm/1st hour
Uremia	66 mg/dL
Creatinine	1.86 mg/dL
Glucose	228 mg/dL
Sodium	142 mEq/L
Potassium	4.2 mEq/L
Total bilirubin	7.25 mg/dL
Direct bilirubin	0.57 mg/dL
Lactate dehydrogenase	1,453 U/L
Albumin	1.93 g/dL

Serum titers of capture-IgM and IgG antibodies 5 days post-onset of symptoms were both 1:19,200. The ELISA test using a CSF sample obtained 15 days post-onset of symptoms revealed titers of 1:80 for IgM and 1:40 for IgG.

Viral amplification was performed by reverse transcriptase-polymerase chain reactions (RT-PCR) and resulted positive in clot sample on admission and negative in CSF. Genotypification of the viral RNA amplified revealed ANDV Lechiguanas lineage.

Sixteen days post-onset of symptoms, he was discharged from the ICU presenting clinical improvement and normalization of the laboratory parameters. Eight months later, a CNS MRI was done in which the result was normal (Fig. 2d).

Discussion

The aim of this report is to describe a case of encephalitis due to ANDV in a patient with HPS, which is interesting because so far there are no reports of encephalitis associated to ANDV circulating in different countries of South America. There were described cases of encephalitis in the Old World hantaviruses (Puumala, Dobrava, and Hantaan virus) (Bergmann et al. 2002; Cerar et al. 2007).

Andes-like viruses are distributed in Argentina, Bolivia, Chile, and Uruguay. In the central region of Argentina, the fatality rate is around 28% (Henry et al. 2006). However, there are reports with mortality rates of more than 40% (Schmaljohn and Hjelle 1997).

In this patient, the suspicion of HPS was based on the presence of positive epidemiological focus, typical signs and symptoms, and laboratory abnormalities and was confirmed by specific serologic and RT-PCR tests. Hantavirus encephalitis was supported by neurological findings such as confusional syndrome, psychomotor excitation, tonic–clonic seizures, neck stiffness, CT and MRI images, and positive IgM and IgG antibodies in CSF.

Hantavirus affects small blood vessels causing disruption of the CNS blood–brain barrier. It is not clear whether the nervous system involvement is mediated by an immune mechanism or directly by the virus. Acute disseminated encephalomyelitis (ADEM), a monophasic autoimmune CNS condition, typically follows febrile illness associated with HPS (Huisa et al. 2009). This case could be an ADEM-like syndrome. None of the available similar communications of encephalitis on other hantaviruses could demonstrate the presence of RNA on CSF, although they showed intrathecal production of specific antibodies (Huisa et al. 2009; Cerar et al. 2007). The viral amplification in CSF of the case reported here was also negative but the sample was taken 15 days post-onset of symptoms, so the virus could have been cleared from the CNS at that time.

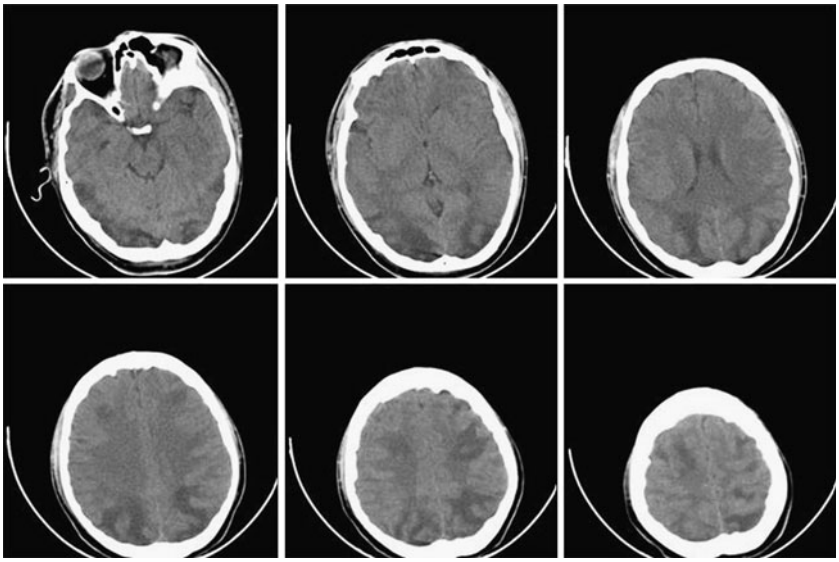

Fig. 1 CT: multiple areas of hipodensity bilateral on frontal, parietal, and occipital lobes

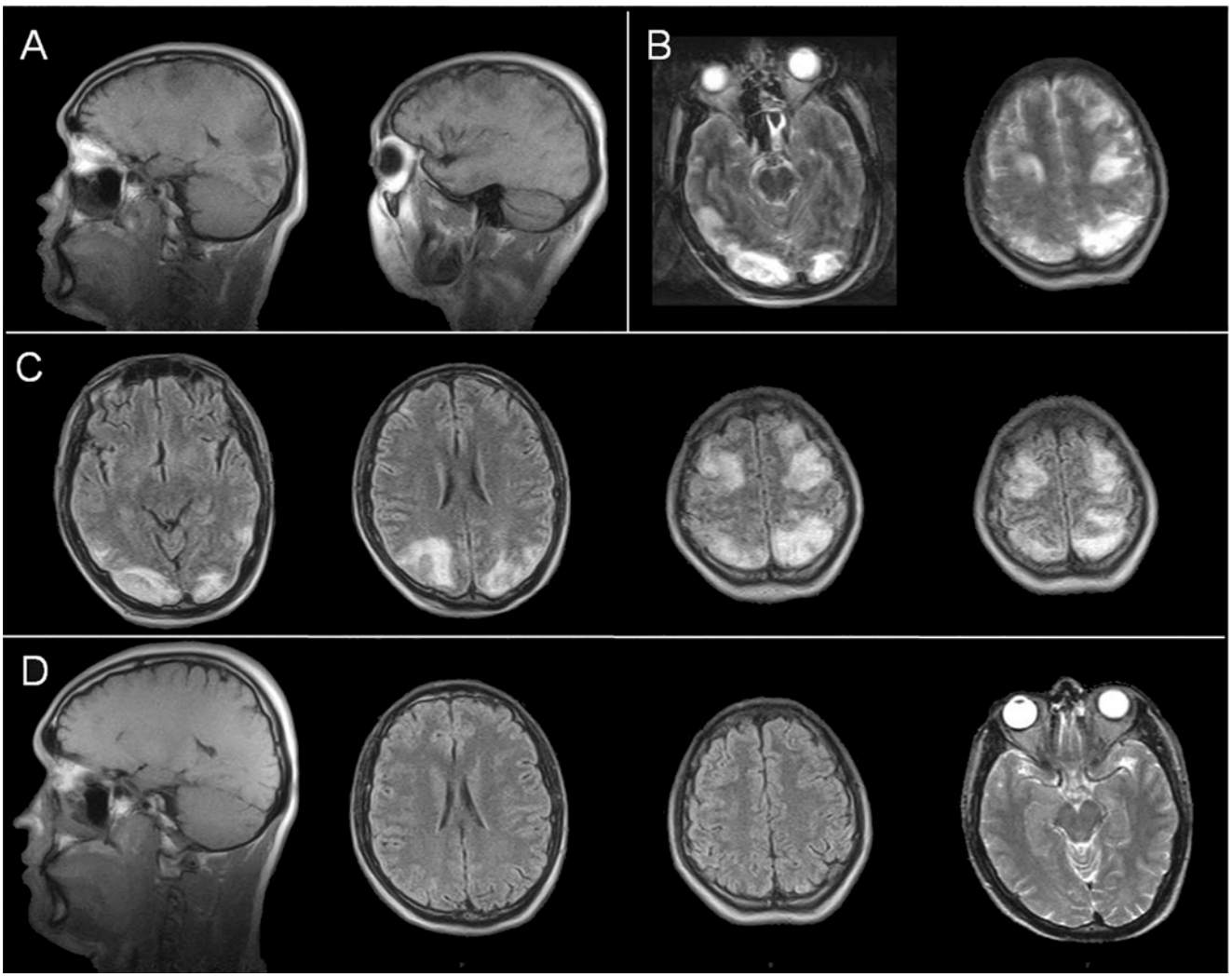

Fig. 2 MRI: multiple areas of hypointensity in T1 sequences (**a**), and hyperintensity in T2 (**b**) and FLAIR (**c**), mainly affecting the cerebral cortex and, to a lesser extent, the underlying white matter, compatible with encephalitis. No signs of bleeding. Normal brain stem and cerebellum. Normal upper spinal cord segments. Full recovery without sequelae after 8 months (**d**)

We do not have a serum paired sample to verify if the viremia persisted. On the other hand, we have evidence of specific antibody presence in the CNS. So, beyond the underlying mechanism, hantavirus infection plays an important role in the pathogenesis of CNS injury. Further studies are needed to determine the prevalence of CNS involvement in ANDV infection and its pathogenesis.

In conclusion, ANDV can be considered within the causes of encephalitis, as well as other species of hantavirus reported.

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