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Case report

Central nervous system complications following Hanta virus cardiopulmonary syndrome

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Hanta viruses are a family of human pathogens, comprising at least 16 different serotypes. The serotype Puumala, most prevalent in western and central Europe, causes hemorrhagic fever with renal syndrome (HFRS). In contrast, serotypes prevalent in the New World (Sin Nombre, Andes) cause a febrile illness, with severe pulmonary and cardiac compromise (Hanta virus cardiopulmonary syndrome (HCPS)). Review of 811 HFRS cases found that only 1% developed severe central nervous system (CNS) complications (Alexeyev and Morozov, 1995). To our knowledge, neurological complications from New World Hanta infection have not been reported. Acute disseminated encephalomyelitis (ADEM), a monophasic autoimmune CNS condition, typically follows febrile illness and ADEM associated with HFRS has been described (Krause *et al,* 2003; Toivanen *et al,* 2002). Transverse myelitis (TM), another presumed postinfectious, autoimmune disorder, has not been previously attributed to any type of Hanta virus infection. We report cases of ADEM-like syndrome and TM that developed during HCPS.

Case 1

A 59-year-old woman from northern New Mexico presented with 4-day history of fever, headache, nausea, and progressive dyspnea that happened after cleaning mouse excrement from her shed. Laboratory data showed thrombocytopenia (49,000/mm^3) and chest radiographs disclosed pulmonary edema with pleural effusion. Her peripheral blood smear was typical for HCPS, showing thrombocytopenia, hemoconcentration, myelocytosis, and more than 10% lymphocytes with immunoblastic features. The strip immunoblot assay (Hanta/Sin nombre virus serology) was positive. She received extracorporeal membrane oxygenation (ECMO) therapy for 5 days but remained ventilator dependent and sedated. Acute renal failure requiring hemodialysis complicated her course. On the 12th day after admission, focal motor seizures involving her right face and upper extremity developed. Video electroencephalography (EEG) demonstrated left hemispheric epileptiform discharges associated with clonic movements. Intravenous fosphenytoin suppressed clinical and electroencephalographic seizures but she remained comatose.

Neurological examination revealed small (3-mm) reactive pupils, areflexia, hypotonia, with no plantar response. Brain magnetic resonance imaging (MRI) showed multifocal white matter signal abnormalities in both cerebral hemispheres, as well as cerebellum, and several punctuate foci consistent with hemorrhage (Figure 1). Lumbar puncture was done 30 days after admission; it revealed xanthochromic cerebrospinal fluid (CSF) with 48 red blood cells (RBCs)/mm^3, 159 white blood cells (WBCs)/mm^3, protein 41 mg/dl, and glucose of 76 mg/dl. Polymerase chain reaction (PCR) was negative for herpes simplex virus type 1 and 2 (HSV1 and HSV2) but no PCR was done for Hanta virus (Table 1). The patient's hospital course was further complicated by sepsis. She had no neurological improvement and on day 32 after admission, all life support measures were withdrawn. Permission for autopsy was denied.

Case 2

An 18-year-old man employed by the forest service in northern New Mexico presented to the emergency department with a 3-day history of cough, fever, nausea with vomiting, diarrhea, and dysuria. The

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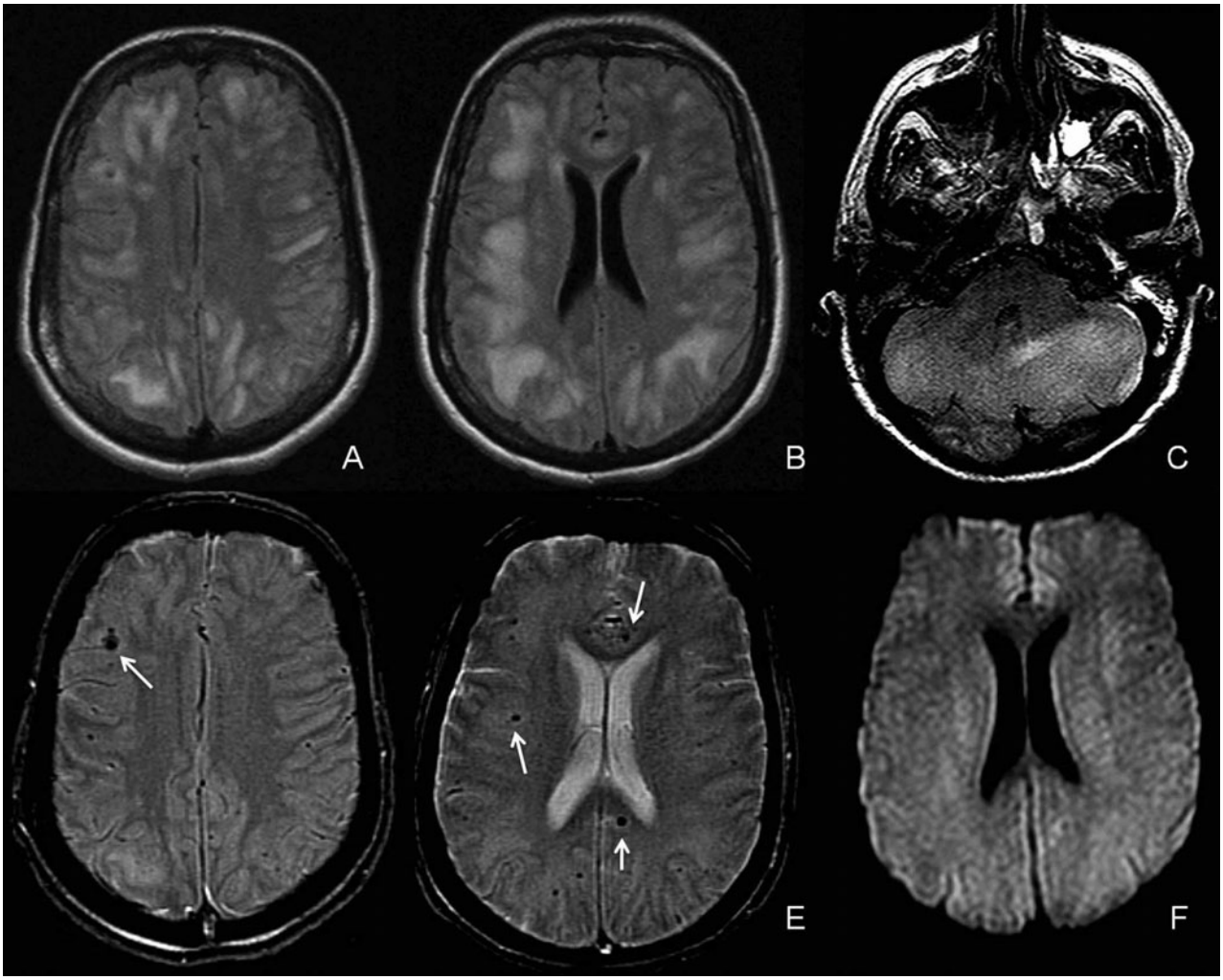

Figure 1 Case 1. (**A**, **B**, and **C**) Extensive pattern of abnormal increased signal intensity on FLAIR sequence in multiple locations in the brain and cerebellum, most notably in subcortical white matter. (**D** and **E**) Echo gradient sequence showing areas of petechilal bleeds (*white arrows*). (**F**) These areas did not demonstrate restricted diffusion on B1000 MRI sequence (**F**).

patient's chest radiograph showed diffuse infiltrates and blood work revealed thrombocytopenia (80,000/mm^3). HCPS was confirmed by positive strip immunoblot assay serology and an abnormal peripheral blood smear that showed thrombocytopenia, hemoconcentration, myelocytosis, and more than 10% lymphocytes with immunoblastic features. His cardiorespiratory status deteriorated, requiring pressor support, mechanical ventilation, and ECMO for 4 days. After extubation, the patient was found to have bilateral flaccid paraplegia, urinary retention and a sensory level at T6. Spine MRI showed diffuse cord edema from medulla to conus (Figure 2). Brain MRI was within normal limits. CSF was obtained 1 week after his admission and demonstrated xanthochromia, with 1000 RBCs/mm^3 and 30 WBCs/mm^3, elevated protein (74 mg/dl) with increased albumin index (10.2; normal 0–9), and normal glucose 64 mg/dl. PCR for HSV1 and HSV2, as well as PCR for Hanta virus, on CSF was negative (Table 1). The patient received high-dose corticosteroids and plasmapheresis without improvement. After 1 year of rehabilitation, he remains paraplegic and wheel chair bound.

Table 1 CSF analysis

CSF	Case 1	Case 2
Appearance	Xanthochromic	Xanthochromic
RBCs	48 cells/mm^3	1000 cells/mm^3
WBCs	159 cells/mm^3	30 cells/mm^3
% Lymphs	94%	50%
% Neutrophils	0%	35%
Protein	41 mg/dl	74 mg/dl
Glucose	76 mg/dl	64 mg/dl
Oligoclonal bands	Not done	Negative
PCR for HSV1 and 2	Negative	Negative
PCR for Hanta	Not done	Negative

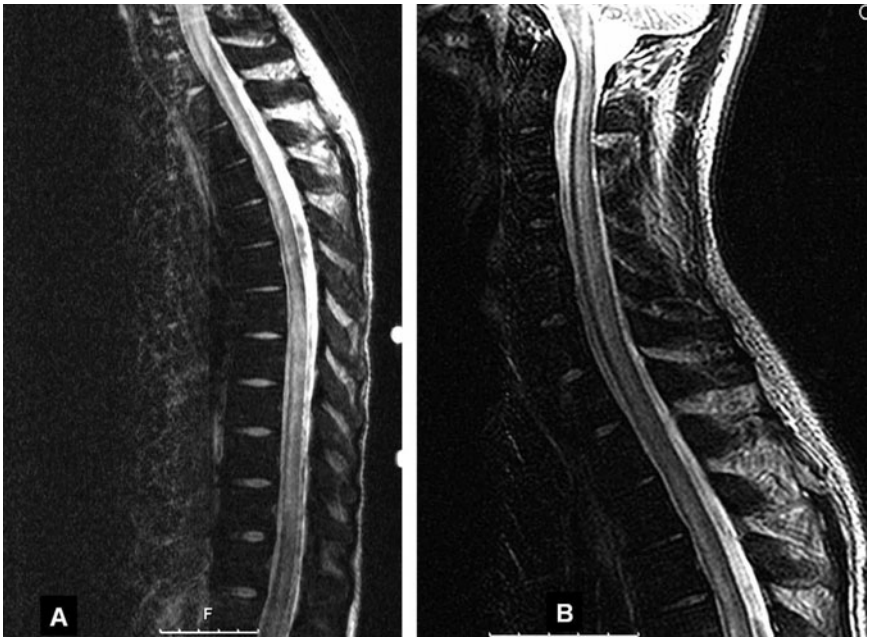

Figure 2 Case 2. Central increase signal in the spinal cord with peripheral sparing showed in T2 sequence, corresponding to edema extending the entire length of the spinal cord from the level of the medulla through the level of the conus.

Discussion

New world Hanta viruses cause a febrile prodrome followed by rapidly evolving respiratory failure, cardiogenic shock, and death in 30% to 40% of cases (Mertz *et al,* 2006). Rodents are the reservoir and humans contract the disease through exposure to infected rodent excretions.

New Mexico has reported the most HCPS cases since the four-corner outbreak in 1999 (Center for Disease Control and Prevention [CDC], 2006). Suspected HCPS can be confirmed by at least four of five criteria in the peripheral blood smear (Koster *et al,* 2001), including thrombocytopenia, hemoconcentration, myelocytocis, and more than 10% immunoblastic lymphocytes as found in our two patients. Further confirmation was accomplished through a nonquantitative strip immunoblot assay (Hjelle *et al*, 1999).

In case 1, abrupt onset of multifocal central nervous system dysfunction following viral infection supports the clinical diagnosis of ADEM. Although no postmortem confirmation was available, clinical history, aided by MRI, is the most reliable means of distinguishing between ADEM from the initial bout of multiple sclerosis (MS) (Brinar, 2004; Poser and Brinar, 2007). Brain MRI findings and sterile inflammation of the CSF strongly argues in favor of ADEM. Symptoms of TM, present in case 2, include rapid development of flaccid paraparesis and sensory level. In a young patient, TM may be the initial manifestation of multiple sclerosis. However, spinal cord involvement extending over multiple segments, inflammatory CSF without oligoclonal bands, and subsequent clinical course indicate isolated TM.

All Hanta viruses affect blood vessels, causing capillary dilatation and edema. Viral antigens in capillary endothelium without evidence of injury suggest that endothelial dysfunction alters vascular permeability (Wichmann *et al,* 2002). Indeed, autopsy of fatal HFRS cases reveal cerebral perivascular edema and microscopic hemorrhage. However, clinical evidence of blood-brain barrier disruption has been found in very few HFRS patients. Features suggesting microvascular disruption in our cases include hemorrhagic CSF, radiographic features consistent with punctuate hemorrhage (case 1), and elevated albumin index.Reports of CNS disorders associated with HFRS include encephalitis, ophthalmic involvement, two cases of ADEM, and intracerebral hemorrhage (ICH) (Alexeyev and Morozov, 1995; Krause *et al,* 2003; Toivanen *et al,* 2002; Ahlm *et al,* 1998; Cerar *et al,* 2007). Thrombocytopenia and microvascular disruption with disruption of the blood-brain barrier may explain the punctuate hemorrhages seen in case 1 as well as previously reported cases of ICH associated with HFRS. Questions remain about the relationship between endothelial dysfunction and CNS injury. Failure to detect viral RNA from CSF, demonstrated in our case 2 as well as from HFRS patients in prior studies, could argue against neurotropic infection. However, at least one report of encephalitis with intrathecal synthesis of Hanta virus antibodies indicates direct CNS infection, despite lack of detection of viral RNA in CSF (Cerar *et al,* 2007). Further pathological study will thus be needed to assess viral antigen in

brain and spinal cord specimens, a finding demonstrated thus far only in hypophyseal tissue (Hautala *et al,* 2002). Conversely, Hanta virus RNA has been detected in one HFRS patient without neurologic symptoms (Mohonen *et al,* 2007). Rather than direct CNS infection, endothelial dysfunction may initiate an autoimmune process, a hypothesis supported by elevated interleukin (IL)-6 and interferon (IFN)-γ levels in HFRS patients with CNS involvement (Ahlm *et al,* 1998; Borges and Figueiredo *et al,* 2008).

Whether neurological complications relate to ECMO therapy, an invasive treatment for respiratory failure, deserves consideration. Early institution of ECMO therapy has shown to decrease complication rates and to improve the overall survival in patients with HCPS (Dietl *et al,* 2008). A recent long-term follow-up of non–Hanta virus adult patients who received ECMO indicates a high prevalence of cerebrovascular injury (Risnes *et al,* 2006). Although case 1 died, precluding observation of lesion resolution, diffusion-weighted characteristics were not consistent with acute ischemia. Ischemic injury seems even less tenable for extensive myelopathy seen in case 2.

Clinicians caring for patients with HCPS should be aware of the potential of Hanta virus–induced CNS injury, including an ADEM-like syndrome and TM.

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