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BRIEF REPORT

Snowshoe Hare Virus Causing Meningoencephalitis in a Young Adult From Northern Manitoba, Canada

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We describe a dramatic presentation of meningoencephalitis, in a young Aboriginal male from Northern Manitoba, due to infection with the Snowshoe hare virus, a member of the California serogroup viruses. Snowshoe hare virus represents a rare cause of meningoencephalitis, and, to date, few Canadian cases have been described in the literature.

Keywords. arbovirus; California serogroup virus; meningoencephalitis; Snowshoe hare virus.

The California serogroup of the genus *Orthobunyavirus* consists of several viruses that are prevalent throughout North America. These include the Snowshoe hare virus (SSHV), Jamestown Canyon virus (JCV), California encephalitis virus, and La Crosse virus, among others, and are spread by mosquitoes species such as *Aedes*, *Culiseta*, and *Anopheles* as the vector [1]. In Canada, there have been over 200 probable and confirmed cases of SSHV and JCV infections since 2006, when immunoglobulin (Ig)M enzyme-linked immunosorbent assay (ELISA) and plaque reduction neutralization test (PRNT) became available [2]. Serological surveys estimate that 1%–42% of the general population carry antibodies to SSHV, although there is wide variability determined by geographic location [3, 4]. Most infected individuals do not present to their healthcare provider because of the nonspecific nature of symptoms and the tendency for resolution of infection without serious sequelae [3]. In contrast, we describe a dramatic presentation of meningoencephalitis in a patient from Northern Manitoba due to SSHV infection. Written consent was obtained from the patient to publish details of the clinical case.

CASE PRESENTATION

A 24-year-old Aboriginal male living on a First Nations Reserve in Nothern Manitoba, Canada, presented to hospital on July 3, 2016 with 1 week of high-grade fevers, headache, nausea, and vomiting, and 2 days of altered mental status and a diffuse macular rash, according to collateral history provided by the patient's mother. He had recent exposure to mosquitoes in his home community and no history of travel outside Manitoba.

On presentation, he was febrile to a temperature of 39.1°C, hypertensive, and tachycardic. He was confused and had nuchal rigidity. A diffuse macular rash involving his face, trunk, and both upper and lower extremities, sparing his palms and soles, and blistering of his mucocutaneous tissues were noted. His conjunctivae were injected and edematous.

Laboratory investigations revealed severe hyponatremia (serum sodium of 114 mmol/L) and neutrophil-predominant leukocytosis. After drawing blood cultures, empiric antimicrobial therapy with vancomycin, ceftriaxone, ampicillin, and acyclovir was initiated. Cerebrospinal fluid (CSF) drawn on the day of presentation 6 hours after antibiotic administration showed elevated protein (1.21 g/L) and pleocytosis (total nucleated cell count 485 × 10^6/L, with the differential showing 88% mature neutrophils, 6% lymphocytes, and 6% monocytes/macrophages). Computed tomography of the brain was normal. He was intubated for airway protection and admitted to the intensive care unit. All blood and CSF cultures returned negative for growth, and 16S ribosomal ribonucleic acid (RNA) polymerase chain reaction (PCR) performed on CSF did not reveal a causative bacterial organism. Cerebrospinal fluid PCR testing for herpes simplex virus and enterovirus were negative, and testing for other arboviruses including West Nile virus ([WNV] IgM), Western equine encephalitis (hemagglutination inhibition [HAI]), and Powassan (HAI) were negative. At this point, he showed signs of clinical improvement, and all antimicrobials were discontinued. He was discharged home 7 days after his initial presentation. The patient declined repeat CSF sampling to detect the presence of antibodies against SSHV or JCV in the CSF.

Immunoglobulin M for JCV and SSHV were detected using IgM antibody-capture ELISA (MAC-ELISA). This is an in-house test used at the National Microbiology Laboratory in Winnipeg, Canada, based on a validated protocol for MAC-ELISA in detection of arboviruses [5]. Captured IgM antibodies directed at JCV or SSHV are bound to cell culture lysate containing SSHV or JCV antigens and then detected by respective enzyme-conjugated monoclonal antibodies, and a positive-to-negative ratio of

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<2 indicates the absence of IgM antibody, 2–3 is equivocal, and ≥3 indicates the presence of IgM antibody. The MAC-ELISA results that are either equivocal or positive are cross-referenced to PRNT for confirmation. This is performed per a standardized protocol where a mixture of diluted serum and target virus are incubated together and inoculated over a confluent cell monolayer, and the last serum dilution that significantly reduces the input dose of virus is determined to be the endpoint [6]. For our patient, sera collected at 8 and 28 days after onset of clinical symptoms were tested in parallel using PRNT (results shown in Table 1).

DISCUSSION

Since methods for reliable detection of California serogroup viruses have become available in Canada and the United States, there has been an increase in identified cases of clinical infection [2, 7]. A retrospective analysis of sera collected in Manitoba from suspected WNV found that a significant number of these cases had IgM antibody to JCV and/or SSHV [8]. The seroprevalence of SSHV has been reported to range between 1% and 10% in southern Ontario and 1% and 42% in northern Quebec [3, 4]. Despite this seroprevalence, prospectively identified clinical infections with SSHV are rare, owing to infrequent testing, nonspecific febrile illness, and an overall favorable prognosis.

The clinical presentation of infection with California serogroup varies along a spectrum ranging from a mild febrile illness to severe neuroinvasive disease, including meningitis and meningoencephalitis [2]. Previous case reports of SSHV disease in Canada have described encephalitis predominantly affecting young children, although cases affecting adults have been described; typical findings on presentation included high-grade fever, nausea and vomiting, and headache, whereas several pediatric patients also presented with confusion, neck rigidity, or seizures [3, 7–9]. The patient in our case presented with confusion, due to a combination of encephalitis and concomitant hyponatremia. Hyponatremia secondary to syndrome of inappropriate antidiuretic hormone has been previously reported to be associated with other California serogroup viruses in children [10]. His other symptoms, including the macular rash, mucocutaneous desquamation, and preceding diarrhea, have not been described in these cases of SSHV but have been documented in cases involving other members of the California serogroup [11].

The diagnostic work-up for California serogroup viruses was initiated after investigations that eliminated other viral, including arboviral, etiologies of meningoencephalitis. Diagnostic criteria from the US Centers for Disease Control and Prevention for infection with California serogroup viruses categorize a "confirmed" case of neuroinvasive disease if any of the following criteria are met: (1) a 4-fold or greater rise in virus-specific IgG antibody titer in paired sera; (2) presence of IgM and neutralization antibodies in CSF and a negative result for other IgM antibodies in CSF for other endemic arboviruses; (3) isolated viral RNA, or positive viral culture from CSF, blood, other bodily fluid, or tissue; and (4) virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or later specimen [12]. There is known serological cross-reactivity between members of the California serogroup virus, and, therefore, MAC-ELISA is run in combination with PRNT [13]. In our case, the diagnosis of a confirmed case was based upon detection of IgM antibodies against SSHV with confirmatory neutralizing antibodies through PRNT. Because the titer of SSHV-specific neutralizing antibody by PRNT was 4-fold greater than that of JCV, SSHV was identified as the culprit. It was found that neutralization antibody levels against SSHV only fell by 2-fold between what were believed to be acute and convalescent phases. Neutralization antibody levels in an arboviral infection rise within 2 days of onset of illness, peak by 14 days, and decline to low levels, where they may persist for lifetime [6]. Given the incubation period of the virus and fast kinetics of antibody rise, it is very likely that so-called acute serum we had collected was in fact collected too late during the course of the infection; therefore, findings suggest that both sets of sera may have been drawn during the convalescent phase. The natural history of the infection is unclear, and an immune-mediated second phase resulting in neuronal injury is possible, as previously described for other arboviruses [14].

Table 1. PRNT IgG Antibody Titers for JCV and SSHV

Virus	8 Days After Reported Onset	28 Days After Reported Onset
JCV	1:5120	1:2560
SSHV	1:20480	1:10240

Abbreviations: Ig, immunoglobulin; JCV, Jamestown Canyon virus; PRNT, plaque reduction neutralization test; SSHV, Shoeshoe hare virus.

CONCLUSIONS

This case highlights that California serogroup viruses should be considered on the diagnostic differential for meningitis or encephalitis in Canada. This case may herald a more frequent diagnosis of neuroinvasive California serogroup viruses, both as testing becomes more routine and as the prevalence of vectors increases with the changing climate [15]. Diagnosis of infection with California serogroup viruses is confirmed through detection of virus-specific antibodies by MAC-ELISA and PRNT run in parallel. In Canada, infection with California serogroup virus does not currently necessitate notification of national or provincial public health agencies. Therefore, more large-scale and prospective studies are needed to shed further light on the true incidence of infections with California serogroup viruses in Canada.

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References

1. LeDuc JW. Epidemiology and ecology of the California serogroup viruses. Am J Trop Med Hyg **1987**; 37:60–8S.
2. Drebot MA. Emerging mosquito-borne Bunyaviruses in Canada. Can Commun Dis Rep **2015**; 41:117.
3. Artsob H, Spence L, Surgeoner G, et al. Snowshoe hare virus activity in Southern Ontario. Can J Public Health **1982**; 73:345–9.
4. Sampasa-Kanyinga H, Lévesque B, Anassour-Laouan-Sidi E, et al. Zoonotic infections in communities of the James Bay Cree territory: an overview of seroprevalence. Can J Infect Dis Med Microbiol **2013**; 24:79–84.
5. Martin DA, Muth DA, Brown T, et al. Standardization of immunoglobulin M capture enzyme-linked immunosorbent assays for routine diagnosis of arboviral infections. J Clin Microbiol. **2000**; 38:1823–6.
6. Lanciotti RS, Roehrig JT. Arboviruses. In: Detrick B, Hamilton RG, Folds JD, eds. *Manual of Molecular and Clinical Laboratory Immunology*, 7th ed. American Society for Microbiology; **2006**: pp 757–65.
7. Artsob H, Spence L, Caughey WC, Wherrett JR. Aseptic meningitis in Ontario. Can Med Assoc J **1981**; 125:958–62.
8. Fauvel M, Artsob H, Calisher CH, et al. California group virus encephalitis in three children from Quebec: clinical and serologic findings. Can Med Assoc J **1980**; 122:60–2, 64.
9. Meier-Stephenson V, Langley JM, Drebot M, Artsob H. Encephalitis in the summer: a case of snowshoe hare (California serogroup) virus infection in Nova Scotia. Can Commun Dis Rep **2007**; 33:23–6.
10. McJunkin JE, de los Reyes EC, Irazuzta JE, et al. La Crosse encephalitis in children. N Engl J Med **2001**; 344:801–7.
11. Rust RS. Human arboviral encephalitis. Semin Pediatr Neurol **2012**; 19: 130–51.
12. National Notifiable Diseases Surveillance System. Arboviral Diseases, Neuroinvasive and Non-neuroinvasive: 2015 Case Definition. Centres for Disease Control and Prevention. Available at: https://wwwn.cdc.gov/nndss/conditions/california-serogroup-virus-diseases/case-definition/2015/. Accessed 14 April 2017.
13. Makowski K, Dimitrova K, Andonova M, Drebot M. Assessing serological cross-reactivity among California serogroup viruses using an IgM ELISA platform. Can J Infect Dis Med Microbiol **2010**; 21:26A.
14. Salimi H, Cain MD, Klein RS. Encephalitic arboviruses: emergence, clinical presentation, and neuropathogenesis. Neurotherapeutics **2016**; 13:514–34.
15. Wudel B, Shadabi E. A Short Review of Literature on the Effects of Climate Change on Mosquito-Borne Illnesses in Canada. National Collaborating Centre for Infectious Diseases; **2016**. Available at: https://nccid.ca/publications/review-of-literature-on-effects-of-climate-change-on-mosquito-borne-illnesses-in-canada/. Accessed 14 April 2017.