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Toscana meningoencephalitis: A comparison to other viral central nervous system infections

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ABSTRACT

Background: Toscana virus (TOSV) is an emerging pathogen causing central nervous system (CNS) infection in Mediterranean countries, mostly during summer season.
Objectives: To compare the clinical and laboratory characteristics of Toscana CNS infections to the most common viral pathogens seen in the United States.
Study design: We performed a case series of patients with 41 TOSV infection and compared the clinical characteristics, laboratory findings, imaging results and clinical outcomes to the most commonly recognized viral causes of meningoencephalitis in the US [enterovirus ($n=60$), herpes simplex virus ($n=48$), and West Nile virus ($n=30$)] from our multi-center study of patients with aseptic meningoencephalitis syndromes in the Greater Houston area.
Results: TOSV infection occurs in different age groups compared to enterovirus, HSV, and WNV. All infections most frequently occur during summer–fall except HSV which distributes throughout the year. All patients with TOSV had history of travel to endemic areas. There are differences in clinical presentation and CSF findings comparing TOSV and enterovirus, HSV, and WNV infection. There are no significant differences in outcomes of each infection except WNV meningoencephalitis which had a poorer outcome compared to TOSV infection.
Conclusions: TOSV is an emerging pathogen that should be considered in the differential diagnosis of patients with CNS infections and a recent travel history to endemic areas.

1. Background

Toscana virus (TOSV) is classified within the genus *Phlebovirus* of the family *Bunyaviridae*. It is an arthropod-borne virus that is transmitted to humans by the bite of an infected sandfly. TOSV has a distinct neurotropism which can cause meningoencephalitis.[1] In Europe, TOSV has been considered an emerging pathogen where it is one of the most frequent causes of central nervous system (CNS) infection during the summer.[2] Endemic areas include Italy, Spain, Portugal, France, Greece and Cyprus.[2] In recent years, there has been a growing number of TOSV infections reported in travelers returning from endemic areas to other regions of Europe. In addition, there have been several case reports of TOSV meningoencephalitis in US travelers returning from the Mediterranean.[3,4] TOSV CNS infection in most cases is associated with a favorable outcome but severe and lethal infections have been recently reported.[5,6]

We recently encountered a patient with TOSV infection in our hospital. The patient is a 51-year-old male physician who traveled to Rome, Italy in July 2011 and returned to the United States in August 2011. Ten days after his return, he awoke with "the worst headache of his life" requiring intravenous morphine. The patient had photophobia and neck stiffness. He denied having fever, malaise, nausea, vomiting, or skin rash. He recalled that he had received several mosquito bites while in Italy but had no known exposure to ticks or rabid animals. On admission, he was afebrile. Neurological examination revealed nuchal rigidity but no signs of encephalitis. The rest of examination was normal. Computed tomographic (CT) scan and magnetic resonance imaging (MRI) of the brain were unremarkable. Examination of cerebrospinal fluid (CSF) showed WBC 530 cells/mm^3 with 75% lymphocytes, RBC 4 cell/mm^3, a protein level of 119 mg/dL, and a glucose level of 64 mg/dL (serum glucose of 116 mg/dL). Polymerase chain reaction (PCR) results for CSF were negative for enterovirus and herpes simplex virus (HSV). CSF culture and CSF for the Venereal Disease Research Laboratory (VDRL) test for syphilis were also negative. Serological studies for West Nile virus (WNV) and HIV were negative as were blood cultures. Paired sera was taken from on days 0 and 31 post-onset of symptoms and were sent to the Center for Diseases Control, Division of Vector-Borne Diseases in Fort Collins,

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Table 1
Demographic characteristics and clinical outcomes for patients with Toscana virus infection compared with patients with enterovirus, herpes simplex virus, and West Nile virus infections.

Characteristic	No. (%) of cases			
	Toscana virus infection ($n=41$)	Enterovirus infection ($n=60$)	HSV infection ($n=48$)	WNV infection ($n=30$)
Age, mean years [range]	30 [2 mo to 80]	10 [2 mo to 53]*	40 [16–77]*	54.5 [14–89]*
Male sex	25/35 (71)	34 (57)	20 (42)*	15 (50)
White race	41 (100)	14 (23)*	26 (54)*	18 (60)*
Duration of symptoms before presentation, median days [range]	1 [1–14]	2 [0–38]	2 [1–21]	4 [1–21]
Season				
Summer-fall	25/26 (96)	48 (80)	29 (60)*	29 (97)
Winter-spring	1/26 (4)	12 (20)	19 (40)	1 (3)
Poor outcome (GOS 1–4)[a]	2/25 (8)	1 (2)	9 (19)	15 (50)*

* $P<0.05$.
[a] A poor outcome was defined as a Glasgow outcome score of 1–4. In this scale, a score of 1 indicates death; a score of 2 indicates a vegetative state (inability to interact with the environment); a score of 3, severe disability (unable to live independently but follows commands); a score of 4, moderate disability (unable to return to work or school but able to live independently); and a score of 5, mild or no disability (able to return to work or school).

CO for further analyses. A phlebovirus consensus RT-PCR assay conducted on day 0 sample generated a suggestive, target-sized faint band upon gel analysis.[7] However, the source of this band could not be confirmed through nucleotide sequencing due to extremely low amounts of generated cDNA. Plaque reduction neutralization assays revealed a >4-fold rise in TOSV between the paired serum samples, with titers of <1:5 and 1:640 for the day 0 and day 31 samples, respectively, indicating a recent TOSV infection. No similar rise in neutralizing antibodies to serologically related sandfly fever Naples and Sicilian viruses was detected. The patient developed post-spinal headache and received supportive care. He completely recovered five days after admission without neurological sequelae.

2. Objectives

The objective of our study was to bring awareness of this emerging pathogen and to compare the clinical characteristics, laboratory findings, imaging results and clinical outcomes of TOSV infection to the most commonly recognized viral causes of meningoencephalitis [enterovirus, HSV, and WNV] in the United States to try to identify clinical clues that should prompt physicians to test for TOSV in patients with recent travel to endemic areas.

2.1. Study design

2.1.1. Toscana virus group

We performed a MEDLINE search from 1971 to 2012 (National Library of Medicine) to identify all cases in the English literature of TOSV meningoencephalitis. We identified 17 case reports that provided information on a total of 40 patients that had detailed demographic and clinical characteristics, radiological studies, and laboratory results.[4–6,8–20] We added the clinical information on our case report to obtain a total sample of 41 patients.

2.1.2. Enterovirus, herpes simplex virus and West Nile virus groups

In order to identify patients with enterovirus, HSV and WNV CNS infections, we conducted a retrospective multi-center study of patients with aseptic meningoencephalitis syndromes at 9 Memorial Hermann Hospitals in the Greater Houston area from January 2005 to January 2010. We screened a total of 986 pediatric (2 months to 17 years) and adult (>18 years) patients with meningitis and/or encephalitis and excluded a total of 239 patients because they had a positive Gram stain for yeast ($n=61$) or bacteria ($n=52$), had nosocomial meningitis ($n=60$), or had incomplete medical records ($n=66$). A total of 747 patients with aseptic meningoencephalitis syndromes were identified with 138 patients (18%) having a viral etiology identified [enterovirus (60), HSV (48), and WNV (30)].

2.1.3. Data collection, laboratory testing and definition of diagnostic outcomes

Baseline patient characteristics were recorded at a specified "zero time", defined as the time when the patient was in the emergency department. Sociodemographic data, comorbid conditions (measured by the Charlson comorbidity scale[21]), immunocompetence, exposures, clinical features (including neurological exam and Glasgow coma scale[22]), laboratory results and management decisions were recorded. Patient's outcomes were assessed at time of discharge from the hospital by using the Glasgow outcome scale[23].

2.1.4. Statistical analysis

Bivariate analysis was performed to compare TOSV infections to enteroviral, HSV, and WNV infections. The t-test was used to analyze differences in clinical characteristics and radiographic finding and the Mann–Whitney *U*-test was used to assess differences in CSF findings. A P value <0.05 was considered to be statistically significant.

3. Results

3.1. Toscana virus meningoencephalitis

A total of 41 patients with TOSV infections with adequate clinical information were identified. Demographic data is shown in Table 1. The mean age was 30 years (range 2 months to 80 years). The majority of patients were male (71%) and white (100%). All of patients described had history of travel to or residence in Mediterranean countries, including Italy, France, Spain, Portugal, and Greece. There were two American patients who traveled to Italy. The disease occurred mainly during the summer and fall months with a maximum peak in August. Clinical characteristics are shown in Table 2. Most common symptoms include fever, headache, and meningeal symptoms but up to forty four percent of patients had encephalitis as their clinical presentation. CSF formula revealed moderate pleocytosis, mildly elevated protein and normal glucose and cranial imaging (CT scan and or MRI of the brain) was done in 13 (31%) of the patients with only two having abnormal results (hydrocephalus in both). Most patients (92%) had a benign and self-limiting disease.

3.2. Toscana virus infection and enterovirus infection

Compared to enterovirus meningitis, TOSV infection tended to occur in older age groups and white race as shown in Table 1.