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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.

Keywords

Toscana virus; enterovirus; west nile virus; herpes simplex virus; meningoencephalitis

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethical approval

The study was approved by the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects and by the Memorial Hermann Hospital Research Review Committee.

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 as 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/mm³ with 75% lymphocytes, RBC 4 cell/mm³, 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, 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 3 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.

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.

Study Design

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.

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)].

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].

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.

Results

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.

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. This latter difference is most likely due to the predominance of whites in European countries and travelers. Both infections presented more commonly in the summer and fall months but up to 20% of enteroviral infections presented in the winter or spring. TOSV infection had more headaches, stiff neck, photophobia, focal neurological exam and seizures compared to enteroviral infections (see Table 2). Patients with TOSV presented with encephalitis more frequently than enteroviral infection (44% vs. 2%, P value <0.05). CSF formulas were similar with the exception that the CSF protein was significantly higher in TOSV infection group. Both viruses had unremarkable CT scans of the brain.

Toscana virus infection and HSV infection

As shown in Table 1, TOSV infection occurred more commonly in the summer and fall months but up to 40% of HSV meningoencephalitis presented in the winter and spring months. Patients with TOSV infections were younger, more frequently male, and presented with a higher incidence of headache, malaise, and stiff neck. Also, although TOSV infections had a higher incidence of focal neurological exam and altered mental status compared to HSV infections, adverse clinical outcomes were not higher in TOSV infections (8% in TOSV vs. 19% in HSV) and abnormal CT scans or MRI were more commonly seen in HSV infections. TOSV and HSV infections had similar CSF formula (see Table 3). Intravenous acyclovir was administered to 28 out of 48 patients with HSV infections (58%); all 11 patients with encephalitis received therapy versus only 17 out of 37 patients (46%) with meningitis.

Toscana virus infection and WNV infection

TOSV affected younger age patients and more white patients compared to WNV infection as shown in Table 1. Both viruses predominantly presented in the summer and fall months. TOSV infection presented more frequently with fever, headache, stiff neck, photophobia, and rash (see Table 2). None of WNV infected patients had rash. Both viruses had similar proportion of encephalitis presentations but patients with WNV had more abnormal cranial imaging and adverse clinical outcomes. CSF formulas for both viruses were similar with the exception that TOSV infections had higher pleocytosis (see Table 3).

Neuroimaging studies

CT and MRI of the brain were performed in patients with viral CNS infections and results are shown in Table 3. Two out of 10 TOSV patients who had MRI done were found to have abnormal MRI with hydrocephalus. One patient with enterovirus infection had restrictive diffusion in the left parietal and temporal lobe as well as bilateral post central gyri and thalami. Eighty one percent of patient with HSV infection had abnormal neuroimaging. The main findings included focal or diffuse inflammation, hyper intense lesion, or hemorrhage mostly involving the temporal lobe and/or parietal and frontal lobes. Five out of 17 (29%) WNV patients who had MRI were found to have abnormal findings; one patient had bilateral basal ganglia hyper intense lesions and one had midbrain and insular cortex hyper intense lesions.

Discussion

Viral meningitis and/or encephalitis have a wide spectrum of causes and clinical presentations. The diagnostic evaluation to identify etiology requires a thorough and detailed epidemiologic and clinical history, including insect or animal bites, recent travel, sexual

exposures, and immunization status, and laboratory data. [24] Patients with viral CNS infections usually present with acute onset of fever, headache, nuchal rigidity, focal neurological deficit, and have CSF pleocytosis, abnormal CT or MRI. It is important to distinguish encephalitis, which can be life-threatening or caused by different etiologies, from benign viral meningitis by the clinical findings such as altered mental status and focal neurological deficit. Viral meningitis is generally benign and self-limiting whereas, delayed treatment initiation in case of encephalitis especially from HSV can increase morbidity and mortality. [25]

Enterovirus is one of the leading causes of aseptic meningitis and encephalitis in the US. [26, 27] These infections generally occur in the summer and fall, but can occur in any season. [28] Enterovirus CNS infections usually affect children but the disease is also common in adults. [29] The course of enterovirus infection is benign but fatal cases have been reported. [30] Clinical presentations depend upon age group. [31] Neonates with enteroviral meningitis present with nonspecific findings and usually do not have nuchal rigidity. Older children and adults with CNS infection frequently present with fever, photophobia, nausea, and vomiting. Nuchal rigidity occurs <70% at presentation and focal neurological deficits are rare. [31] Patients with enteroviral meningoencephalitis in our study have shown similar presentations to previous reports. When compared to enteroviral infection, TOSV infected older age group of people. Both TOSV and enterovirus infection occurs during summer and fall. It appears that TOSV patients more commonly presented with headache, neck stiffness, nausea, and encephalitis. There is no difference in laboratory findings except TOSV infection had higher CSF protein levels. Outcomes in both diseases were excellent.

HSV is the most common cause of viral encephalitis, which most of the cases are caused by HSV-1. [32, 33] The disease occurs 1 case per 250,000-500,000 population annually and cases are distributed throughout the year. [33] HSV encephalitis develops with a biphasic age distribution, less than age of 20 and more than 50 years of age. [33] Clinical hallmark of HSV encephalitis is acute onset of fever and focal neurologic symptoms. Aseptic meningitis is usually caused by HSV-2 and can have recurrent episodes (Mollaret's meningitis). In our study, we included both patients with meningitis and encephalitis. Unlike TOSV infection, we found that HSV CNS infection occurred more in female patients and distributed throughout the year. Fever, stiff neck, malaise, and change in mental status are less frequent in HSV patients. However, patients with HSV infection had more frequent abnormal MRI findings. There is no difference in clinical outcome between TOSV and HSV infection.

WNV meningoencephalitis is an arthropod-borne virus (arbovirus), transmitted to humans through mosquito bite. Transmission related to transfusion and organ transplantation has been reported, which led to blood product screening requirement. [34] The national incidence of WNV neuroinvasive disease in the US is 0.20 per 100,000 population [35] and increases with age. [35] In our study, both WNV and TOSV infections occur mostly during summer-fall months but WNV infection occurred in older age group compared to TOSV patients. More than half of WNV patients had encephalitis but there is no statistically significant difference from TOSV infection. TOSV patients had nonspecific symptoms including fever and headache more frequently than WNV patients. Meningeal signs and symptoms were more prominent in TOSV-infected patients. However, WNV infection had poorer clinical outcome compare to TOSV infection.

Neuroimaging is one of the diagnostic methods for patient with suspected viral encephalitis. MRI is more sensitive and specific than CT in the clinical setting. [36] We compared 6 neuroimaging studies between TOSV infection and other viral CNS infections in our study. Most of our HSV patients revealed abnormalities on MRI mostly in the temporal lobe as

typical MRI findings of HSV encephalitis patients. [37] Enterovirus encephalitis, mostly caused by enterovirus 71, typically have hyper intense lesion in the brainstem and dentate nuclei of the cerebellum on MRI but some may have lesions in the thalamus, putamen, and spinal cord. [37] One enterovirus patient in our study with clinical encephalitis had abnormal MRI but with diffused restrictive diffusion in bilateral thalami and cerebral cortex. Patients with WNV encephalitis usually have normal CT and < 30% of patients may reveal hyper intense lesion within the basal ganglia, thalamus, and pons on MRI. [37] We similarly found that two WNV patients had hyper intense lesions in basal ganglia and midbrain and one patient had brain edema in the thalamus. There is no typical MRI finding for TOSV CNS infection reported. Interestingly, two out of 10 TOSV patients who had MRI done were both found to have hydrocephalus on the MRI. Neuroimaging may provide helpful information in viral CNS infection however the ability to distinguish viral etiologies is limited and the mainstay of diagnosis remains detection of the pathogen by PCR amplification and serology.

We present the results of a large study that compares clinical characteristics and CSF findings of viral CNS infections caused by TOSV, enterovirus, HSV, and WNV. TOSV infection should be considered in differential diagnosis in a patient presented with meningitis and/or encephalitis symptoms during summer, and has recent travel to Mediterranean area.

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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 [2mo-80]	10 [2mo-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) [¶]	2/25 (8)	1 (2)	9 (19)	15 (50)*

* P < 0.05.

[¶]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).

Table 2

Clinical findings 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)
Symptoms				
Fever	38/39 (97)	50/59 (85)	8/47 (17) *	18/29 (62) *
Headache	36/36 (100)	44/59 (75) *	46/48 (96)	17/27 (63) *
Stiff neck	33/38 (87)	21/59 (36) *	30/47 (64) *	3/27 (11) *
Nausea/vomiting	14/18 (78)	41/59 (65)	35/48 (73)	18/27 (67)
Photophobia	6/7 (86)	18/57 (32) *	20/46 (43)	3/25 (12) *
Malaise	8/13 (62)	6/50 (12) *	8/45 (18) *	11/27 (41)
Respiratory symptom	0/1 (0)	0/60	2/47 (4)	0/27
Focal neurological deficit	6/28 (21)	0/58 (0) *	7/48 (15)	12/29 (41)
Seizure	3/25 (12)	2/58 (3)	4/48 (8)	0/29
Signs				
Altered mental status [†]	14/34 (41)	1/55 (2) *	8/48 (17) *	12/29 (41)
Nuchal rigidity	33/37 (89)	12/55 (22) *	24/44 (55) *	6/29 (21) *
Rash	4/10 (40)	4/57 (7) *	5/48 (10) *	0/29 *
Focal neurological deficit [‡]	6/17 (35)	0/57 (0) *	3/48 (6) *	4/29 (14)
Encephalitis s/s	16/36 (44)	1/60 (2) *	11/48 (23)	17/29 (59)

* P < 0.05.

[†] Confusion or Glasgow coma scale <14.

[‡] TOSV: cranial neuropathy (1), hem paresis (3), aphasia (2), ataxia (1); HSV: cranial neuropathy (1), expressive aphasia (2); WNV: hemiparesis (3), ataxia (1).

Table 3

Laboratory results and imaging studies for patients with Toscana virus infection compared with patients with enterovirus, herpes simplex virus, and west nile virus infections

Laboratory/Radiology result	No. (%) of cases			
	Toscana virus infection (n = 41)	Enterovirus infection (n = 60)	No (%) of cases HSV infection (n = 48)	WNV infection (n = 30)
CSF WBC (cells/mm ³) [†]	208 [8-3500]	149 [7-13625]	242.5 [12-3500]	103.5 [1-2830] [*]
CSF lymphocyte (%) [†]	85 [60-100]	31 [2-96]	90 [2-100]	62 [7-98]
CSF protein (mg/dL) [†]	88 [20-757]	45 [22-171] [*]	98 [18-445]	99 [18-154]
CSF glucose (mg/dL) [†]	60 [29-131.94]	58 [9-87]	53.5 [35-169]	58 [43-129]
CT abnormal	0/13 (0)	0/29 (0)	3/42 (7) [¶]	4/26 (15) [#]
MRI abnormal	2/10 (20) [‡]	1/5 (20) [§]	12/16 (75) ^{*¶}	5/17 (29) [#]

^{*} P < 0.05.

[†] Data are median value [range].

[‡] TOSV MRI findings: hydrocephalus (2).

[§] Enterovirus MRI finding: diffuse restricted diffusion (1).

[¶] HSV CT findings: old stroke (1), focal hemorrhage (2); MRI findings: focal inflammation (2), focal hyper intense lesion (2), focal brain edema (1), diffuse hemorrhages (1), diffuse hyper intense lesions (2), diffuse restricted diffusion (1), non-specific white matter changes (3).

[#] WNV CT findings: old stroke (3), focal hemorrhage (1); MRI findings: old stroke (1), diffuse brain edema (1), diffuse hemorrhages (1), diffuse hyper intense lesions (2).