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SHORT COMMUNICATION

Unusual Clinical Features of Toscana Virus Central Nervous System Infections in Italy

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Abstract

Objective: This study was aimed at reviewing a case series of 35 patients with neuroinvasive Toscana Virus (TOSV) infections, to evaluate clinical findings and outcomes.

Methods: A retrospective analysis was conducted in two secondary referral facilities in Italy. Patients with confirmed TOSV infection were included. Biochemical and serological analyses of blood and cerebrospinal fluid (CSF), as well as radiological imaging, were conducted.

Results: A total of 35 cases of neuroinvasive TOSV infection were analyzed (in 28 men and 7 women): 32 (in 25 men and 7 women) with a diagnosis of meningitis with clear CSF and 3 (in only men) with a diagnosis of encephalitis. No fatalities or permanent outcomes were observed in the meningitis cases. Three patients with encephalitis were admitted to intensive care because of psychomotor agitation that lasted at least 12 hours and tended to worsen. All but one patient with encephalitis fully recovered with no neurological sequelae after a mean of 6.3 days of acute care. A 73-year-old man developed a chronic psycho-organic syndrome.

Conclusions: Most TOSV infections are asymptomatic, mild, or undiagnosed; however, cases of severe disease are increasing, because of TOSV's specific affinity for the nervous system, both central and peripheral.

Key words: Toscana Virus, Meningitis, Encephalitis, Meningo-Encephalitis

INTRODUCTION

Toscana virus (TOSV) is an emerging pathogen causing central nervous system (CNS) infections in Mediterranean countries, primarily during the summer season [1–8]. We performed a retrospective analysis of a case series of patients with neuroinvasive TOSV infections, to evaluate their clinical findings and outcomes. We also reviewed the literature on cases of neuroinvasive TOSV infections presenting unusual, rarely described clinical manifestations, which might potentially be confused with other morbid causes.

METHODS

To review all laboratory-confirmed cases of TOSV infection in patients admitted to the "G. B. Morgagni -L. Pierantoni" Hospital in Forlì and the "Annunziata" Hospital in Cosenza, between 2012 and 2025, we evaluated clinical records for all patients discharged with a diagnosis of TOSV neuroinvasive infection.

RESULTS

Thirty-five cases of neuroinvasive TOSV infection were analyzed (in 28 men and 7 women): 32 (in 25 men and 7 women)

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with a diagnosis of meningitis with clear cerebrospinal fluid, and 3 (in only men) with a diagnosis of encephalitis.

The mean age was 48.54 years (range, 25–80 years) overall, 47 years (range, 25–80 years) among men, and 48.14 years (range, 39–71 years) among women. The mean age of the 20 patients with meningitis was 46 years (range, 25–72 years) overall, 44.94 years (range, 25–72 years) among men, and 48.14 years (range, 39–71 years) among women.

The mean overall hospital stay was 6.42 days (range, 4–9 days) overall, 5.8 days (range, 4–8 days) among male patients, and 6.8 days (range, 5–9 days) among female patients.

No fatalities or permanent outcomes were observed among the meningitis cases, whereas one case of encephalitis resulted in a frank chronic psycho-organic syndrome.

In two cases of encephalitis, the acute psychomotor agitation syndrome resolved at the end of hospitalization, without neurological sequelae.

The patient with encephalitis resulting in a frank chronic psycho-organic syndrome died after approximately 3 months during a stay at a long-term rehabilitation facility.

All patients had a history of sandfly bites and clinical findings of CNS infections. Two cases of encephalitis were observed in patients >70 years of age (73 and 75 years), whereas the third case of encephalitis occurred in a 52-year-old patient. All but three patients presented to the hospital within 5 days after disease onset. Two patients from the same family developed mild neuroinvasive infection.

Laboratory confirmation of human cases of TOSV neuroinvasive infection involves molecular and serological testing. Laboratory evidence of cases of TOSV infection involves molecular and serological testing [9].

The diagnostic workup included testing for the presence of CSF TOSV RNA in specimens through real-time reverse transcription polymerase chain reaction for TOSV, targeting the TOSV N gene [10], and anti-TOSV IgG and IgM detection in serum or plasma samples through an indirect immunofluorescence assay [9] (Sandfly fever virus Mosaic 1 types Sicilian, Naples, Toscana, Cyprus IgG and IgM assay, EuroImmun, Luebeck, Germany). On the basis of laboratory findings, TOSV infections were classified as acute (positive PCR with or without IgM detection) or recent (IgM detection alone), according to testing [9].

In all cases (except one in which the RNA test in CSF was positive, and the serology test in peripheral blood was negative), the RNA test in CSF and the serology test in peripheral blood were positive.

Coinfections with other pathogens were excluded. The same type of vector-borne infection with leishmaniasis was assessed through serological testing for leishmaniasis in all patients, which yielded negative results.

An imaging study using a cerebral computed tomography scan and/or magnetic resonance imaging documented mild-moderate meningeal salience in 60% of cases (Fig 1). Of the 35 patients, 30 underwent EEG 1–5 days into the illness course: 9 showing a normal pattern and 21 showing diffuse slowing waves.

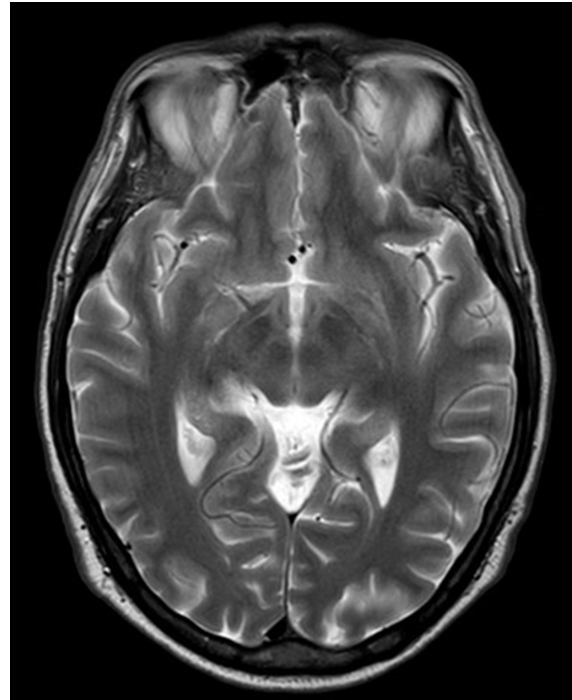

FIGURE 1 | Head magnetic resonance imaging showing weak leptomeningeal-venular enhancement in the bilateral cerebellar region.

Laboratory test findings revealed mild elevations in C-reactive protein in most cases (mean 35 mg/L, n.v. 0.00–5.00) but were otherwise normal.

Initial laboratory findings indicated normal leukocyte counts and mild lymphocytic pleocytosis with an average lymphocyte percentage of 45%.

Lumbar puncture revealed clear, colorless CSF in all cases.

The mean CSF protein was 95 mg/dL (n.v., 0.00–35.00), the mean glucose was 65 mg/dL (n.v., 0.00–70.00), and the mean IgG was 9.60 mg/dL [n.v., 0.00–3.40]. CSF microscopy revealed a mean of 125 white blood cells per mm^3 (normal value [n.v.] 0–5) and 90% lymphocytes.

No growth was observed in CSF cultures. PCR tests for herpes simplex virus, varicella-zoster virus, cytomegalovirus, enterovirus, chikungunya, West Nile virus, and tick-borne encephalitis virus on CSF were negative. Testing for Lyme disease and *Rickettsia conori* was negative. Blood cultures from admission were negative.

Empirically, until the conclusion of the diagnostic workup, each patient was empirically treated with acyclovir and ceftriaxone, which were immediately suspended as soon as the etiological diagnosis was acquired. No patients received steroid therapy.

All but one patient with encephalitis fully recovered with no neurological sequelae after a mean of 6.3 days of acute care.

Three patients with encephalitis were admitted to the intensive care unit because of serious psychomotor agitation that lasted at least 12 hours and tended to worsen, and was unresponsive to common medications, to the point of requiring sedation in the intensive care unit.

These three patients exhibited fever, headache, and severe mental changes, including confusion, agitation, irritability, and hallucinations; two of these patients also showed personality alterations with heightened aggressiveness.

A 73-year-old man experienced persistent frontal headache for several days, accompanied by a moderate fever, confusion, and agitation. After 3 days, he exhibited prominent insomnia with increasing psychological changes, anxiety, confusion, auditory hallucinations, hypersensitivity to mechanical stimuli, slight weakening of the lower limbs with mild footdrop, complete disorientation and stupor, and sensory and motor aphasia, thereby suggesting a psycho-organic syndrome.

His clinical condition became increasingly serious and resulted in death approximately 1 month after admission. In these three patients, EEG showed diffuse and bilateral spikes, particularly at the fronto-temporal lobes, whereas in 32 other patients, the EEG findings indicated diffuse non-specific abnormalities.

DISCUSSION

Severe acute psychomotor agitation is a rare adult presentation of TOSV neuroinvasive infection.

Agitation can be a symptom of various neurological or medical conditions, including CNS infections [1]. Severe acute psychomotor agitation is not a primary or typical presentation of TOSV infection, which involves primarily fever, headache, and neurological symptoms, such as meningitis and encephalitis. Although agitation can occur as a non-specific symptom in CNS involvement, reports of TOSV have focused on typical neurological signs such as confusion, ataxia, and seizures, rather than severe psychomotor agitation, as a hallmark presentation [2,3].

If psychomotor agitation were to occur with TOSV, it would be likely to be within the broader context of meningoencephalitis and its effects on the brain, rather than a specific sign of the virus itself [4].

Of the five patients with encephalitis, four made a full recovery, whereas one developed a psychoorganic syndrome with a severe, permanent altered mental state. Psychiatric syndromes with evidence of intrathecal inflammation temporally associated with TOSV infections have not been described previously, to our knowledge.

TOSV has become recognized as a leading cause of CNS infections in Italy during the summer. Although illnesses caused by TOSV usually mimic a flulike syndrome, the severity of CNS involvement can range from aseptic meningitis to meningo-encephalitis. The disease usually has favorable outcomes, and reports of severe courses are rare. However, patients with unusual symptoms and life-threatening complications have been reported, including two cases of meningo-encephalitis with severe sequelae in Umbria [5]; a case of postencephalitic seizures and subsequent persistent personality alterations including aggressive behavior and sexual disinhibition in a 49-year-old man [6]; and a case of acute hydrocephalus due to impaired CSF resorption [7].

In another case, a 33-year-old woman with TOSV meningoencephalitis developed typical symptoms of acute cerebellar ataxia 72 hours after hospital admission. Intravenous steroid therapy achieved prompt symptom resolution, and she was discharged at day 10 in good clinical condition [8]. Our experience and findings from an extensive literature review confirmed that neuroinvasive TOSV infections should not be underestimated as a possible cause of severe clinical syndromes, although these infections progress favorably without worrisome clinical manifestations in most cases. Knowledge of the description of unusual clinical presentations with more severe and uncommon symptoms should prompt clinicians' suspicions that TOSV might be a potential infectious agent responsible for more severe and uncommon neurological and/or neuropsychiatric conditions.

CONCLUSIONS

In summary, most TOSV infections are asymptomatic, mild, or undiagnosed; however, an increasing number of cases develop severe disease, owing to TOSV's specific affinity for the nervous system, both central and peripheral [3]. Indeed, this neurotropism is a potential cause of severe neurological diseases such as meningitis and encephalitis [3].

The clinical and epidemiological relevance of TOSV infections has been hypothesized to be associated with strain-specific phenotypic differences, particularly in severe infections [11].

Different host-pathogen interactions might underlie the various clinical courses of TOSV neuroinvasive infections, as hypothesized in a recent study comparing the pathobiological features of two distinct clinical TOSV strains [11].

DATA AVAILABILITY STATEMENT

The data supporting the findings of this case report are available from the corresponding author on reasonable request. To protect patient privacy and confidentiality, some data might not be made publicly available.

ETHICS STATEMENT

This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent to publication of this brief report was obtained from the patients. The Local Research Ethics Board Committee, Annunziata Hospital, Cosenza, Italy, approved the study and data protection compliance according to relevant Italian and European regulations (ethical approval number 56/2024, CET, Cosenza, Regione Calabria, Italy).

AUTHOR CONTRIBUTIONS

Antonio Mastroianni, Simona Di Cesare, Sonia Greco, and Valeria Vangeli collected the clinical data and contributed to patient management. Vittorio Sambri and Robert Tenuta performed the

microbiological analyses. Antonio Mastroianni and Sonia Greco supervised the study and coordinated the writing of the manuscript. Antonio Mastroianni is the corresponding author. All authors contributed to the manuscript preparation, critically revised the work, and approved the final version.

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None.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. Del Casale A, Arena JF, Napoli C, Grassi F, Mancino S, Di Legge C, et al. A comprehensive understanding of psychomotor agitation: from causes to hospital care. Curr Neuropharmacol. 2025;23(13):1666-1682.
2. Peyrefitte CN, Devetakov I, Pastorino B, Villeneuve L, Bessaud M, Stolidi P, et al. Toscana virus and acute meningitis, France. Emerg Infect Dis. 2005;11(5):778-780.
3. Keskek Turk Y, Ergunay K, Kohl A, Hughes J, McKimmie CS. Toscana virus - an emerging Mediterranean arbovirus transmitted by sand flies. J Gen Virol. 2024;105(11):002045.
4. Ayhan N, Eldin C, Charrel R. Toscana virus: a comprehensive review of 1381 cases showing an emerging threat in the Mediterranean regions. J Infect. 2025;90(2):106415.
5. Baldelli F, Ciufolini MG, Francisci D, Marchi A, Venturi G, Fiorentini C, et al. Unusual presentation of life-threatening Toscana virus meningoencephalitis. Clin Infect Dis. 2004;38(4):515-520.
6. Serata D, Rapinesi C, Del Casale A, Simonetti A, Mazzarini L, Ambrosi E, et al. Personality changes after Toscana virus (TOSV) encephalitis in a 49-year-old man: a case report. Int J Neurosci. 2011;121(3):165-169.
7. Oechtering J, Petzold GC. Acute hydrocephalus due to impaired CSF resorption in Toscana virus meningoencephalitis. Neurology. 2012;79(8):829-831.
8. Suardi LR, Di Lauria N, Pozzi M, Rogasi PG, Barilaro A, Azzolini F, et al. Acute cerebellar ataxia: a rare Toscana Virus (TOSV) meningoencephalitis complication. Int J Neurosci. 2020;130(3):276-278.
9. Calzolari M, Angelini P, Finarelli AC, Cagarelli R, Bellini R, Albieri A, et al. Human and entomological surveillance of Toscana virus in the Emilia-Romagna region, Italy, 2010 to 2012. Euro Surveill. 2014;19(48):20978.
10. Pérez-Ruiz M, Collao X, Navarro-Marí JM, Tenorio A. Reverse transcription, real-time PCR assay for detection of Toscana virus. J Clin Virol. 2007;39(4):276-281.
11. Vogiatzis S, Gori Savellini G, Terrosi C, Trevisan M, Anichini G, Rizzo L, et al. Phenotypic characterization of two neuroinvasive Toscana virus strains clinically associated with self-limited and persistent infections in human neural cells and brain organoids. Front Cell Infect Microbiol. 2025;15:1658107.