Toscana Virus and Acute Meningitis, France

To the Editor: Sandfly fever is caused by Toscana virus, a member of the family Bunyaviridae, genus Phlebovirus. It has been recognized as an etiologic agent of human illnesses in countries bordering the Mediterranean Sea. The virus is responsible for rapidly resolving diseases in patients with nonspecific symptoms such as fever and myalgia. However, infection with Toscana virus may involve the central nervous system; severity may range from aseptic meningitis to meningoencephalitis (1). In most cases, illnesses caused by Toscana virus mimic a flulike syndrome with fever, photophobia, headache, red eyes, and stiff neck. Recently, 2 cases of Toscana virus meningoencephalitis in patients with unusual symptoms and life-threatening complications were described in Italy (2). However, sequelae have never been reported.

Toscana virus infection is now epidemic in Italy and Spain (1,3). Furthermore, sporadic cases have been reported in travelers returning from Italy, Spain, Greece, Portugal, and the South of France (4–6). The epidemiology of Toscana virus in France is still unknown. Although infections with this virus have been diagnosed by serologic tests in French patients and in tourists residing in southeastern France, this pathogen has reportedly never been isolated in France (7,8). Here we describe the clinical and biologic features of autochthonous meningitis due to Toscana virus.

On July 9, 2004, a 57-year-old woman who had never left the southeastern coast of France reported malaise and vomiting. On hospital admission, her body temperature was 38.5°C, and clinical examination showed photophobia and stiff neck.

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Skin and abdomen were normal. Cardiopulmonary and neurologic functions were also normal. Analysis of hematologic and biochemical blood tests revealed mild hyperglycemia (6.88 mmol/L) and elevated γ-glutamyltransferase (104 IU/L) and C-reactive protein levels (57 mg/L). Cerebrospinal fluid (CSF) analysis showed 3,500 leukocytes/µL (70% lymphocytes, 30% neutrophils), and glucose and protein levels of 2.5 mmol/L and 2.749 mg/L, respectively. Blood and CSF cultures were bacteriologically sterile. Polymerase chain reaction (PCR) assays of CSF for herpes simplex virus were also negative. The patient received intravenous amoxicillin and acyclovir for 3 days. The patient recovered after 6 days without sequelae.

Serum and CSF samples collected during the acute phase were tested for immunoglobulin (Ig)M and IgG antibodies to a battery of arboviruses. These samples contained no antibodies (optical density [OD] ratio <1.5) to flaviviruses, dengue virus, West Nile virus, and tickborne encephalitis, Tahyna virus, or Sandfly fever Sicilian virus (Table). However, the IgM OD ratios (≥2.5) obtained against Toscana virus antigen were high. A second serum sample tested 1 month later showed seroconversion to Toscana virus with OD ratios >3 for both IgM and IgG (Table).

Virus isolation was attempted by incubation of peripheral blood mononuclear cells and CSF collected on the day of onset with C6/36 (Aedes albopictus) and Vero (E6 clone) monolayers. Toscana virus was found only on Vero cells by indirect immunofluorescence by using mouse hyperimmune ascitic fluid against Toscana virus. In contrast, no fluorescence was found by using mouse hyperimmune ascitic fluids against Rift Valley fever and Sandfly fever Sicilian virus.

S segment of Toscana virus genome was partly amplified from culture supernatants by reverse-transcription PCR and sequenced (9). Nucleotide and peptide sequences obtained (GenBank accession no. AY766034) displayed 87% and 100% identity, respectively, with Toscana virus sequences available on GenBank database, thus confirming the infection by Toscana virus.

Toscana virus, transmitted to humans by Phlebotomus vectors, has been recognized as a major cause of aseptic meningitis in Italy and Spain. P. perniciosus, proven to be a vector of Toscana virus (10), is abundant along the French Mediterranean coast. The isolation of an autochthonous Toscana virus strain shows that the conditions of an efficient transmission cycle were combined in southern France. Until now, human infection by Toscana virus was fortuitously detected by serologic means, suggesting that subclinical infection may also occur (8). Thus, Toscana virus infection in France likely has been underestimated. Moreover, meningitis caused by Toscana virus has been underestimated and other diseases caused by Toscana virus may have also been underestimated. The requirement for virus growth in cell culture delays a diagnosis based on viral isolation, which is limited by the transitory presence of the virus in blood or CSF. As reported here, Toscana virus infection was only confirmed after the patient relapsed. Considering that signs and symptoms of Toscana virus meningitis are not pathognomonic, this case highlights the need for rapid and specific diagnostic tools, such as PCR assays, to identify infections caused by Toscana virus and other neurotropic viral agents. Moreover, a systematic serologic study of recovered meningitis patients may help to better characterize viral meningitis of unknown etiology.

Finally, this work suggests that, in addition to West Nile virus, Toscana virus should now be considered as a potential etiologic agent of acute meningitis in the southeastern part of France. Entomologic and epidemiologic surveys, however, will have to be conducted in the near future to determine the risk for the people living in that area.

Acknowledgments

We thank Matthieu Kaltenbach for reviewing the manuscript. We also thank J-P. Durand for skillful discussions and scientific rigor.

This work was supported by the French Délégation Générale de la Santé.

Christophe N. Peyrefitte,* Ivan Devetakov,† Boris Pastorino,* Laurent Villeneuve,† Mael Bessaud,* Philippe Stolidi,† Jerome Depauquit,‡ Laurence Segura,† Patrick Gravier,* Fabienne Tock,* Francoise Durand,† Jean-Paul Vagneur,† Hugues J. Tolou,* and Marc Grandadam*
LETTERS

Helicobacter pylori, Republic of Georgia

To the Editor: Helicobacter pylori infection is a principal cause of chronic active gastritis and peptic ulcer disease as well as gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma (1). Poverty and crowding have been associated with infection epidemiologically (2,3). The Republic of Georgia has a per capita annual income of US $591, making it one of the poorest countries in the world (4,5). Georgia also reports a high annual incidence of gastric cancer, 17/100,000 population in 2002 (National Center for Disease Control, Tbilisi, unpub. data), which suggests an elevated prevalence of H. pylori infection. Testing and treatment for H. pylori are not practiced in this country, and diagnostic capacity for H. pylori is nonexistent. In October 2003, we conducted an exploratory pilot study of H. pylori infection to begin characterizing prevalence and risk factors for infection.

We studied a convenience sample of adults residing in or near the capital city of Tbilisi. Urban participants were enrolled in 11 of Tbilisi’s 12 residential districts and in 1 district of Rustavi, a city 20 miles south of Tbilisi. Rural participants were recruited from 3 villages within 10 miles of Tbilisi. In each district or village, we nonsystematically selected 10 households and recruited 1 adult per household. Exclusion criteria included age <18 years; reported allergy to omeprazole, clarithromycin, or amoxicillin; or treatment with any antimicrobial agent within the preceding 2 weeks. This protocol was reviewed and approved by the Human Subjects Review Board at the National Center for Disease Control, Tbilisi. Active infection with H. pylori was measured by a validated, point-of-care 13C-urea breath test (Meretek Corporation, Lafayette, CO, USA) (6). Participants responded to a questionnaire that requested information about gastrointestinal symptoms during the preceding 12 months; diagnosis of gastritis, peptic ulcer disease, and gastric cancer made by a physician; family history of peptic ulcer disease or gastric cancer; and knowledge about H. pylori. Low, medium, or high socioeconomic status categories were designated on an ecologic basis, according to average real estate prices and common perception of the living standard of the participant’s district or village of residence. Analyses were conducted with SAS (SAS Institute, Cary, NC, USA) version 9.0. Measures of inference are not reported because participants did not constitute a rigorously selected population sample.

Of 136 persons eligible to participate in the study, 135 (99%) consented to take part. Median age was 39 (range 19–79); 82 participants (61%) were women. Twenty-seven (20%) reported having some knowledge of H. pylori, but none had been tested or treated for the infection. Ninety-seven (72%) participants had active infection. Ninety-seven (71%) of 82 women and 39 (74%) of 53 men. Thirty (77%) of 39 participants ≥50 years of age tested positive for H. pylori compared to 67 (70%) of 96 participants <50 years of age.

Seventy-one (84%) of 85 participants residing in neighborhoods of low-socioeconomic status were infected versus 26 (52%) of 50 participants residing in neighborhoods of medium- or high-socioeconomic status (crude prevalence odds ratio 4.68). Twenty-three (85%) rural participants were infected compared to 74 (69%) of 108 urban participants (crude prevalence odds ratio 2.64).

Gastrointestinal symptoms were common, but did not correlate with active infection. One hundred five participants (78%) reported recurrent epigastric pain within the past year;

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Address for correspondence: Christophe N. Peyrefitte, IMTSSA, Unité de Virologie Tropicale, BP 46 13998, Marseille, France; fax: 33-4-91-15-01-72; email: publi.viro@laposte.net