Infections Due to Sandfly Fever Virus Serotype Toscana in Spain

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Of the sandfly fever viruses known to be human pathogens (serotypes Toscana [TOS], Sicilian [SFS], and Naples [SFN]), only TOS has demonstrated neurotropic activity. Infections by TOS have been reported in Mediterranean countries, but the virus was previously isolated only in Italy and Portugal. We isolated 15 strains of TOS between 1988 and 1996 from the cerebrospinal fluid of patients with acute aseptic meningitis in Granada, Spain. This finding led us to study the presence of antibodies to TOS, SFS, and SFN in 1,181 adults and 87 children from different regions of Spain. We found that the prevalence of antibodies to these viruses was 26.2%, 2.2, and 11.9%, respectively; these rates imply that TOS infections are common in Spain.

Three serotypes of sandfly virus are recognized human pathogens: Sicilian (SFS), Naples (SFN), and Toscana (TOS). All of these serotypes are transmitted by *Phlebotomus* species in the Mediterranean region, the Middle East, and central Asia. *Phlebotomus papatasii* is the vector for SFS and SFN, and *Phlebotomus perniciosus* transmits TOS. Sandfly fever is a self-limiting illness of abrupt onset that has a duration of 3 to 5 days; it is characterized by high grade fever, headache, and myalgia. However, TOS infection can result in aseptic meningitis and meningoencephalitis [1]. Although SFS and SFN have not been isolated recently in southern Europe (probably because of the decrease in the *P. papatasii* population brought about by measures to eradicate malaria), TOS infections are now common [1].

Serological evidence of TOS infection has been reported in different countries in southern Europe [2–5], but the virus was previously isolated only in Italy and Portugal [1, 6]. We isolated 15 strains of TOS from CSF of patients with aseptic meningitis in Spain and studied serum samples from individuals in different regions of Spain to estimate the prevalence of antibodies to TOS, SFS, and SFN.

Materials and Methods

Between April 1988 and December 1996, samples of CSF were obtained from 184 patients with acute aseptic meningitis. The diagnosis of TOS meningitis was based on positive results of Vero cell culture of CSF after incubation and observation of the characteristic cytopathic effect. Cell cultures were incubated for 3 weeks, although all strains grew within 1 week. Isolates were identified by physicochemical testing and the plaque reduction neutralization assay with murine antisera [7, 8].

Indirect immunofluorescence assays were done to detect antibodies to TOS, SFS, and SFN in a total of 1,268 serum samples from 1,181 adult blood donors and 87 children (none transmitted TOS). Sandfly fever is a self-limiting illness of abrupt onset that has a duration of 3 to 5 days; it is characterized by high grade fever, headache, and myalgia. However, TOS infection can result in aseptic meningitis and meningoencephalitis [1]. Although SFS and SFN have not been isolated recently in southern Europe (probably because of the decrease in the *P. papatasii* population brought about by measures to eradicate malaria), TOS infections are now common [1].

Received 3 December 1997; revised 6 April 1998.
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Clinical Infectious Diseases 1998;27:434–6
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1058-4838/98/2703–0005$03.00
of glucose and proteins; 12 of 15 patients had lymphocytic pleocytosis (range, 20–515 cells/mm³). The patients were hospitalized for <1 week, and all patients recovered spontaneously.

Analysis of the serum samples revealed that the prevalence of antibody to SFS, SFN, and TOS was 2.2% (28 samples), 11.9% (151), and 26.2% (332), respectively. Of the 1,268 serum samples, 126 (9.9%) were simultaneously positive for TOS and SFN antigens. Of these 126 serum samples, 116 (92%) had titers of antibody to TOS that were higher than those of antibody to SFN; three (2.4%) had titers of antibody to SFN that were higher than those of antibody to TOS.

The highest prevalences were related to the distribution of Phlebotomus in the Mediterranean regions of Spain (Granada, Barcelona, Jerez, and Palma de Mallorca) (table 1). The relatively high prevalence of antibodies to SFN was probably caused by cross-reaction between TOS and SFN as previously described [10]. Among the population we studied, titers of antibody to TOS appeared in the 10- to 19-year-old age group. The prevalence appeared to be stable until the age of 50 years, when it increased, perhaps reflecting a period 40 to 50 years ago when the incidence of infection was higher than the rate today (table 2).

Discussion

Neurovirulent TOS caused 155 cases of meningitis and meningoencephalitis in central Italy between 1977 and 1988 [1]. Nicoletti and colleagues [1] isolated 10 strains from CSF of 72 patients with aseptic meningitis. Several cases of sandfly fever in German tourists returning from Tuscany, Italy, were described in 1993 [5] and 1995 [11]; one case of sandfly fever was described in a United States citizen returning from Italy [3], and one case occurred in a Swedish man who had visited Portugal [6]. Serological evidence of infection was also found in Swedish troops in Cyprus [2]. Eitrem and colleagues [4] cited one case of TOS infection in Catalonia, Spain, but none of 56 serum samples from Swedish tourists who had vacationed in Palma de Mallorca was positive for sandfly fever viruses.

P. perniciosus and P. papatasii are known to be present in Spain; the former is the more abundant species [12] and is the vector for leishmaniasis, a parasitosis prevalent in Spain. Nicoletti and colleagues [1] isolated 10 strains from CSF of 72 patients with aseptic meningitis. Several cases of sandfly fever in German tourists returning from Tuscany, Italy, were described in 1993 [5] and 1995 [11]; one case of sandfly fever was described in a United States citizen returning from Italy [3], and one case occurred in a Swedish man who had visited Portugal [6]. Serological evidence of infection was also found in Swedish troops in Cyprus [2]. Eitrem and colleagues [4] cited one case of TOS infection in Catalonia, Spain, but none of 56 serum samples from Swedish tourists who had vacationed in Palma de Mallorca was positive for sandfly fever viruses.

P. perniciosus and P. papatasii are known to be present in Spain; the former is the more abundant species [12] and is the vector for leishmaniasis, a parasitosis prevalent in Spain. However, the vector for sandfly fever virus infections in this country remains unknown. In areas of endemicity, people are probably infected during childhood and may suffer only a mild illness. Nonimmune adults, such as tourists who enter an area of endemicity, may have more noticeable symptoms. It should be pointed out that our rate of detection of TOS in CSF may have been somewhat underestimated because we did not use gene amplification techniques [11, 13]. However, our findings show that sandfly fever viruses are endemic in Spain, where TOS infection should be considered a possible diagnosis in cases of neurological disorders.

Table 1. Prevalence of antibodies to SFN, SFS, and TOS in different regions of Spain.

<table>
<thead>
<tr>
<th>Region</th>
<th>No. of serum samples</th>
<th>Percent of samples with antibodies to indicated virus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SFN</td>
</tr>
<tr>
<td>Granada</td>
<td>316</td>
<td>7.9</td>
</tr>
<tr>
<td>Barcelona</td>
<td>176</td>
<td>19.3</td>
</tr>
<tr>
<td>Santiago de Compostela</td>
<td>96</td>
<td>30.2</td>
</tr>
<tr>
<td>Las Palmas de Gran Canaria</td>
<td>100</td>
<td>20.0</td>
</tr>
<tr>
<td>San Sebastian</td>
<td>97</td>
<td>4.1</td>
</tr>
<tr>
<td>Jerez</td>
<td>97</td>
<td>6.1</td>
</tr>
<tr>
<td>Murcia</td>
<td>100</td>
<td>4.0</td>
</tr>
<tr>
<td>Madrid</td>
<td>186</td>
<td>6.4</td>
</tr>
<tr>
<td>Palma de Mallorca</td>
<td>100</td>
<td>1.8</td>
</tr>
<tr>
<td>Total</td>
<td>1,268</td>
<td>11.9</td>
</tr>
</tbody>
</table>

NOTE. SFN = sandfly fever virus serotype Naples; SFS = sandfly fever virus serotype Sicilian; TOS = sandfly fever virus serotype Toscana.

We thank K. Shashok for reviewing the use of English in the manuscript.

References