Serologic Evidence of Human Granulocytic Ehrlichiosis, Greece

To the Editor: Human granulocytic ehrlichiosis (HGE), a tickborne infectious disease, was first described in 1994 (1). Several cases have been reported in the United States; reports of acute cases in Europe have been rare, although European serosurveys of the prevalence of antibodies to the HGE agent have been conducted (2–4). No similar serosurvey has been conducted in Greece, although *Ixodes ricinus*, thought to be the principal tick vector in Europe (5), is present in northern Greece (6). Lyme disease, which is transmitted by the same tick, has never been reported, and the seroprevalence of Lyme borreliosis in Greece is very low (7).

We examined sera of 300 persons (100 men and 200 women) ages 15–78 years (mean age ± standard deviation 52.7±18.0 years), which were collected at six county hospitals in northern Greece and sent to our laboratory from April to October 2000. The participants were mostly farmers, all of whom lived in rural areas of northern Greece. All participants were healthy and had been hospitalized for routine blood tests. Each patient completed a questionnaire about medical history. The selected patients had no known history of rickettsiosis and reported no febrile or influenza-like illness during the past 6 months. Each participant provided oral consent for the serum to be used for detecting antibodies against several infectious agents related to zoonoses. The following information was recorded for each participant: age, sex, occupation, and area of residence.

Serum samples were tested by indirect immunofluorescence (IFA) with commercially available antigen (Focus Technologies, Cypress, California), which uses HGE-1–infected HL60 cells. Titers >64 were considered positive. All sera were also tested for *Rickettsia conorii*, *R. typhi*, *Coxiella burneti*, and *Ehrlichia chaffeensis* by IFA and for *Borrelia burgdorferi* by enzyme-linked immunosorbent assay and Western blot. Sera that reacted positively to more than one of these agents were excluded. Biostatistical analysis was performed by using the statistical package SPSS for Windows 10.0.1 (Standard version, SPSS Inc., Chicago, IL).

The overall prevalence of antibodies to the HGE agent was 7.3% (8.0% for men and 7.0% for women). No statistically significant differences were observed in the prevalence of antibodies in the six prefecture hospitals. Participants had no statistically significant differences in sex or age. Antibody titers to HGE were low (of 22 positive sera, 12 had titers ≥64 and 10 had titers ≥128).

Several serosurveys of the prevalence of antibodies to the HGE agent have been conducted across Europe in both healthy persons and patients with suspected or confirmed Lyme borreliosis (2,3,8). Since cases of *B. burgdorferi* infection are rare or nonexistent in Greece and the seroprevalence of Lyme borreliosis is very low, we selected as participants 300 healthy farmers who lived in rural areas. These persons compose a group at high risk for exposure to tick bites and therefore to *I. ricinus*. Our prevalence is higher than those observed in Bulgaria (2.9%) and Germany (1.9%) (2,3). This finding could be attributed to the fact that the prevalence in these countries was based on blood donors, unlike our survey. However, our prevalence is substantially lower than that in Slovenia, where 15.4% of the examined population had detectable antibodies to the HGE agent and several cases of HE have been confirmed (4). Our observation that no significant differences occurred in the prevalence of antibodies to the HGE agent in the six prefectures studied could be explained by the fact that these districts are small, with little variation in environmental and climatic conditions. Even though the antibody titers to the HGE agent were low in our survey, they suggest infection at an undetermined time (9). Seven of our sera were antibody positive to both the HGE agent and at least one other rickettsial agent or *B. burgdorferi*. This fact, which has been observed elsewhere (9), may result from coinfection or crossreaction. These sera were excluded. Our data suggest the possibility that HGE cases exist in Greece. Since such cases have been not been reported to date, they are likely underdiagnosed. Further research is needed to clarify the presence of the HGE agent in Greece.

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References
To the Editor: Hantaviruses are enveloped RNA viruses belonging to the family Bunyaviridae (1,2), for which a number of species have been identified, including the Hantaan, Seoul, Puumala, Dobrava-Belgrade, and Sin Nombre viruses (1,2). Each hantavirus is associated with a specific rodent reservoir (1,2). Hantaan virus, found throughout northeastern Asia, causes a life-threatening illness known as hemorrhagic fever with renal syndrome (HFRS). Main symptoms and signs of HFRS are fever, myalgia, severe vascular leakage with ascites and retroperitoneal edema and pain (abdominal, loin, or headache), shock, acute renal failure, proteinuria and hematuria, thrombocytopenia, and bleeding complications (3). Seoul virus, found worldwide, and Puumala virus, found in Scandinavia and Eastern Europe, cause mild forms of HFRS. Sin Nombre virus, found in the United States, causes hantavirus pulmonary syndrome, which is characterized by increased pulmonary capillary permeability and pulmonary edema and can progress to severe respiratory distress syndrome and shock as a result of low cardiac output (4,5).

Despite the fact that HFRS is frequently reported in People’s Republic of China, no indigenous cases of HFRS have been reported in Taiwan. Previous serologic studies found that the Seoul strain is endemic in the areas of Taiwan and two isolated islands nearby, Kinmen and Matzu; in contrast, in the People’s Republic of China, the Hantaan and Seoul strains concurrently predominate (6,7).

Our patient, a 38-year-old man, had onset of sore throat, headache, cough, myalgia, and intermittent fever (up to 38.3°C) on February 2, 2001. A resident of Matzu for more than 30 years, he had traveled to the People’s Republic of China 3 months before the symptoms began. Laboratory tests at a local hospital showed thrombocytopenia (58,000/mL) and leukopenia (3,800/mL). Because his symptoms persisted, he was transferred to the National Taiwan University Hospital on February 7, 2001. Initial tests there showed a temperature of 36.4°C, heart rate 74 beats/min, and respiratory rate 18/min; there was no skin rash. The rest of the physical examination was normal. He had a platelet count 73,000/µL; leukocytes 5,670/µL with 59.1% segments, 19.8% lymphocytes, and 18.2% monocytes; urea nitrogen 7.4 mg/dL; and creatinine 0.94 mg/dL. His chest radiography was normal. Abdominal ultrasound showed a fatty liver.

After admission, the patient’s laboratory values gradually improved and his proteinuria subsided. He had no fever. On February 10, 2001, he had marked sinus bradycardia (as low as 33 beats/min) and became fatigued. His blood pressure was 120–130/70–80 mmHg. No abnormal serum electrolytes, urea nitrogen, creatinine, creatine kinase, and troponin-I were noted. Echocardiogram showed normal atrium and ventricle size, good left ventricle contractility, and small amount of pericardial effusion. His heart rate gradually increased. He was discharged on February 15, 2001, without event.

A substantial increase of serum immunofluorescent immunoglobulin (Ig) G titers (1:640 on February 6; 1:5120 on February 19, 2001) and positive IgM titers of 1:80 against hantavirus antigen (Seoul type) confirmed that this virus was responsible for the illness.

A few reports of hantavirus infection with cardiac involvement have been published. A case report by Chun and Godfrey showed right atrium dilation with diffuse atrial hemorrhage, interstitial edema, and vascular congestion without surrounding myocardial fibers and conduction system involvement in a 19-year-old soldier who died from epidemic (Korean) hemorrhagic fever, sinus tachycardia, paroxysmal supraventricular tachycardia, and congestive heart failure (8). Marked sinus bradycardia (as low as 34 beats/min) in a patient with a severe form of hemorrhagic fever with renal syndrome (acute renal failure) has been reported (9). However, this finding was not observed in patients with mild cases of the disease.

The possibility that our patient acquired the infection during his travel to the People’s Republic of China 3 months earlier is extremely low because of the length of the incubation period (typical incubation period 4–28 days) (10) and the different hantavirus strains prevalent in the People’s Republic of China (6). Although viral genetic sequence data from the patient and rodents in Matzu were not available in this study, our patient was infected with the Seoul strain, which is highly seroprevalent in rodents in Matzu (6,7).

In summary, this case was probably the first indigenous case of hantavirus infection in Taiwan. Its characteristics suggest that marked sinus bradycardia should be included as a protean manifestation of hantavirus.

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References