Is Q fever an emerging infection in Turkey?

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هل حمى Q تمثِّل عدوى مستجدَّة في تركيا؟

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الخلاصة: تم الإبلاغ فيما بين يومي الرابع من أيار/مايو والثامن من آب/أغسطس 2002، عن 46 حالة حمى حادة بالقرب من منطقة البحر الأسود في شمال تركيا. وتم علاج الحمى بسرعة وبنجاح باستخدام التتراسيكلين، مما جعل التشخيص السريري للإصابة بالريكيتسيات أو الإيرليخيات يؤخذ في الحُسْبان. وقد أمكن للتحليل المصلي لعينات الدم التي أخذت من 19 مريضاً، أن يحدِّد الجرثومة المسبِّبة للمرض على أنها الكوكسيلة البورنيتية *Coxiella burnetii*. وقد أبلغ عن سبع حالات بوصفها حالات حادة من حمى Q، وثماني حالات على أنها إيجابية المصل لعدوى سابقة. وقد كان أكثر الأعراض السريرية شيوعاً في الحالات الحادة: القيء (100.0٪)، والغَثَيَان (85.7٪)، والإسهال (57.1٪)، والحمى (42.9٪)، وآلام البطن (42.9٪)، والصداع (42.9٪). وكانت إنزيمات الكبد مرتفعة لدى جميع المرضى. ويرى الباحثون أن الاستقصاءات الوبائية لحمى Q، سوف تكون ضرورية في المستقبل، في المنطقة التي حدثت بها الإصابة.

ABSTRACT Between 4 May and 8 August 2002, 46 cases of acute fever were reported near the Black Sea region in northern Turkey. The infection was treated rapidly and successfully with tetracyclines, so clinical diagnosis of rickettsial or ehrlichial infection was considered. Analysis of serum and blood samples taken from 19 patients identified the causative organism as ***Coxiella burnetii***; 7 cases were reported as acute Q fever and 8 as seropositive for past infection. The most common clinical symptoms among the acute cases were vomiting (100.0%), nausea (85.7%), diarrhoea (57.1%), fever (42.9%), abdominal pain (42.9%) and headache (42.9%). Liver enzymes were elevated in all patients. It is considered that epidemiological investigation for Q fever will be essential in the affected region in future.

La fièvre Q est-elle une infection émergente en Turquie?

RÉSUMÉ Entre le 4 mai et le 8 août 2002, 46 cas de fièvre aiguë ont été signalés près de la Région de la mer Noire au nord de la Turquie. L'infection a été traitée rapidement et avec succès par des tétracyclines ; aussi un diagnostic clinique de rickettsiose ou d'ehrlichiose a-t-il été retenu. L'analyse des échantillons sériques et sanguins prélevés sur 19 patients a permis d'identifier l'agent causal comme étant ***Coxiella burnetii.*** Sept cas ont été rapportés comme étant une fièvre Q aiguë et huit comme ayant une sérologie positive séquellaire d'une infection ancienne. Les symptômes cliniques les plus courants chez les cas aigus étaient les vomissements (100,0 %), les nausées (85,7 %), la diarrhée (57,1 %), la fièvre (42,9 %), les douleurs abdominales (42,9 %) et les céphalées (42,9 %). Les taux d'enzymes hépatiques étaient élevés chez tous les patients. On estime que l'investigation épidémiologique pour la fièvre Q sera essentielle dans la région touchée à l'avenir.

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Introduction

Q fever (Query fever) is a zoonosis caused by *Coxiella burnetii*, which occurs worldwide, except in New Zealand. Sheep, goats and cattle are considered the main reservoirs for the organism, which is shed in milk, urine, faeces and birth products of infected animals. In humans, the infection is caused mainly via inhalation of contaminated aerosols from amniotic fluid, placenta or wool [*1*], but oral (contaminated milk) [*2,3*], percutaneous [*4*], vertical, and even person-to-person, e.g. during delivery of an infant or via blood transfusion [*5,6*] or ticks [*4*], can be considered other modes of transmission.

The clinical manifestations of Q fever in humans are highly variable. The most common symptoms are fever, pneumonia, hepatitis, and meningoencephalitis in the acute form, whereas endocarditis is the main symptom in chronic cases. Nevertheless, asymptomatic infection occurs in about 50% of cases [*3,7,8*].

Serology is the main tool in the diagnosis of Q fever since clinical diagnosis, in most instances, lacks specificity. The most reliable methods are indirect immunofluorescence, complement fixation, enzyme-linked immunosorbent assay and microagglutination, all of which are very commonly used. Currently, immunofluorescence assay is the reference method for the serodiagnosis of Q fever [*1,9*].

The aim of this study is to investigate the sociodemographic, clinical and laboratory features of cases in an outbreak of Q fever to call attention to a newly emergent infection in our country.

Methods

In June 2002, a number of acute cases of fever were reported from Tokat, near the Black Sea region in northern Turkey. Doctors from the General Directorate of Primary Health Care and the Department of Communicable Diseases Research at the Refik Saydam National Hygiene Institute drew up a questionnaire after investigation in the field and analysis of the clinical symptoms of the cases. The questionnaire requested information about the participating health centre; sociodemographic, clinical and laboratory features of the infection, including treatment of people suspected of having the infection; and additional epidemiological information. According to the analysis of preliminary hospital based data, the probable case definition was established as: people who were living in or near Tokat and neighbouring provinces with symptoms of fever, myalgia/arthralgia, nausea, vomiting, abdominal pain, diarrhoea, thrombocytopenia, leukopenia and elevated liver enzyme levels since 4 May 2002.

The questionnaire was circulated to only those patients whose symptoms met the case definition and blood samples were collected from them. The epidemiological investigation was carried out from 4 May 2002 until 8 August 2002. The operation was conducted by the health facilities located in the affected region in order to collect the information about the probable cases via questionnaires.

The sera and blood samples from a total of 26 convalescent patients and people with acute disease were sent to the Communicable Diseases Research Department of Refik Saydam National Hygiene Institute. Serum samples from 19 patients were sent to the WHO Collaborative Centre for Rickettsial Reference and Research, Marseille, France in July 2002. The samples were investigated for rickettsial infection (*Rickettsia conorii, R. slovaca, R. helvetica, R. israeli, R. massiliae, R. mongolotimonae, R. aeschlimanii, R. felis* and *R. typhi*), human

granulocytic ehrlichiosis, leptospirosis and *C. burnetii* using indirect immunofluorescence assay methods. Although an anti-phase II IgG antibody titre of ≥ 1:200 and an anti-phase II IgM titre of ≥ 1:50 are considered significant in serologic diagnosis of acute Q fever [*4,9–11*], an anti-phase II IgG titre of ≥ 1:100, and an anti-phase II IgM titre ≥ 1:25 were accepted in our group as cut off values in accordance with the clinical and epidemiological data.

Five patients died during the outbreak. It was not possible to get samples or to do any post-mortem evaluation in these cases.

This was a descriptive epidemiologic study. Statistical analysis was done using Fisher's exact test and, owing to the low number of cases, Kruskal–Wallis analysis of variance was implemented to compare the means.

Results

Between 4 May and 8 August 2002, 46 people, 38 of them from Tokat, became ill with symptoms that were consistent with those of the case definition. The clinical symptoms were recorded as: abdominal pain (77.8%), nausea (66.7%), vomiting (66.7%), arthralgia/myalgia (66.7%), headache (55.6%), fever (55.6%), diarrhoea (33.3%) and rash (33.3%). The aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase levels were elevated in 77.8%, 66.7% and 55.6% respectively. Leukopenia and thrombocytopenia were noted in 66.7% of patients.

The interval between the onset and the end of the outbreak was 94 days for confirmed cases. The mean duration of the illness in those who recovered was 11 days for probable cases. Eleven people suspected of having the infection reported tick contact. Only 2 of the patients had family members with similar symptoms.

A total of 19 serum samples were sent to the WHO Collaborative Centre for Rickettsial Reference and Research, Marseille, France for further evaluation (the limited facilities available in Turkey precluded testing locally). Sera and blood samples were tested for rickettsial infection, ehrlichiosis and leptospirosis using indirect immunofluorescence assay methods and all were evaluated as negative. Acute Q fever was confirmed for 7 samples and 8 others were found to be seropositive. The other 4 were negative for Q fever.

The first acute case of Q fever was detected on 25 May 2002 and the last was on 17 June 2002, an interval of 23 days. The infection started at the end of the spring season and continued till the beginning of summer. Recovery from the illness was reported as minimum 5 days and maximum 10 days.

The median age was 48 years in individuals with acute infection and 60 years in those with evidence of past infection. The median age was 54 years in people who were identified as seronegative for *C. burnetii*. These differences were, however, not statistically significant. In addition, there was no statistical significance between males and females for seropositivity. The number of people seropositive for acute infection was higher in rural areas than in urban areas, but again, the difference was not statistically significant (Table 1). Three of the 7 people who had acute infection reported having had close contact with ticks.

The most common clinical symptoms among the acute cases were vomiting, nausea and diarrhoea (Table 2). The fever was subfebrile.

Table 1 **Characteristics of 19 people with suspected Q fever (*Coxiella burnetii*) infection**

Characteristic	Seropositive for *C. burnetii*				Seronegative for *C. burnetii* (*n* = 4)	
	Acute (*n* = 7)		Past infection (*n* = 8)			
	No.	%	No.	%	No.	%
Age (years)						
10–29	2	28.5	0	–	0	–
30–49	2	28.5	1	12.5	2	50.0
50–69	2	28.5	4	50.0	1	25.0
≥ 70	1	14.3	3	37.5	1	25.0
Median	48		60		54	
Mean (SD)	46.5 (19.1)		62.6 (12.2)		52.0 (16.4)	
	Kruskal–Wallis statistic: 0.351; ***P*** > 0.05					
Sex						
Male	4	57.1	6	75.0	1	25.0
Female	3	42.9	2	25.0	3	75.0
	Likelihood ratio: 2.807; ***P*** > 0.05					
Residence						
Rural	6	85.7	7	87.5	4	100
Urban	1	14.3	1	12.5	0	–
	Likelihood ratio: 2.807; ***P*** > 0.05					
Contact with tick						
Yes	3	42.9	2	25.0	1	
No	4	57.1	6	75.0	3	
	Likelihood ratio: 0.642; ***P*** > 0.05					

SD = standard deviation.

Discussion

Communicable diseases continue to be an important cause of morbidity and mortality in Turkey, acute upper respiratory tract infections being the most common infections. The control programmes for acute respiratory tract infections, acute diarrhoea and neonatal tetanus; the elimination programme for measles; and the eradication programme for poliomyelitis have been operating since the 1980s.

There has also been significant progress towards achieving the goals of measures which were implemented for the control and prevention of re-emerging diseases such as malaria and tuberculosis. Future programmes and activities are planned to target the control of bacterial, parasitic and viral diseases [*12*].

In May–June 2002, near the Black Sea region of Turkey, an infection characterized by abdominal pain, nausea, vomiting, myalgia/arthralgia, headache, fever and rash in addition to laboratory findings of leukopenia, thrombocytopenia and elevated liver enzymes was noted. As the infection was treated rapidly and successfully with tetracyclines, rickettsial or ehrlichial infec-

Table 2 **Some clinical and laboratory features of the cases**

Clinical symptoms	Seropositive				Seronegative (*n* = 4)	
	Acute cases (*n* = 7)		Past infection (*n* = 8)			
	No.	%	No.	%	No.	%
Physical						
Vomiting	7	100.0	0	–	0	–
Nausea	6	85.7	3	37.5	0	–
Diarrhoea	4	57.1	1	12.5	0	–
Fever	3	42.9	6	75.0	1	25.0
Abdominal pain	3	42.9	2	25.0	1	25.0
Headache	3	42.9	3	37.5	1	25.0
Myalgia/arthralgia	2	28.5	2	25.0	4	100
Rash	1	14.3	3	37.5	1	25.0
Biochemistry						
Elevated AST/ALT	7	100.0	5	62.5	1	25.0
Elevated LDH	4	57.1	4	50.0	1	25.0
Haematology						
Thrombocytopenia	6	85.7	4	50.0	4	100
Leukopenia	6	85.7	6	75.5	4	100

AST = aspartate aminotrasferase.
ALT = alanine aminotrasferase.
LDH = lactate dehydrogenase.

tions were considered possible causes, resulting in a great interest in the region. The outbreak was confirmed as Q fever by the laboratories of WHO Collaborative Centre for Rickettsial Reference and Research. Although it was not possible to take liver biopsies, all cases were reported as Q fever according to their clinical and laboratory features [*3,7,13,14*]. Verification of the cause of the infection did, however, take some time as Q fever was not expected in the country.

The first outbreak of Q fever in Turkey was reported from Aksaray province in 1948. That outbreak had also begun in May and ended in August. Twenty-one cases were detected by complement fixation test. The disease showed up among animals, being transported by the stool of infected ticks via inhalation by the lambs [*15*]. Since then, there has been no outbreak of Q fever identified by epidemiological investigation until our study. Of the 46 probable cases, 38 (82.6%) were living in Tokat, where there are a lot of livestock farms especially for cattle, sheep and goats.

Acute Q fever has been reported as occurring as either an outbreak or as sporadic cases in spring or early summer in Europe, which was the case in this outbreak in our country. Incidence is most frequent during spring, and is epidemiologically related to the environmental contamination caused during the outside lambing and shearing seasons [*13,16–19*]. Although the first probable case in this outbreak was detected on 4 May, the first confirmed cases were notified on 25 May. Six of those identified

as having the infection (85.7%) were living in rural areas. The onset of the outbreak corresponds to the time that animals such as sheep and goats living in that region have their young. Three of the patients with acute Q fever had close contact with ticks. Although Q fever has also been defined as an arthropod-borne infection, the transmission of *C. burnetii* from ticks to humans has rarely been reported [*4*].

The Q fever seropositivity of goats, sheep and cows has been reported ranging from 3% to 30% in different regions of Turkey, and the occurrence of the infection in both humans and animals at the same time suggests that it is endemic [*20–23*]. The incidence period of the outbreaks and the probable routes of transmission suggest that the diseases may occur again in the same season. We found 8 people with evidence of past infection. They had probably been exposed to Q fever infection before. It was not established when.

Epidemiologic data, therefore, suggest that Q fever is an endemic infection in the region, and surveillance should be strengthened for tick-borne and zoonotic infections. Since diagnosing this group of cases and the (probable) outbreak, we have started to establish plans for the diagnosis of Q fever. Indirect immunofluorescence has been accepted as the most reliable method, and we are still continuing laboratory surveillance activities in our institute.

Q fever infection is often asymptomatic in farm animals, but can cause considerable morbidity in humans. Because Q fever is an occupational hazard [*14,18,24*], specific epidemiological studies in endemic areas to establish for example, seroprevalence in farm animals and farmers, may help to define the target population, extent of transmission and potential need for a vaccine. Control and eradication measures require a multidisciplinary approach and cooperation between farmers, veterinarians and public environmental health workers.

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Addendum

Subsequent to the identification of the cases reported in this paper, new cases where reported in the same area the following year accompanied by some different clinical symptoms. The new cases were identified as Crimean–Congo haemorrhagic fever in late 2003. After this was recognized, it was suspected that the cases from the previous year, reported in this paper, might also be related to Crimean–Congo haemorrhagic fever. Samples were therefore sent for reanalysis and it was then found that some of the cases were indeed Crimean–Congo haemorrhagic fever. Details of these cases are published in: [Epidemiological evaluation of a possible outbreak in and nearby Tokat province] Gozalan A, Akin L, Rolain JM, Tapar FS, Oncul O, Yoshikura H, Zeller H, Raoult D, Esen B. *Mikrobiyoloji bülteni*, 2004, 38(1–2):33–44 [Article in Turkish].

It should be noted that a multidisciplinary approach to the control of tick-borne diseases is being carried out by the involved sectors in the country and general practitioners and clinicians have been alerted to the emergence of these pathogens.

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