RESEARCH ARTICLE / ARAŞTIRMA

DOI: 10.4274/mjima.galenos.2021.2021.5
Mediterr J Infect Microb Antimicrob 2022;11:5
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2021.2021.5

An Overlooked Zoonotic Disease: Retrospective Evaluation of Q Fever Seropositivity with Clinical Findings

Gözden Kaçabilen Bir Zoonotik Hastalık: Q Ateşi Seropozitifliğinin Klinik Bulgularla Retrospektif Olarak Değerlendirilmesi

Fatma SIRMATEL[1], Selçuk KILIÇ[2], Oya KALAYCIOĞLU[3], Pınar BÜCÜK[4], Talat Oğulcan ÖZARSLAN[1], Tuğçe DAMARSOY[1], Hasan Tahsin GÖZDAŞ[1]

[1]Bolu Abant İzzet Baysal University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Bolu, Turkey
[2]T.C. Ministry of Health, General Directorate of Public Health, Department of Microbiology Reference Laboratories and Biological Products, Ankara, Turkey
[3]Bolu Abant İzzet Baysal University Faculty of Medicine, Department of Medical Statistics, Bolu, Turkey
[4]Edirne Sultan Murat 1st State Hospital, Clinic of Internal Medicine, Edirne, Turkey

Abstract

Introduction: Q fever is a zoonotic disease with a high seroprevalence in our region and a low awareness in our country. Patients who were diagnosed as having Q fever clinically, serologically, and radiologically during 2017-2020 were evaluated retrospectively and classified according to the organ involvement.
Materials and Methods: The diagnosis was made according to the radiological, clinical and serological findings of the patient. The patients were distinguished as acute, acute/possible, and chronic/persistent according to phase I and phase II antibody titration. Serological studies were carried out via immune fluorescent method. Patients included in the study were evaluated in terms of age, gender, admission date, organ involvement, responses to treatment, and acute phase indicators.
Results: A total of 107 patients were evaluated retrospectively. Sixty three patients (58.9%) were defined as having acute disease, 29 (27.1%) acute/possible disease and 15 (14%) chronic/persistent disease. Patients with acute disease were admitted to the hospital in winter, patients with acute/possible disease were admittedin summer/spring and patients with chronic/persistent disease in summer. Lung involvement was found in 45.8% of patients with positive Q fever serology, kidney involvement in 30.8%, neurological involvement in 29.9%, liver involvement in 22.4%, joint involvement in 18.7%, heart involvement in 5.6%, lymphadenomegaly in 4.7%, and bone involvement in 1.9%. Hepatic involvement was higher in patients with chronic/persistent disease (22.4%), while fever (39.7%) and muscle-joint pain (23.8%) were seen more frequently in patients with acute disease. There were no statistically significant differences in demographical data and levels of acute phase reactants.
Conclusion: Since a non-routine test is used in the diagnosis of the disease, occupational exposure should be evaluated in complaints of unknown origin. The patients having unexplained organ involvement and elevated acute phase reactants should be examined serologically for Q fever, especially in endemic areas.
Keywords: Q fever, *Coxiella burnetii* infection, Q fever serology, acute Q fever, chronic Q fever

Öz

Giriş: Q ateşi bölgemizde seroprevalansı yüksek, fakat ülkemizde farkındalığı düşük olan bir zoonotik hastalıktır. Bölgemizde 2017-2020 yılları içinde klinik, serolojik ve radyolojik olarak tanımlanan Q ateşi olguları retrospektif olarak değerlendirildi ve organ tutulumuna göre sınıflandırıldı.
Gereç ve Yöntem: Tanı hastanın klinik, radyolojik ve serolojik bulgularına göre kondu. Olgular faz I ve faz II antikor titrasyonuna göre akut, akut/olası ve kronik/persistan olarak ayırt edildi. Serolojik çalışmalar immünfloresan yöntemi ile yapıldı. Çalışmaya alınan hastalar yaş, cinsiyet, başvuru tarihi, organ tutulumları, tedaviye cevapları ve akut faz göstergeleri açısından değerlendirildi.

Cite this article as: Sırmatel F, Kılıç S, Kalaycıoğlu O, Bücük P, Özarslan TO, Damarsoy T, Gözdaş HT. An Overlooked Zoonotic Disease: Retrospective Evaluation of Q Fever Seropositivity with Clinical Findings. Mediterr J Infect Microb Antimicrob. 2022;11:5.

Address for Correspondence/Yazışma Adresi: Fatma Sırmatel MD, Bolu Abant İzzet Baysal University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Bolu, Turkey
Phone: +90 532 657 11 33 **E-mail:** sirmatel@yahoo.com **ORCID ID:** orcid.org/0000-0003-0442-5981
Received/Geliş Tarihi: 03.05.2021 **Accepted/Kabul Tarihi:** 08.11.2021

Presented in: This study was presented as an oral presentation (SS-043) at the "8th Turkey EKMUD Congress" Mediterr J Infect Microb Antimicrob. 2020;8:(Supplement 1):1-268.

Published: 17 January 2022

Öz

Bulgular: Toplam 107 olgu retrospektif olarak değerlendirildi. Olgular 63 (%58,9) akut, 29 (%27,1) akut/olası ve 15 (%14) kronik/persiste olarak tanımlandı. Başvuru zamanı olarak akut olgular kış, akut olası olgular yaz/ilkbahar ve kronik persiste olgular yaz aylarında hastaneye başvuruda bulunmuşlardı. Q ateşi serolojisi pozitif olgularda sırası ile %45,8 akciğer, %30,8 böbrek, %29,9 sinir sistemi, %22,4 karaciğer, %18,7 eklem, %5,6 kalp, %4,7 lenf bezi ve %1,9 kemik tutulumu saptandı. Kronik persiste olgularda karaciğer tutulumunun fazla olduğu (%22,4) ve akut olgularda ateş şikayetinin (%39,7) ve kas-eklem ağrılarının (%23,8) daha sık görüldüğü saptandı. Olguların demografik incelemesinde ve akut faz göstergelerinin yüksekliği açısından istatistiksel bir farklılık saptanmadı.
Sonuç: Hastalığın tanısı rutinde kullanılmayan bir test ile konduğu için nedeni açıklanamayan şikayetlerde mesleki maruziyet değerlendirilmelidir. Nedeni açıklanamayan organ tutulumunda, akut faz gösterge yüksekliğinde ve özellikle endemik alanlarda, hastalar Q ateşi açısından serolojik olarak incelenmelidir.
Anahtar Kelimeler: Q ateşi, *Coxiella burnetii* enfeksiyonu, Q ateşi serolojisi, akut Q ateşi, kronik Q ateşi

Introduction

Q fever is a disease caused by *Coxiella burnetii*, which was previously thought to be from the *Rickettsia* family and was later identified as a separate group[1,2]. It was a disease called Q fever in the sense of question/unknown fever, which was first defined as a tick-borne *Rickettsia* disease by Derrick and Burnet from Australia in 1934[3,4]. In the following years, it was shown to cause atypical pneumonia first in the USA and then in Germany, Greece and the Balkan countries during the Second World War[3,5-7]. Q fever is an overlooked and neglected zoonosis that occurs after oral ingestion of unpasteurized milk/milk products of animals with causative pathogenic bacteria, and being exposed to congenital secretions or infected wastes of animals by contact or airborne inhalation. The rate of seropositivity in sheep, goats and cattle is different in the world. It was detected at a rate of 20% in the milk of our country's animals[1,8]. The first patients described by Payzın in 1947 in our country were neglected and then reported after 1970[9,10]. The bacterium is in the form of Gram-negative coccobacillus, and it is found phylogenetically closer to *Legionella* and *Barthonella* by using 16S rRNA analysis[11]. *C. burnetii* is a microorganism that forms spore-like forms, unlike *Rickettsias*, with a structure in two phases: a small non-infective form (small dense-phase II) and a large infective form (large dense-phase I). In the definition of the disease, titrations of antibodies formed according to the phase status and clinical complaints should be evaluated together[12]. The isolation of the bacteria is difficult and it requires special media. While it is not very significant in acute patients, its isolation from the tissue is significant in chronic patients. Diagnosis of the disease is made by immunofluorescence, complement fixation test and ELISA test for specific antibodies, and detection of antigens by polymerase chain reaction (PCR) in tissue and blood. After ingestion of the bacterium, the antibody formed can remain positive at low titration in the blood for life. Clinically, patients are defined as probable or definite, temporally as acute or chronic/persistent[13]. Phase I antibodies are positive in chronic infection, and phase II antibodies are positive in acute infection[7,14]. A diagnosis of acute infection is made when the phase II IgG titration is >1/128 and the IgM titration is >1/50 and/or the IgG titration is quadrupled within 2-4 weeks and/ or IgG and IgM are positive together. It is observed that phase II IgG antibodies are positive within 2-3 weeks after exposure to the agent and in the following months[13,15]. Chronic/persistent disease is defined as the presence of complaints lasting more than six months and the development of phase I antibodies serologically in patients who ingest the bacterium. Especially in persistent patients, phase I IgG or phase II IgG antibodies may remain positive at low titer for a long time.

Q fever is seen at a higher rate in those who are engaged in animal husbandry such as butchers, farmers and veterinarians. It spread all over Europe with an epidemic in the Netherlands in 2007 and its effects lasted for years. It has been reported to lead to serious clinical pictures, especially in immunosuppressive patients and patients with cardiac problems[5,16]. Although Q fever was a neglected disease, it caused epidemics affecting many countries in Europe in 2007-2014 and caused serious economic losses[6,17]. In a study published from Spain, it was stated that 4214 patients were seen mostly in March-August, and it was noted that the most common involvement was lung involvement[18]. In this study, mortality was found to be 2.8% in hospitalized patients with Q fever, and it was reported that it costed 36000 Euros for each patient[18].

Although it is known clinically that Q fever usually starts with the common cold and continues with pneumonia, hepatitis and neurological findings, a fatal outcome has been reported very rarely[1,19,20]. Q fever, a neglected zoonotic disease, can affect many organ systems with its different clinical forms[11,16,21]. The aim of this study is to retrospectively examine the patients with positive serology in our clinic in the light of the literature in terms of demographic and seasonal features, and organ involvement, between 2017-2020.

Materials and Methods

This study was conducted by retrospectively scanning the files of the patients who were admitted to Bolu Abant İzzet Baysal University, Faculty of Medicine between 2017-2020 and were diagnosed as having Q fever clinically, radiologically and serologically. The study was approved by Bolu Abant İzzet Baysal University Clinical Research Ethics Committee's decision dated 18.02.2020, numbered 86-2020/18. Q fever serology of all patients was studied with the indirect immunofluorescence method in the Ministry of Health Public Health Microbiology Laboratory. Patients were classified as acute, acute/possible, and chronic/persistent. Acute patients were evaluated as serologically confirmed, acute/possible patients as having clinical complaints suggesting Q fever but positive antibody titration at low titer, and chronic/persistent patients as those whose complaints lasted more than six months and whose serology was positive. Those with positive phase I antibodies in chronic infection and those with positive phase II antibodies in acute infection were included in the study. Evaluation in terms of titration was as follows;

a. Acute patients: IgG >1/128 and IgM>1/50 titration of phase II antibodies and/or IgG+ IgM positivity and/or phase II IgG titration quadrupling within 2-4 weeks.

b. Acute/possible patients: Those whose clinical complaints are compatible with the symptoms of Q fever, whose sedimentation/C-reactive protein (CRP) elevation cannot be attributed to any other cause, and who improve with antibiotic treatment and whose phase II IgG titration is ≥1/256.

c. Chronic/persistent patients: Phase I IgG>1/800 and/or phase I IgG (<1/800) + phase II IgG (<1/256) positivity and complaints due to organ involvement for more than six months.

The patients were classified according to organ involvement based on pathological findings in specific blood biochemistry tests in line with their complaints, high level of acute phase reactants (sedimentation and CRP) that could not be attributed to another cause, and radiological imaging methods. At least two of the following criteria and seropositivity were considered organ involvement;

- Lung involvement: Cough, fever and pathological findings (lobar or lobular consolidation, hilar fullness, nodular involvement) in radiological imaging (X-ray and computed tomography),

- Liver involvement: Jaundice, weakness, elevation in blood liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), total/direct bilirubin level, alkaline phosphatase and gamma glutamyl transpeptidase)] and ultrasonography findings,

- Nausea, vomiting, high blood urea and creatinine levels, and proteinuria in the urine in renal involvement,

- Neurological involvement: Headache, fever and unidentified central nervous system complaints, radiological imaging findings (cranial tomography and magnetic resonance imaging if there are findings suggesting encephalitis, meningoencephalitis and meningitis) and elevated protein in the cerebrospinal fluid (CSF),

- Palpitations, echocardiography and electrocardiography changes or underlying cardiac valvulopathy in cardiac involvement,

- Pain, swelling, redness in the joints and increase in the number of cells in the joint fluid and X-ray graphy findings in locomotor and bone involvement.

Since the study was retrospective, the patients who had clinical complaints, organ involvement, other comorbidities during the serological positivity process and did not improve with antibiotic treatment were excluded from the study. Patients with positive organ findings and serology, but whose complaints and laboratory findings did not improve as a result of treatment were not included in the evaluation. The focus of infection was investigated in patients with elevated sedimentation and CRP who were referred to our clinic. Routine Q fever serology was studied in the patients in whom the focus could not be found. Q fever serology was studied again after 2-4 weeks in patients with low titer antibody positivity and those with increased titration were included in the evaluation. Patients with occupational exposure who had low titer antibody positivity and considered clinically positive were evaluated as having probable acute disease.

In all patients, elevated sedimentation and CRP levels due to another cause, malignancy, connective tissue diseases, bacterial, viral, fungal and parasitic diseases were examined by using clinical, serological and radiological differential diagnosis methods, and patients with other causes were excluded from the study. No patient was examined for antibodies to *Barthonella* and *Legionella*, but the patients were evaluated for exposure and occupational status. Doxycycline was preferred as the treatment for Q fever, since all patients were followed up by us. Response to treatment, decrease in sedimentation and CRP levels, resolution of complaints and improvement in pathological findings were considered as parameters supporting our diagnostic criteria. The results were evaluated in terms of age, gender, seasonal presentation, organ involvement and clinical complaints. Because our study was retrospective, the patients could not be confirmed by using culture and PCR. Evaluation of all patients only serologically, clinically, radiologically and in terms of response to treatment was among the limitations of our study.

Statistical Analysis

Numerical variables were summarized as mean±standard deviation, and categorical variables were summarized as frequency (percentage). Variables with normal distribution were compared with a one-way ANOVA test. Pearson's chi-square analysis and Fisher's Exact test were used in the analysis of categorical variables. Statistical significance level was accepted as $p \leq 0.05$ in all tests. Statistical Package for Social Sciences for Windows 25.0 package program was used for statistical analysis of the data.

Results

In the last three years, 45 (42.1%) of the 107 patients that we diagnosed clinically and serologically were female and 62 (57.9%) were male, with a mean age of 57.9±17.4 years. Of these patients, 63 (58.9%) were defined as acute, 29 (27.1%) acute/probable, and 15 (14.0%) chronic/persistent. When these groups were compared according to their demographic characteristics, no difference was found in terms of age and gender.

When the seasons of admission to the hospital were examined, a statistically significant difference was found between the groups (p=0.049) (Table 1). Chronic/persistent patients were mostly admitted to the hospital in summer, acute patients mostly in winter, and acute/possible patients mostly in summer and spring.

The most common organ involvements in patients were lung, kidney, nervous system, liver, joint (arthritis or atralgia), heart, lymphoid tissues (>0.5-1 cm lymphadenomegaly) and bone (Table 1). Patients with Q fever serology positivity with headache and neurological involvement, and without focal infection focus who were referred by the neurology clinic were evaluated as having neurological involvement. Cranial tomography/magnetic resonance was performed in all of these patients and lumbar puncture was performed in patients with meningeal irritation findings.

The rate of unexplained ALT and AST elevations in liver involvement were significantly different between the diagnostic groups (p<0.050). Liver involvement was higher in chronic/persistent patients than in acute and acute/possible patients (Table 1). There was no statistically significant difference between the groups in terms of other organ involvement.

Elevated sedimentation was detected in 78 (80.4%) and elevated CRP level in 71 (72.4%) of all patients, but there was no statistically significant difference between clinical groups in terms of elevation in sedimentation and CRP. Average sedimentation and CRP levels are shown in Table 1.

The most common complaints in the patients were listed as cough, fever, weakness, muscle/joint pain, shortness of breath, headache, rash, nausea, vomiting and diarrhea (Table 2). There was a statistically significant difference between the rates of fever (p=0.041) and muscle/joint pain (p<0.050) complaints in the diagnostic groups (Table 2). Complaints of fever and muscle/joint pain were observed more frequently among acute patients than in other groups (Figure 1). In chronic/persistent patients, cough and fatigue complaints were more common. However, there was no statistical difference between the groups in terms of these complaints.

Discussion

During windy seasons, bacteria from animal wastes can spread over a wide area[1,5,16,17]. The variation in the disease risk is shown from spring to summer and from winter to spring in Germany[22]. The seroprevalence of Q fever is high (23.8%) in our region[23]. In our study, it was observed that hospital admissions due to Q fever were more common in winter-spring months. All of our patients had a relationship with farming and animal husbandry, and all of them were consuming traditional village products in our region.

Acute Q fever is a clinical picture that lasts more than 15 days and presents with complaints of fever, cold, chronic fatigue symptoms, hepatitis, weakness, myalgia, headache, retro-orbital pain and loss of appetite. The complaints and increased seropositivity of our acute and acute/possible patients were evaluated together. Of the patients 39.7% had fever and 23.8% had muscle/joint pain. In our study, elevated sedimentation (80.4%) and CRP (72.4%), which were common acute phase reactants, were found to be an important laboratory finding in patients with Q fever.

In our study, the most common organ involvement was lung with the rate of 45.8%, while renal involvement was the second most common organ involvement with the rate of 30.8%. No other comorbidity was found in the patients with renal involvement. Renal involvement in acute Q fever were reported as case reports[24]. The third most common involvement was neurological involvement with the rate of 29.9% which was similar to the literature. The fourth most involvement was liver involvement with the rate of 22.4% which was observed in the chronic persistent group and in the summer months. This shows that we should consider Q fever in patients with positive hepatitis markers. In our case series, arthritis was found in 18.7%, lymphadenomegaly in 4.7%, and bone involvement in 1.9%. In our study, culture and blood PCR could not be performed in patients with acute Q fever. Our use of only serology and clinical features in diagnosis is similar to many retrospective studies[25-27].

Bernit et al.[19] suggested in their review that recurrent occupational exposure and younger age were associated with

Table 1. Demographic analysis of the patients according to their clinical findings

	Clinical diagnosis				
Variables	**Total (n=107)**	**Chronic/Persistent (n=15)**	**Acute (n=63)**	**Acute/Possible (n=29)**	**p**
Age (year), mean±SD	57.9±17.4	55.9±18.2	57.5±17.5	59.7±17.3	0.777*
Gender, n (%)					0.839†
Female	45 (42.1)	7 (46.7)	27 (42.9)	11 (37.9)	
Male	62 (57.9)	8 (53.3)	36 (57.1)	18 (62.1)	
Season, n (%)					**0.049‡**
Spring	19 (17.8)	1 (6.7)	9 (14.3)	9 (31.0)	
Summer	34 (31.8)	8 (53.3)	15 (23.8)	11 (37.9)	
Autumn	18 (16.8)	3 (20.0)	12 (19.0)	3 (10.3)	
Winter	36 (33.6)	3 (20.0)	27 (42.9)	6 (20.7)	
Organ involvement, n (%)					
Lung	49 (45.8)	9 (60.0)	27 (42.9)	13 (44.8)	0.515†
Kidney	33 (30.8)	5 (33.3)	21 (33.3)	7 (24.1)	0.698†
Neurological	32 (29.9)	6 (40.0)	21 (33.3)	5 (17.2)	0.192†
Liver	24 (22.4)	7 (46.7)	11 (17.5)	6 (20.7)	**0.050†**
Arthritis	20 (18.7)	3 (20.0)	11 (17.5)	6 (20.7)	0.925†
Heart	6 (5.6)	2 (13.3)	4 (6.3)	0 (0.0)	0.128‡
Lymphadenomegaly	5 (4.7)	0 (0.0)	3 (4.8)	2 (6.9)	0.675‡
Bone	2 (1.9)	1 (6.7)	1 (1.6)	0 (0.0)	0.333‡
Sedimentation, median (min-max)	46.0 (2-131)	35.5 (12-105)	52.0 (2-131)	36.0 (6-116)	0.327§
CRP, median (min-max)	18.8 (0.01-341)	82.8 (0.1-306)	21.0 (0.01-341)	13.7 (0.05-242)	0.470§
Sedimentation (>15), n (%)	78 (80.4)	11 (78.6)	49 (86.0)	18 (96.2)	0.201†
CRP (>5), n (%)	71 (72.4)	9 (64.3)	46 (78.0)	16 (64.0)	0.323†

CRP: C-reactive protein, min-max: Minimum-maximum, mean±SD: mean±standard deviation, *one-way ANOVA, †Pearson's chi-square test, ‡Fisher's Exact test, §Kruskal-Wallis test. Bold p values indicate statistical significance at the p≤0.05 level.

Table 2. Distribution of complaints in patients

	Clinical diagnosis				
Complaint	**Total (n=107)**	**Chronic/Persistent (n=15)**	**Acute (n=63)**	**Acute/Possible (n=29)**	**p***
Cough	36 (33.6)	7 (46.7)	20 (31.7)	9 (31.0)	0.514
Fever	33 (30.8)	4 (26.7)	25 (39.7)	4 (13.8)	**0.041**
Weakness	32 (29.9)	6 (40.0)	18 (28.6)	8 (27.6)	0.651
Muscle/Joint pain	18 (16.8)	0 (0.0)	15 (23.8)	3 (10.3)	**0.050**
Shortness of breath	15 (14.0)	2 (13.3)	8 (12.7)	5 (17.2)	0.857
Headache	14 (13.1)	1 (6.7)	10 (15.9)	3 (10.3)	0.777
Rash	9 (8.4)	1 (6.7)	6 (9.5)	2 (6.9)	0.884
Nausea	7 (6.5)	0 (0.0)	3 (4.8)	4 (13.8)	0.218
Diarrhea	5 (4.7)	1 (6.7)	3 (4.8)	1 (3.4)	1.000
Vomiting	5 (4.7)	1 (6.7)	2 (3.2)	2 (6.9)	0.532

n (%) *Pearson's chi-square test or Fisher's exact test. Bold p-values indicate statistical significance at the p≤0.05 level.

neurological findings in particular. Meningitis, meningo-encephalitis and encephalitis are seen in patients with neurological involvement[19,25]. In a study of 1383 patients, 1% of the patients had meningo-encephalitis[28], while acute pneumonia was the most common in 121 patients reported from Greece. Confusion was found in 4.1% and meningitis was found in 0.8% and both were described in some patients in that study[25].

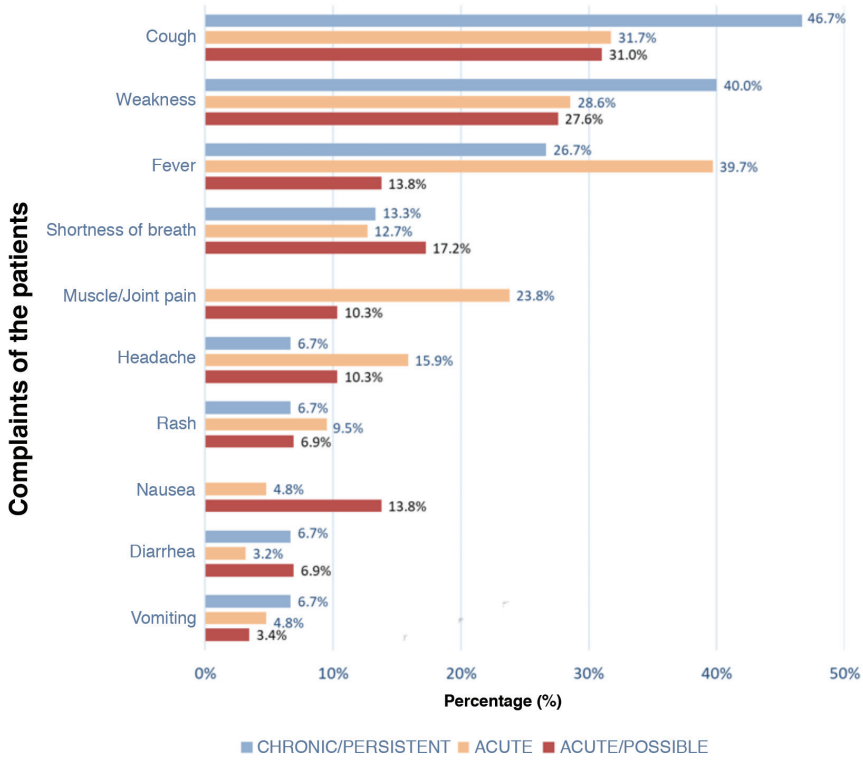

Figure 1. Distribution of complaints in chronic/persistent, acute and acute/possible patients

In our study, we found neurologic involvement with a rate of 29.9%. Two of our patients presented with fever and meningo-encephalitis and they died. The serological diagnosis of the fatal patients was delayed and PCR could not be performed. At the same time, postmortem examination of the patients could not be done. In our study, radiological, neurological and CSF findings were evaluated together in the diagnosis of two acute fatal meningo-encephalitis. There was no response to the empirical treatment of ceftriaxone + acyclovir at the dose of meningitis[29]. The diagnosis of all patients was made serologically. PCR and culture could not be performed due to limited opportunities. Mortality in Q fever is very low, and studies have shown mortality in acute patients, especially in patients with neurological involvement[30,31]. The mortality rate is less than 2%, and if it is diagnosed and treated in a short time, a rapid recovery is observed[19,31,32]. Mortality was observed in two (1.9%) of 107 patients in our series.

In the serological follow-up of patients with suspected Q fever, 46% of those with liver involvement showed chronicity[1,6]. In our patients, liver involvement was most common in chronic/persisted patients. The reason why we saw it more frequently in the chronic/persistent patient group was that these patients were investigated in different clinics for other diseases and that the cause of elevated liver enzymes could not be found. The Q fever serology positivity of the patients and the response to treatment indicate that this zoonotic disease should be investigated in patients of unexplained hepatitis. It was important for the awareness of Q fever that the patients who presented with elevated liver enzymes and were followed up with prolonged mild hepatitis recovered with treatment.

Cough (n=7, 46.7%) and fatigue (n=6, 40.0%) were more common in chronic/persistent patients. In the follow-up of our patients, clinical and serological findings were consistent with the chronic/persistent infection (Table 1)[1,11]. Endocarditis is seen in 60-70% of chronic patients and if untreated, mortality is between 25-60%[33-35]. Although it has been stated in some publications that endocarditis can be seen in 1-6% of the patients with chronic Q fever, this rate may vary in patients with cardiovalvular problems[33]. In a study on 125 patients with cardiovascular involvement, although the phase I antibody titer was low there were patients in whom the causative pathogen was demonstrated with PCR in valve biopsy[36]. In our series, cardiac involvement was seen with a rate of 5.6%. Two of our patients had chronic/persistent infection and the other 4 patients were found to have acute Q fever. All patients responded well to doxycycline treatment, and only our chronic/persistent patients received 18 months of treatment. Although chloroquine and doxycycline were recommended in the treatment of Q fever with cardiac involvement, chloroquine could not be used in our patients because it caused bone marrow suppression.

The most important limitation of our study was the retrospective collection of these patients over a three-year period. It was observed that the patients presented sporadically were more common in recent years and only serology was used in the diagnosis.

Conclusion

In conclusion, in this single-center study, we wanted to draw attention to this disease in our country by examining the patients that we found serologically positive considering Q fever. In a total of 107 patients that we encountered in the last three years, it was seen that chronic/persistent patients were admitted mostly in July-August, acute patients in January-February, and acute/possible patients in March-August. This can be interpreted as the fact that acute patients come into contact with animals most frequently during the winter months, and the overlooked symptoms of acute-possible patients are seen in the spring and summer months. Chronic/persistent patients were patients whose complaints were always attributed to another cause, and who were diagnosed when they were admitted to our clinic when no results could be obtained. In our region, where animal husbandry is common, we think that the bacteria are transmitted to humans by inhalation, as animals are kept indoors, especially in winter. Examining the Q fever serology which is not a routine, in unexplained organ involvement and clinical complaints was realized thanks to our past clinical experience. We believe that Q fever serology, which is not routinely performed, should be performed in suspected patients in terms of diagnosis and treatment. Despite the high seroprevalence of Q fever in animals in our country, studies in humans are insufficient and urgent measures are required. We believe that the presence of Q fever in different clinical manifestations and persistent infection should be taken into account by physicians and awareness should be raised in clinical practice.

Ethics

Ethics Committee Approval: The study was approved by Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (decision no: 86-2020/18, date: 18.02.2020).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: F.S., Design: F.S., S.K., Data Collection or Processing: F.S., S.K., P.B., T.D., H.T.G., Analysis or Interpretation: O.K., T.O.Ö., Literature Search: F.S., T.O.Ö., Writing: F.S., P.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Eldin C, Mélenotte C, Mediannikov O, Ghigo E, Million M, Edouard S, Mege JL, Maurin M, Raoult D. From Q fever to *Coxiella burnetii* infection: A paradigm change. Clin Microbiol Rev. 2017;30:115-90.
2. Kersh GJ, Fitzpatrick KA, Self JS, Priestley RA, Kelly AJ, Lash RR, Marsden-Haug N, Nett RJ, Bjork A, Massung RF, Anderson AD. Presence and Persistence of *Coxiella burnetii* in the environments of goat farms associated with a Q fever outbreak. Appl Environ Microbiol. 2013;79:1697-703.
3. Fournier PE, Marrie TJ, Raoult D. Diagnosis of Q fever. J Clin Microbiol 1998;36:1823-34.
4. Reilly S, Northwood JL, Caul EO. Q fever in Plymouth, 1972-88: A review with particular reference to neurological manifestations. Epidemiol Infect. 1990;105:391-408.
5. Georgiev M, Afonso A, Neubauer H, Needham H, Thiery R, Rodolakis A, Roest H, Stark K, Stegeman J, Vellema P, van der Hoek W, More. Q fever in humans and farm animals in four European countries, 1982 to 2010. Euro Surveill. 2013;18:20407.
6. Porter SR, Czaplicki G, Mainil J, Guattéo R, Saegerman C. Q fever: Current state of knowledge and perspectives of research of a neglected zoonosis. Int J Microbiol. 2011;2011:248418.
7. Vranakis I, Kokkini S, Yachnakis E, Tselentis Y, Chochlakis D, Psaroulaki A. Q fever in Greece: Findings of a 13 years surveillance study. Comp Immunol Microbiol Infect Dis. 2020;69:101340.
8. Parın U, Kaya O. Detection of *Coxiella burnetii* prevalence in bovine, ovine and caprine herds. Ankara Univ Vet Fak Derg. 2015;62:177-81.
9. Kılıç S, Çelebi B. Türkiye'de *C. burnetii*'nin Epidemiyolojisi. Turk Hij Den Biyol Derg. 2008;65:21-31.
10. Yıldırmak T, Şimşek F, Çelebi B, Çavuş E, Kantürk A, Efe-Iris N. Ağır sarılıkla başvuran, nadir görülen bir akut Q ateşi olgusu ve literatüre bakış. Klimik Derg. 2010;23:124-9.
11. Olivier-Gougenheim L, Freychet C, Collardeau-Frachon S, Roure-Sobas C, Di Filippo S, Riva R, Lega JC, Belot A. A quest for Q fever. Lancet. 2019;394:419.
12. Reisfeld S, Hasadia Mhamed S, Stein M, Chowers M. Epidemiological, clinical and laboratory characteristics of acute Q fever in an endemic area in Israel, 2006-2016. Epidemiol Infect. 2019;147:131.
13. Wielders CC, Wuister AM, de Visser VL, de Jager-Leclercq MG, Groot CA, Dijkstra F, van Gageldonk-Lafeber AB, van Leuken JP, Wever PC, van der Hoek W, Schneeberger PM. Characteristics of hospitalized acute Q fever patients during a large epidemic, the Netherlands. PLoS One. 2014;9:e91764.
14. Bae M, Jin CE, Park JH, Kim MJ, Chong YP, Lee SO, Choi SH, Kim YS, Woo JH, Shin Y, Kim SH. Diagnostic usefulness of molecular detection of *Coxiella burnetii* from blood of patients with suspected acute Q fever. Medicine (Baltimore). 2019;98:e15724.
15. Wegdam-Blans MC, Wielders CC, Meekelenkamp J, Korbeeck JM, Herremans T, Tjhie HT, Bijlmer HA, Koopmans MP, Schneeberger PM. Evaluation of commonly used serological tests for detection of *Coxiella burnetii* antibodies in well-defined acute and follow-up sera. Clin Vaccine Immunol. 2012;19:1110-5.
16. Hanssen DAT, Morroy G, de Lange MMA, Wielders CCH, van der Hoek W, Dijkstra F, Schneeberger PM. Notification data and criteria during a large Q-fever epidemic reassessed. Epidemiol Infect. 2019;147:191.
17. de Boer PT, de Lange MMA, Wielders CCH, Dijkstra F, van Roeden SE, Bleeker-Rovers CP, Oosterheert JJ, Schneeberger PM, van der Hoek W. Cost-effectiveness of screening program for chronic q fever, the netherlands. Emerg Infect Dis. 2020;26:238-46.
18. Rodríguez-Alonso B, Almeida H, Alonso-Sardón M, López-Bernus A, Pardo-Lledias J, Velasco-Tirado V, Carranza-Rodríguez C, Pérez-Arellano JL, Belhassen-García M. Epidemiological scenario of Q fever hospitalized

patients in the Spanish Health System: What's new. Int J Infect Dis. 2020;90:226-33.

19. Bernit E, Pouget J, Janbon F, Dutronc H, Martinez P, Brouqui P, Raoult D. Neurological involvement in acute Q fever: A report of 29 cases and review of the literature. Arch Intern Med. 2002;162:693-700.
20. Rehman HU, Hagel K. Q Fever. Int J Clin Ther Diagn. 2014;1:1-4.
21. Gozdas HT, Sırmatel F, Karabörk Ş, Akdeniz H. Are we aware of Q fever enough? experience from a single centre. Kocaeli Med J. 2019;8:66-71.
22. Hellenbrand W, Breuer T, Petersen L. Changing epidemiology of Q fever in Germany, 1947-1999. Emerg Infect Dis. 2001;7:789-96.
23. Karabay O, Kocoğlu E, Baysoy G, Konyalıoğlu S. *Coxiella burnetii* seroprevalence in the rural part of Bolu, Turkey. Turk J Med Sci. 2009;39:641-5.
24. Korman TM, Spelman DW, Perry GJ, Dowling JP. Acute glomerulonephritis associated with acute Q fever: Case report and review of the renal complications of *Coxiella burnetii* infection. Clin Infect Dis. 1998;26:359-64.
25. Kofteridis DP, Mazokopakis EE, Tselentis Y, Gikas A. Neurological complications of acute Q fever infection. Eur J Epidemiol. 2004;19:1051-4.
26. Dragan AL, Voth DE. *Coxiella burnetii*: international pathogen of mystery. Microbes Infect. 2020;22:100-10.
27. Miller HK, Binder AM, Peterson A, Theel ES, Volpe JM, Couturier MR, Cherry CC, Kersh GJ. Trends in Q fever serologic testing by immunofluorescence from four large reference laboratories in the United States, 2012-2016. Sci Rep. 2018;8:16670.
28. Raoult D, Tissot-Dupont H, Foucault C, Gouvernet J, Fournier PE, Bernit E, Stein A, Nesri M, Harle JR, Weiller PJ. Q fever 1985-1998. Clinical and epidemiologic features of 1,383 infections. Medicine (Baltimore). 2000;79:109-23.
29. Sırmatel F, Özarslan TO, Türkoğlu ŞA, Bücük P, Kılıç S. Q Ateşi Seropozitifliğinde Nörolojik Bulgular. Flora J Infect Dis Clin Microbiol. 2021;26:504-17.
30. Lim JA, Kim JM, Lee ST, Jung KH, Kim YS, Lee SK, Chu K. Brainstem encephalitis caused by *Coxiella burnetii*. J Clin Neurosci. 2014;21:699-701.
31. Sukocheva OA, Manavis J, Kok TW, Turra M, Izzo A, Blumbergs P, Marmion BP. *Coxiella burnetii* dormancy in a fatal ten-year multisystem dysfunctional illness: Case report. BMC Infect Dis. 2016;16:165.
32. Al-Shahi R, Scolding NJ, Bell JE, Zeman AZ, Warlow CP. A young man with a fatal encephalopathy. Pract Neurol. 2002;2:26-35.
33. Moradnejad P, Esmaeili S, Maleki M, Sadeghpour A, Kamali M, Rohani M, Ghasemi A, Bagheri Amiri F, Pasha HR, Boudagh S, Bakhshandeh H, Naderi N, Ghadrdoost B, Lotfian S, Dehghan Manshadi SA, Mostafavi E. Q Fever Endocarditis in Iran. Sci Rep. 2019;9:15276.
34. Allan-Blitz LT, Sakona A, Wallace WD, Klausner JD. *Coxiella burnetii* endocarditis and meningitis, California, USA, 2017. Emerg Infect Dis. 2018;24:1555-7.
35. Younis S, Stein M, Reisfeld S. Screening for Q Fever during Other Bacterial Endocarditis in Endemic Areas: Our Experience with Three Patients. Case Rep Infect Dis. 2019;2019:9890656.
36. Lepidi H, Houpikian P, Liang Z, Raoult D. Cardiac valves in patients with Q fever endocarditis: Microbiological, molecular, and histologic studies. J Infect Dis. 2003;187:1097-106.