Q FEVER IN CHILDREN IN GREECE

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Abstract. The aim of this study was to investigate the incidence, epidemiology, and clinical manifestations of Q fever among hospitalized children in Greece. During a two-year period, 1,200 children with various clinical manifestations were prospectively tested for *Coxiella burnetii* infection by indirect immunofluorescence. Acute Q fever was diagnosed in eight (0.67%) patients. No chronic case of infection was detected. Multivariate analysis showed that children 11–14 years old and children reporting consumption of cheese from rural areas were at increased risk for this illness. Clinical manifestations of acute Q fever were pneumonia (two patients), meningitis (two), prolonged fever (two), hepatitis (one), and hemolytic-uremic syndrome (one). Q fever accounted for 2.9% of the cases with prolonged fever, 1.2% of the cases of meningitis, and 0.5% of the cases of pneumonia. Fever and headache were the most common symptoms at presentation. Our study indicates that Q fever is a rare cause of hospitalization during childhood.

INTRODUCTION

Q fever is a worldwide zoonosis. First described in 1937 by Derrick, the disease is caused by the obligate intracellular bacterium *Coxiella burnetii*, which lives in the macrophages of the host but may survive outside the cell. Farm animals, mainly cattle, sheep, and goats, are the primary reservoirs of infection. High numbers of *C. burnetii* are present in the placentas of infected parturient animals and are shed in the environment following labor or abortion. Humans acquire the infection mainly via inhalation of contaminated aerosolized particles or ingestion of unpasteurized dairy products. Outbreaks following exposure to birth products of cats, dogs, and rabbits have also been reported.

Q fever is associated with a wide spectrum of clinical manifestations. Following primary infection with *C. burnetii*, half of the patients remain asymptomatic. Among those who are symptomatic, acute Q fever typically manifests as a self-limited febrile illness, pneumonia, or hepatitis. Endocarditis is the predominant form of chronic Q fever and mostly affects patients with underlying valvulopathy. The overwhelming knowledge on Q fever concerns adults. Q fever in children has been rarely reported and may remain underdiagnosed.

This is a two-year prospective study of the incidence, epidemiology, and clinical manifestations of Q fever among children hospitalized in a tertiary care hospital in Athens, Greece. Investigation for Q fever was performed at the French National Reference Center and World Health Organization Collaborative Center for Rickettsial Diseases in Marseille, France.

MATERIALS AND METHODS

Patients. The University of Athens Second Department of Pediatrics is located in P. & A. Kyriakou Children’s Hospital, a tertiary care pediatric hospital in Athens, Greece. This department is in charge of approximately one-fourth of the hospitalizations required among approximately 730,000 children living in Athens. In addition, this hospital serves as a referral hospital for the greater part of southern Greece. The study population was composed of children 0–14 years old who were consecutively admitted to the Second Department of Pediatrics from January 2000 to December 2001 because of one of the following manifestations: fever (temperature > 38.0°C) for more than three days; prolonged fever (fever more than seven days); fever and headache; fever and rash; fever and anemia (hemoglobin level < 9.0 mg/dL of blood); leukopenia (< 4,000 white blood cells [WBC]/mL of blood), and/or thrombocytopenia (< 150,000 platelets/mL of blood); hepatitis (more than a two-fold increase in levels of hepatic transaminases); pneumonia (fever and/or acute respiratory signs and symptoms in association with infiltrates on a chest radiograph); asthma exacerbation of presumed infectious etiology (expiratory airway obstruction on auscultation and signs and symptoms of respiratory tract infection); persistent cough (cough for more than three weeks); central nervous system (CNS) infection (symptoms of CNS infection with or without abnormal findings in cerebrospinal fluid [CSF]); osteomyelitis (signs and symptoms of bone infection and abnormal findings on radionuclide bone scanning); arthritis (signs and symptoms of infection in the joint space without contiguous osteomyelitis); myositis (transient muscle pain and weakness and increased creatine phosphokinase); pericarditis (electrocardiographic findings compatible with pericarditis and pericardial fluid on ultrasound); endocarditis (defined in accordance with the modified Duke criteria); chronic superficial lymphadenitis (superficial lymph node enlargement for more than four weeks); and syndromes of presumed infectious or post-infectious etiology (hemolytic-uremic syndrome [HUS], nodular erythema, urticaria, Henoch-Schonlein purpura, idiopathic thrombopenic purpura, and seventh cranial nerve paresis). Patients were enrolled in the study irrespective of epidemiologic characteristics. The study protocol was reviewed and approved by the Ethics Committee of the hospital and informed consent was obtained from the parents or legal guardians of all patients.

Collection of information and management of patients. The characteristics of the patients were collected within 24 hours of admission. These included age, sex, underlying disease, country of origin, residence area, family occupation, contact with farm or other animals, consumption of unpasteurized dairy products or dairy products from rural areas, tick bite, and month of admission. The signs and symptoms of patients and their duration from the onset of illness were recorded. Levels of hepatic transaminases were estimated in all patients. Additional laboratory and imaging tests were performed as indicated by the clinical findings. The patients were treated by the medical staff of the department without inter-
vention from the investigators. Since serologic tests for Q fever were performed at a later stage, the medical staff was not notified of the results during the acute phase of illness of their patients. The duration of hospitalization and the use of antibacterial agents were also recorded. At discharge, a follow-up examination was scheduled approximately four weeks after admission. Patients with Q fever were followed for one year following diagnosis. Beginning in 2001, echocardiographic examination was performed in all children diagnosed with acute Q fever, to detect any underlying valvulopathy and promptly administer prophylaxis for the possibility of evolution to chronic Q fever endocarditis.5

Diagnosis of Q fever. Within 24 hours of admission, one serum specimen was drawn from all patients (acute phase). A second specimen was obtained four weeks later at the follow-up visit (convalescent phase). Sera were frozen at −70°C until transported to the reference laboratory. Specimens were transported on dry ice, in accordance with the international regulations. Serologic testing for C. burnetii infection was performed at the French National Reference Center and World Health Organization Collaborative Center for Rickettsial Diseases (Unité des Rickettsies, Faculté de Médecine, Université de la Méditerranée) in Marseille, France. Titters of phases I and II IgM and IgG antibodies against C. burnetii were estimated by the indirect immunofluorescence assay. Nine Mile C. burnetii strains grown in the laboratory were used as antigens, as previously described.6 All sera were tested at a screening dilution of 1:50 for phase I and phase II antibodies to C. burnetii. Positive specimens were further tested at serial two-fold dilutions to estimate IgM and IgG titers. The IgM antibodies were detected following a pretreatment procedure with rheumatoid factor adsorbent (Behring, Mannheim, Germany) to remove IgG antibodies. The IgM and IgG titers were estimated using goat antiserum (Fluoline Mannheim, Germany) to remove IgG antibodies. The IgM antibodies tested at serial two-fold dilutions to estimate IgM and IgG antibody titer of 1:800.7 Paired serum specimens were tested respectively. Chronic Q fever was diagnosed by a phase I IgG titer of 1:800.7

Statistical analysis. Differences between categorical variables were estimated with the Fisher’s exact test. Differences between continuous variables were estimated with the Student’s t-test. Logistic regression analysis was used to identify the multivariate risk factors for the development of Q fever. Odds ratios (ORs) and their 95% confidence intervals (CIs) were obtained. P values < 0.05 were considered statistically significant. All statistical tests were two-sided. Statistical analyses were performed using the Statistical Package for Social Sciences, version 10.05 software program (SPSS, Chicago, IL).

RESULTS

Incidence and seasonal and age distribution of Q fever. A total of 1,200 children were enrolled in the study. Paired sera were available in 1,044 (87%) of them. Acute Q fever was diagnosed in eight (0.67%) patients. No chronic form of the infection was detected. The yearly incidence rate of Q fever was 0.49% (3 of 612) in 2000 and 0.85% (5 of 588) in 2001 (P = 0.498). Cases were evenly distributed from January through September. With regard to distribution per age groups, an age-specific increase of the incidence rate was evident. In particular, acute Q fever was diagnosed in 0.15% (1 of 654) of patients < 5 years of age, in 0.77% (3 of 391) of patients 5–10 years of age, and in 2.58% (4 of 155) of patients 11–14 years of age (P = 0.005).

Risk factors for the development of Q fever. A comparison between patients with and without Q fever showed that the former were significantly older and more frequently had a history of consumption of cheese from rural areas (Table 1). Multivariate analysis showed that the following variables were significant risk factors for the development of Q fever: an age of 11–14 years compared with groups < 5 years old and 5–10 years old (P = 0.04, OR = 11, 95% CI = 1.2–101.5), and consumption of cheese from rural areas (P = 0.04, OR = 6, 95% CI = 1.1–33.2).

Table 1. Multivariate analysis of risk factors for the development of Q fever among children in Greece.

| Variable | Patients (%) with Q fever | Patients (%) without Q fever | P
|----------|--------------------------|----------------------------|---
| Male sex, no. (%) | 4 (50) | 667 (56) | NS
| Admission from January to June, no. (%) | 6 (75) | 772 (65) | NS
| Underlying disease, no. (%) | 1 (12.5) | 277 (23) | NS
| Immigrants, no. (%) | 1 (12.5) | 190 (16) | NS
| Rural residence, no. (%) | 4 (50) | 506 (26) | NS
| Contact with animals, no. (%) | 6 (75) | 812 (68) | NS
| Contact with farm animals, no. (%) | 5 (62.5) | 492 (41) | NS
| Mean no. of animal species (range) | 3.8 (2–6) | 2.8 (1–11) | NS
| Consumption of cheese from rural areas, no. (%) | 6 (75) | 335 (28) | 0.008
| Tick bite, no. (%) | 0 (0) | 67 (5.5) | NS

* NS = not significant.
sent with fever, which lasted for a mean of 5.2 days (range = 1–10 days). Four of them had fever for 7–10 days. There was no case of isolated fever. Headache and rash were present in five and four patients, respectively. The rash was purpuric or maculopapular (two patients each) and was localized in face and trunk or lower limbs (two patients each) (Figure 1). The HUS case has been described in detail elsewhere.8

Laboratory findings of children with acute Q fever. The mean laboratory values of the patients with Q fever were as follows: WBC count = 10,562/mm³ (range = 4,600–18,900/mm³), absolute neutrophil count = 6,879/mm³ (range = 2,070–16,254/mm³), absolute platelet count = 239,125/mm³ (range = 5,000–354,000/mm³), hemoglobin = 11.5 g/dL (range = 5.3–14.2 g/dL), and C-reactive protein = 82 mg/dL (range = 14–320 mg/dL). Elevated hepatic transaminase levels were found in three patients (one with hepatitis, one with HUS, and one with pneumonia). Direct bilirubinemia was present in the patient with HUS and in the patient with hepatitis. Hepatic function test results normalized within 10 days in all of these patients. Chest radiographs showed unilateral segmental infiltrates in both children with pneumonia in association with a small pleural effusion in one. Chest radiographs were also performed in five of the remaining patients (two with prolonged fever, two with meningitis, and one with HUS) and were normal. Lumbar puncture revealed the following CSF values in the patients with meningitis: WBC count = 245/mm³ (92% lymphocytes, 8% neutrophils), glucose = 48 mg/dL, and protein = 26 mg/dL in one case; and 235/mm³ (42% lymphocytes, 56% neutrophils, 2% monocytes), glucose = 65 mg/dL, and undetectable protein in the second case.

Management and outcome of children with acute Q fever. Children with acute Q fever were hospitalized for a mean of 6.1 days (range = 3–11 days). Treatment was administered in three of them with penicillin (two patients with pneumonia) and cefotaxime (one with meningitis). None of the patients with Q fever received any specific treatment against C. burnetii. The results of an echocardiographic examination in five children were normal. All children with acute Q fever recovered completely, with no complications within a one-year follow-up.

DISCUSSION

During the past decade, major advances have been made in the understanding of Q fever; however, the published information involves almost exclusively adults.3,6,9 The current study was conducted to investigate the incidence, epidemiology, and clinical spectrum of Q fever among hospitalized children in Greece. During a two-year period, 1,200 children with various clinical manifestations were prospectively tested and acute Q fever was diagnosed in 0.67% of them. Our results indicate that Q fever is a rare cause of hospitalization during childhood.

Q fever in children has been rarely reported. In a recent review of this topic conducted using the standard diagnostic criteria, we identified only 46 published pediatric cases.10 However, seroepidemiologic surveys show that children are frequently exposed to C. burnetii.10 Increased prevalence rates have been reported in children in Europe, namely 37% in boys and 70% in girls in The Netherlands, 23.3% in Switzerland, 18.46% in Spain, and 18.6% in Greece.11–14 It appears that following infection with C. burnetii, children experience a milder clinical course compared with adults.10 Indeed, during an outbreak of Q fever that occurred in Switzerland in 1983 and involved 415 people, children up to 14 years accounted for 80 (19%) of the patients, but only for 10 (5%) of the 191 symptomatic patients, and none of the

TABLE 2

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>No. of patients with Q fever (n = 8)</th>
<th>No. of tested patients (n = 1,200)</th>
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<tr>
<td>Pneumonia</td>
<td>2</td>
<td>393</td>
</tr>
<tr>
<td>Meningitis</td>
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<td>166</td>
</tr>
<tr>
<td>Prolonged fever</td>
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<td>69</td>
</tr>
<tr>
<td>Hepatitis</td>
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<td>23</td>
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<td>Hemolytic-uremic syndrome</td>
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<td>2</td>
</tr>
<tr>
<td>Others *</td>
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<td>547</td>
</tr>
</tbody>
</table>

* 547 patients who tested negative for Q fever presented with the following manifestations: fever and headache (134), fever and rash (134), asthma exacerbation (105), isolated fever (51), persistent cough (29), Henoch-Schonlein purpura (15), arthritis (14), chronic lymphadenitis (14), idiopathic thrombocytopenic purpura (7), encephalitis (6), seventh cranial nerve paresis (5), osteomyelitis (5), encephalitis (4), fever and neutropenia (4), hemolytic (4), urticaria (4), myositis (3), nodular erythema (3), fever and thrombocytopenia (3), fever and anemia (2), and pericarditis (1).

TABLE 3

<table>
<thead>
<tr>
<th>Sign/symptom</th>
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<tbody>
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<tr>
<td>Headache</td>
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</tr>
<tr>
<td>Vomiting</td>
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</tr>
<tr>
<td>Rash</td>
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<td>Fatigue</td>
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<tr>
<td>Abdominal pain</td>
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</tr>
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<td>Cough</td>
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<td>Hepatomegaly</td>
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<td>Nuchal rigidity</td>
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<tr>
<td>Superficial lymphadenitis</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
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</table>
eight hospitalized patients. In this outbreak, 70 (87.5%) of the 80 children were asymptomatic compared with 121 (36%) of 335 patients > 14 years old \( (P < 0.001) \). Similarly, during an outbreak of Q fever that occurred in a school in England, it was estimated that only one of every 30 children with serologic evidence of *C. burnetii* infection has been identified as a symptomatic case of Q fever. In our analysis of risk factors for Q fever, the small number of patients in the case group require conservative conclusions. However, having an age of 11–14 years was an independent risk factor for the development of Q fever requiring hospitalization and was associated with an 11-fold increased risk for this illness compared with younger age groups. The fact that adolescents are more symptomatic following infection compared with young children, is consistent with the results of large series, where an age-related increase of the incidence and severity of symptomatic infection is evident.

Q fever has been typically regarded as an occupational illness affecting people in contact with farm animals or their products. In our study, none of the children with Q fever was involved in stockbreeding, whereas half of them lived in urban areas. Nowadays, there is an increasing number of cases among urban residents, which may be attributed to the increased exposure opportunities to farm animals and pets, through travel to the countryside and involvement in outdoor activities, but also to urbanization of rural areas. In Greece, lambing occurs during winter and early spring, and may explain the increased incidence of Q fever during the first half of the year.

Consumption of cheese from rural areas was a source of infection in our patients. Although this is a common experience in Greece, it may also be the case in other countries, where cheese is frequently distributed directly from stockbreeders and farms and the distribution is not well regulated. In a recent outbreak of Q fever in Newfoundland, Canada, consumption of cheese made from pasteurized milk emerged as a risk factor for infection for the first time. These findings raise questions about the control of infection with *C. burnetii* in the dairy industry.

Among our patients with Q fever, boys and girls were equally represented. Similarly, the sex ratio was 1:1 among 26 recently diagnosed pediatric cases at the French National Reference Center and World Health Organization Collaborative Center for Rickettsial Diseases in Marseille, France (Raoult D and others, unpublished data). This is consistent with large studies reporting data on children. In contrast, among adults with Q fever, a numerical predominance of males is clearly evident, e.g., in France the male to female ratio is 2.45. This may be partly attributed to the greater representation of men in professions in contact with farm animals; however, sex-specific seroprevalence data from this country do not support such an explanation. It is possible that the clinical expression following infection with *C. burnetii* is milder in women compared with men, and this could be associated with a protective role of female hormones on clinical expression.

Acute Q fever is a multi-system infection with a variety of manifestations. More than half of our patients presented with a self-limited febrile course and headache. Similarly, in a pediatric series from Spain, half of the children presented with fever and headache. Headache is frequently encountered in patients with Q fever. The duration of fever in our patients was generally short, with fever ceasing within seven to ten days in all of them. This is in agreement with two other pediatric series. In contrast, longer febrile courses have been observed in adults, with fever lasting for more than two weeks in 60% of those > 40 years old.

Meningitis accounted for two of the eight cases of Q fever diagnosed in our study, which is noteworthy. Pediatric cases of Q fever meningitis and encephalitis have been occasionally reported. In the largest series on Q fever to date of 1,383 patients hospitalized in France over a 14-year period, CNS infection represented approximately 1% of the acute cases. The difference in the incidence of CNS infection between this study and ours may be attributed to the variations in tissue tropism of the different *C. burnetii* strains that prevail within different regions. Lumbar puncture is more readily attempted in febrile children compared with adults, which may also have had an impact. Overall, *C. burnetii* is a rare cause of childhood meningitis, accounting for 1% of cases.

Three of our patients had increased levels of hepatic transaminases. This is common in patients with Q fever and may be detected in as many as 45–85% of the cases. Furthermore, half of our patients developed rash. Rash is not part of the typical Q fever in adults. It appears that children are more likely to develop rash in the course of acute Q fever. Pulmonary involvement was detected in only two of our patients. In contrast, in two other pediatric series, most children presented with respiratory symptoms. Differences in the incidence of clinical manifestations of Q fever have also been described among adults, with pneumonia being the major manifestation in Nova Scotia (Canada), Switzerland, the Basque country (northern Spain), and the island of Crete (southern Greece), whereas hepatitis predominates in France, Andalusia (southern Spain) and Ontario (Canada). Overall, *C. burnetii* was a rare cause of community-acquired pneumonia necessitating hospitalization among our patients.

All of our patients with acute Q fever had a favorable outcome. Similar results have been reported in two other pediatric series. Fatal cases have been occasionally recorded among children with acute Q fever. In contrast, among adults older age has been associated with severe morbidity, and mortality rates of 1% have been reported.

Our study indicates that Q fever is a rare cause of hospitalization during childhood. Children 11–14 years of age and children with a history of consumption of cheese from rural areas were at increased risk for this illness. The prevalent case was a school age child with a self-limited febrile illness and headache. In contrast to adults, Q fever during childhood equally affects boys and girls, and appears to be associated with a milder course and more favorable outcome. Q fever should be considered in the differential diagnosis of a febrile illness in children with epidemiologic risk factors for infection with *C. burnetii*.

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