QUESTING ONE BRAZILIAN QUERY: REPORTING 16 CASES OF Q FEVER FROM MINAS GERAIS, BRAZIL

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SUMMARY

Q fever has been considered non-existing in Brazil where reports of clinical cases still cannot be found. This case-series of 16 patients is a result of a systematic search for such illness by means of clinical and serologic criteria. Serologic testing was performed by the indirect microimmunofluorescence technique using phase I/II *C. burnetii* antigens. Influenza-like syndrome was the most frequent clinical form (eight cases - 50%), followed by pneumonia, FUO (fever of unknown origin), mono-like syndrome (two cases - 12.5% each), lymphadenitis (one case - 6.3%) and spondylodiscitis associated with osteomyelitis (one case - 6.3%). The ages varied from four to 67 years old with a median of 43.5. All but one patient had positive serologic tests for phase II IgG whether or not associated with IgM positivity compatible with acute infection. One patient had both phase I and phase II IgG antibodies compatible with chronic Q fever. Seroconvertion was detected in 10 patients. Despite the known limitations of serologic diagnosis, the cases here reported should encourage Brazilian doctors to include Q fever as an indigenous cause of febrile illness.

KEYWORDS: Q fever; *Coxiella burnetii*; Brazil.

INTRODUCTION

Coxiella burnetii is a Gram-negative bacterium, intracellular obligate, former *Rickettsiae* now belonging to the *Legionellacea* family of the γ group of proteobacteria[2,7,12]. It is the etiologic agent of a worldwide human infection named Q fever[2,11,12], a disease initially described in Australia by Derrick (1935) and so nominated "Query fever", giving its enigmatic etiologic nature at that time[11].

The infection occurs in a zoonotic cycle involving several mammals and birds species[2,11,12]. Arthropod vectors have been considered important in animal but not in human transmission[11,12] and human infections occur mainly by contaminated dust inhalation, infected tissues manipulation or raw milk ingestion[2,11,12]. Cattle, goats and sheep have been frequently linked to rural *C. burnetii* infections[2,11,12] but dog and cat-associated Q fever have been described in both urban and rural areas[15].

C. burnetii can be transported by the wind and infected people sometimes never recall direct contact with animals[11,12,21] and such unusual fitness along the very small number of bacteria required for infection makes this agent eligible for biological warfare[2]. Since *C. burnetii* does not yield in standard culture medium[7,12] the laboratory diagnosis relies mostly on serological tests[2,4,5,7,11,12] not routinely available in developing countries. Fortunately, most human infections are asymptomatic or mild[11,12] resembling a self-limited influenza, but hepatitis, pneumonia and the so-called chronic Q fever, associated or not with endocarditis, can have severe outcomes if not properly treated[2,7,11,12,16]. Newly described syndromes such as Q fever in pregnancy, chronic vascular graft infection, myocarditis, pericarditis, osteomyelitis, cholecystitis, pancreatitis and meningitis reinforce the need of proper identification of *C. burnetii* infections everywhere[8,12,16].

C. burnetii infections are supposed to occur throughout the world but reports from South America have been deemed scarce[13,22]. The more recent published Brazilian serologic survey for Q fever backs 1975[18] and published case reports remain to be found so the aim of this publication is to report 16 cases of Q fever serologically and clinically diagnosed.

PATIENTS AND METHODS

From January 2001 to June 2004, 726 febrile patients were screened for rickettsial infections as part of a specific protocol for etiologic investigation[3]. These patients were seen in five different health care services from Juiz de Fora city, Minas Gerais State, Brazil. They were classified into different clinical syndromes according to their symptoms and signs and current diagnostic criteria[3]. Serum samples were tested by indirect microimmunofluorescence technique as described elsewhere[14] with phase I and phase II *C. burnetii* (Nine Mile strain) antigens. Serologic

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testing for other rickettsial agents were also performed using the following antigens: *Rickettsia typhi* (Wilmington strain), *Rickettsia rickettsii* (Sheila Smith strain), *Bartonella henselae* (Vero cells-Houston strain), *Bartonella quintana* (Vero cells) and *Ehrlichia chaffeensis* (DH 82 infected cells - Arkansas strain). Viral and Rickettsial Branch of CDC Atlanta USA provided all antigens and control sera. Fluorescein-conjugated goat anti-human IgG and IgM (BioMérieux) obtained commercially were used for antibody detection. All samples were collected during the symptomatic phase of the disease and whenever possible convalescent samples (two to four weeks apart) were additionally collected. Serum samples were initially screened at the dilution of 1:64 and those positive were subsequentially titered to the end-point considered the final titer. The slide readings were done blindly and a fluorescence of at least 2+ was required for positivity. Rheumatoid factor absorption was not performed but the tested samples were directly checked for the presence of rheumatoid factors (Latex agglutination and Waaler-Rose test). Extensive array of laboratory tests such as blood cell counts, biochemical analysis, blood cultures and serologic assays for *Mycoplasma pneumonia*, *Chlamydia pneumoniae*, *Leptospira interrogans*, *Brucella* spp., *Salmonella*, EB virus, CMV, *Toxoplasma gondii*, *Treponema pallidum* and dengue fever were performed in referral commercial laboratories. Other tests like those for parvovirus B19, Lyme disease, schistosomiasis, American trypanosomyasis and influenza were performed in some but not all patients.

Current serologic criteria for Q fever diagnosis[2,4,5,7,12] were used: anti-phase II *C. burnetii* IgG and/or IgM seroconversion - confirmed[7,11]; IgG ≥ 1:256 and/or IgM ≥ 1:64 - probable (sensitivity 58.4% - specificity 92.2%[7]); IgG ≥ 1:128 and or IgM ≥ 1:32 - possible[2]. For seroconvertion IgG and or IgM negative to positive the cut-off values were respectively 1:64 and 1:32[7,12]. The absence of seroconvertion between acute and convalescence samples precluded the serologic diagnosis. Anti-phase I *C. burnetii* IgG ≥ 1:800 associated or not with anti-phase II *C. burnetii* antibodies were considered for chronic Q fever diagnosis (sensitivity 100% - specificity 98.6%[7]).

RESULTS

Twelve out 16 patients (75%) were males and the age varied from four to 67 years old with a median of 43.5 years old. Three cases (18.8%) occurred in children. The fever median duration time was 10.5 days varying from two to 20 days. Twelve patients corresponding to 75% reported frequent animal contact but just seven (43.7%) came from rural areas (data not shown). Influenza-like syndrome was the most frequent diagnosis with eight cases (50%) followed by pneumonia, FUO and mono-like syndrome with two cases (12.5%) each. Lymphadenitis (one case - 6.3%) and spondylodiscitis associated with osteomyelitis (one case - 6.3%) completed the series.

All patients recovered either with (10 cases - 62.5%) or without (six cases - 37.5%) proper therapy. Gatifloxacin was antimicrobial agent used in six cases, ciprofloxacin in two cases and doxyciclin plus ciprofloxacin plus hydroxychloroquine in one case (spondylodiscitis associated with vertebral osteomyelitis). Seroconvertion was observed in 10 cases (62.5%) and these were considered confirmed. Four cases had serologic findings in isolated samples compatible with probable acute Q fever and two cases with possible acute Q fever. All but one case had compatible IgM serologic response detected. High IgG titers for phase I and phase II *C. burnetii* antigens were detected in a case of spondylodiscitis/osteomyelitis compatible with chronic Q fever[3,7,12]. Cross-reactivity with other rickettsial agents was detected in five cases (31.2%), and all patients had some degree of cross-reactivity between phase I and phase II *C. burnetii* antibodies. Extensive cross-reactivity with *R. rickettsii* and *R. typhi* associated with IgG seroconvertion was observed in one case but IgM seroconvertion exclusively to *C. burnetii* suggested Q fever diagnosis. Rheumatoid factor however was detected in this case. Increased CRP was observed in all cases ranging from 12 to 90 mg and leukocyte counts ranged from 3.5 to 14 x 10^3 /mm³. Slightly increased AST and ALT (less than three times the higher normal value) was detected in 10 cases (62.5%).

Table 1 shows the demographics, clinical and serologic findings of the reported cases.

DISCUSSION

Although considered a worldwide zoonosis, published human cases of Q fever from Brazil remain to be found. Extensive search in Index Medicus, Lilacs, PubMed, MEDLINE and other Internet search machines did not find any reference to the isolation of this agent from clinical samples in Brazil but at least one Brazilian group has been studying experimental *C. burnetii* infection[23]. Nevertheless serosurveys were reported in the past when RIBEIRO-NETO *et al.*[17] carried out the pioneering studies in the state of São Paulo founding a seroprevalence rate of 8.5% among 200 dairy farm workers as compared with 0.47% among 212 urban industry employees. Ten years later, RIEMANN *et al*. observed an infection rate of 22% among 219 veterinary personnel[19] and of 29% among 144 slaughterhouse employees[18] in the Minas Gerais State capital, Belo Horizonte. Recent serosurvey in the Piau county, Minas Gerais State, found a 3.9% seropositivity rate among healthy population[3]. These data despite their limitations suggest the presence of *C. burnetii* in Brazil but for some reason Q fever, reported southern[20] and northern of Brazil[22] has remained forgotten in this Country.

The majority of cases here reported had influenza-like symptoms and the most frequent clinical presentations of Q fever have been both influenza-like syndrome and intermediate duration undifferentiated fever[2,11,12].

Two cases of pneumonia were identified as being caused by *C. burnetii* in this series and pneumonia is one classical form of Q fever[2,7,12,16]. Contrarily to the previously thought[11], alveolar infiltrates indistinguishable from other bacterial pneumonia is the most common pattern[1,12,16] as observed in the cases reported here.

Hepatic attack in the form of granulomatous hepatitis has been classically associated to Q fever[2,7,11,12] but the only liver abnormality detected in the cases of this series was slightly increased AST/ALT in some but not all patients. Asymptomatic liver attack characterized by increased AST/ALT moreover is a very common pattern in Q fever[12].

Two cases here reported had lymphadenitis resembling cat scratch disease, a syndrome that has been not frequently linked to *C. burnetii* infections[11,12]. Recent evidences however suggests that this presentation can be far more common than previously thought[6].

Table 1
Clinical, laboratory, and demographic data of Q fever cases (*C. burnetii*)

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Diagnosis	Co	Co	Co	Co	Co	Co	Co	Co[2]	Co	Co	Pr	Pr	Pr	Pr	Ps	Ps
Age	39	34	45	12	47	20	23	67	46	67	4	42	46	4	55	48
Sex	M	M	F	F	M	F	M	M	M	M	M	M	M	M	F	M
Clinical form	In	In	Pn[1]	In	In	Pn[1]	In	Fu[3]	M	Sd	La	In	Fu	In	Ml	In
Days of fever	15	10	3	17	15	4	10	14	20	5	4	3	18	2	12	11
Therapy	N	N	G	G	G	G	G	C	D	D	N	G	N	A	N	*N*
C. burnetii I IgG	1:128	1:1024	1:64	1:64	1:1024	1:64	1:32	1:2048	1:256	1:1024	1:64	1:256	1:512	1:512	1:32	1:64
C. burnetii I IgM	1:64	1:1024	1:64	1:64	1:64	1:64	1:64	1:2048	1:128	1:2048	1:128	1:32	1:64	1:512	1:16	1:32
C. burnetii II IgG	1:1024	1:1024	1:64	1:256	1:1024	1:64	1:32	1:2048	1:256	1:1024	1:256	1:256	1:512	1:512	1:128	1:128
C. burnetii II IgM	1:64	1:1024	1:128	1:128	1:64	1:64	1:128	1:2048	1:128	1:1024	1:128	1:32	1:64	1:512	1:32	1:32
B. henselae IgG	-	-	-	-	1:64	-	-	-	-	-	1:64	-	-	-	-	-
B. henselae IgM	-	-	-	-	1:64	-	-	-	-	-	-	-	-	-	-	-
B. quintana IgG	-	-	-	-	1:64	-	-	-	-	-	1:64	-	-	-	-	-
B. quintana IgM	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R. rickettsii IgG	-	-	-	-	-	-	-	1:2048	-	1:64	-	-	-	-	-	-
R. rickettsii IgM	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R. typhi IgG	-	-	1:32	-	-	-	-	1:2048	-	-	-	-	-	-	-	-
R. typhi IgM	-	-	1:16	-	-	-	-	-	-	-	-	-	-	-	-	-
E. chaffeensis IgG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
E. chaffeensis IgM	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Seroconvertion	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N
Rheumatoid factor	N	N	NT	N	N	N	N	Y	N	N	N	N	NT	N	N	N
Leukocyte count 10[3]	6	5.5	11	8	8	7	9	14	12	9	13	7	6	3.5	8	11
Increased AST/ALT	Y	N	N	Y	Y	N	Y	Y	Y	N	N	N	Y	Y	Y	Y
CRP	23	30	45	37	18	28	31	90	30	50	40	12	20	26	19	15
Epidemiology	Y	Y	Y	N	Y	N	Y	N	Y	N	Y	Y	Y	Y	Y	Y
Outcome	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R

M = male; F = female; N = no; Y = yes; Co = confirmed; Pr = probable; Ps = possible; - = negative; G = gatifloxacin; C = chloramphenicol; D = doxycyclin; A = azithromycin; R = recovery; CRP = C reactive protein; In = influenza-like; La = lymphadenitis; Pn = pneumonia; FU = FUO; Ml = mono-like; Sd = spondylitis plus vertebral osteomyelitis; [1] = lobar infiltrate; [2] = rheumatoid factor positive; [3] = echocardiogram suspected of endocarditis (mural vegetation).

FUO cases were described in this series and such clinical syndrome has been associated with both acute and chronic Q fever. The former has a pattern of fever of intermediate duration associated with influenza-like symptoms[12] and the last with either multisystemic disease or endocarditis[12].

Two cases of mono-like syndrome were identified in this series and *C. burnetii* usually does not appear as causing such syndrome[8,12]. Superposing symptoms between mono-like syndrome, FUO and influenza-like syndrome might be hiding the real occurrence of the former.

A wide range of osteoarticular manifestations has been recently associated with *C. burnetii* infections and spondylodiscitis associated with vertebral osteomyelitis as in one case here reported, has been one of them[12,16]. Such infections have the tendency of chronicity and demand long-term specific therapy[12,16].

Most of the cases here reported fit with acute Q fever, which is the most prevalent form of this infection[2,7,11,12]. Contrarily to acute Q fever, which has a benign course, chronic Q fever is a severe disease difficult to treat and associated with bad outcomes[2,11,12,16]. Chronic pulmonary infiltrates associated or not with infective endocarditis is the most frequent clinical scenario in chronic Q fever[11,12,16]. Recent reports of chronic Q fever causing vascular grafts infections, osteomyelitis and chronic fatigue syndrome[2,7,8,12,16], all long-lasting conditions, demand changes in our paradigms about this outstanding infectious agent.

Animal contact was reported by most of the patients in this series but many of them came from urban areas. Q fever is no longer considered an exclusively rural zoonosis and urban outbreaks have been reported[12,15]. A recent outbreak in French Guyana found an urban rather than rural pattern of infection distribution[22] and the former idea of rural zoonosis has been replaced by "everywhere zoonosis" given the multiple ways of transmition of *C. burnetii*, an expected consequence of its powerful fitness and infectivity[2,11,12].

Most of the cases here reported occurred in males and this is an expecting and frequently reported finding considering the outdoor activities and closer contact with animals associated with this gender[2,12]. The possible protective role of estrogens against *C. burnetii* infection however could be an alternative explanation[10].

Only few patients in this series were children. Q fever has been labeled as a disease of adults, especially because the increased outdoors activities of this group but Q fever in infancy is well known and the clinical picture quite similar[11].

Increased CRP as observed in all cases of this series has been a common finding in Q fever[12] and considered a useful tool especially for the differential diagnosis with viral infections[12]. Leukocyte counts within normal range or slight leukocytosis has been also commonly found in Q fever as in the cases here reported[11,12].

All patients recovered either with or without therapy and this is the most common pattern of acute Q fever considered a benign and self-limited disease[2,7,11,12]. New generation quinolones have been a good option for suspected cases and especially useful for therapeutic approach in cases of pneumonia[1,12]. Chronic Q fever on the other hand requires long-term combined therapy and doxycyclin associated with ciprofloxacin and chloroquine, the last promoting alkalinization of phagolysosome, are supposed to be effective[12,16].

All cases here reported had serologically diagnosed Q fever according to current criteria[2,4,5,7,12,16] and from the practical standpoint serology, especially immunoflourescence, is a well-established way for such diagnosis[2,7,12]. High titers IgG antibodies to phase II antigens associated or not with IgM antibodies are characteristically representative of acute Q fever while the presence of IgG phase I antibodies alone or associated with anti IgG phase II antigens suggests chronic Q fever[2,4,7,12,16].

As in other rickettsial infections, cross-reactivity has been frequently an important obstacle for serologic tests[4,5,7,12] but this aspect, with one exception, was not prominent in this series. The presence of rheumatoid factor could be an additional explanation[7] for the extensive cross-reactivity in that particular case. Extensive cross-reactivity between phase I and phase II *C. burnetii* antibodies was observed here and this is a well-known phenomenon, possibly resulting from antigenic similarities between these antigens[4,5,7,12]. The most troublesome aspects of serology in this sense are the cross-reactivity with *Chlamydia*, *Legionella* and *Bartonella* spp.[9,12,13] all causative agents of very close clinical syndromes. Other rickettsial agents are also prone in inducing cross-reactivity with *C. burnetii* usually in lower titers[4,5,7,12] as observed in some cases here reported.

Far more sophisticated and reliable tests such as cell culture, PCR and immunohistochemical also could be used for diagnostic purposes in Q fever but these are expensive, have low sensibility once set the antibody response, and are not readily available[7,12].

The data presented here has shown clinical and serologic evidences of symptomatic human *C. burnetii* infection in Brazil making important to consider Q fever among the infectious syndromes occurring in the region. Actually, they represented 2.2% of the etiologies in 726 febrile patients from that region[3]. Given the unique laboratorial requirements for such diagnosis and the uncharacteristic clinical aspects, Q fever cases might have been overlooked and despite the usually favorable outcome, specific treatment has been required sometimes thus making the questing for the proper diagnosis necessary[2,12,16]. Given the known limitations of serologic tests and the uncharacteristic clinical findings, more specific and sophisticated methods should be used in the future to access this exquisite infection.

RESUMO

Investigando uma interrogação brasileira: relatando 16 casos de febre Q em Minas Gerais, Brasil

A febre Q continua sendo considerada inexistente no Brasil onde publicações de casos clínicos ainda não são encontráveis. Esta série de casos de 16 pacientes é resultado de uma busca sistemática para esta doença usando-se critérios clínicos e sorológicos. Os testes sorológicos foram realizados pela técnica de microimunofluorescência indireta utilizando-se antígenos de *C. burnetii* fase I e fase II. Síndrome influenza símile foi a forma clínica mais frequente (oito casos - 50%), seguida pela pneumonia, FOI (febre de origem indeterminada), síndrome mononucleose símile (dois casos - 12,5% cada) e por fim linfoadenite (um caso - 6,3%) e espondilodiscite associada à osteomielite (um caso - 6,3%). As idades variaram de quatro a 67 anos com mediana de 43,5. Todos os pacientes, com exceção de um, tinham testes sorológicos positivos para IgG anti fase II, associado ou não a IgM anti fase II, compatíveis com infecção aguda. Um paciente tinha tanto anticorpos IgG anti fase I quanto anti fase II compatíveis com febre Q crônica. Soroconversão foi detectada em 10 pacientes. A despeito das conhecidas limitações do diagnóstico sorológico os casos aqui relatados devem encorajar os médicos brasileiros a incluir a febre Q como causa nativa de doença febril neste país a ser pesquisada.

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