Long term vascular complications of *Coxiella burnetii* infection in Switzerland: cohort study

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Abstract

Objective To evaluate the range of long term vascular manifestations of *Coxiella burnetii* infection.
Design Cohort study in Switzerland of people affected in 1983 by the largest reported outbreak of Q fever and who were followed up 12 years later. Follow up information about possible vascular disease and endocarditis was obtained through a mailed questionnaire and death certificates.
Setting Val de Bagnes, a rural Alpine valley in Switzerland.
Participants 2044 (87%) of 2355 people who had serum testing for *Coxiella burnetii* infection in 1983: 1247 were classed as not having been infected, 411 were classed as having been acutely infected, and 386 were classed as having been infected before 1983.
Main outcome measures Relative risk controlled for age and sex and 12 year risk of vascular diseases and endocarditis among infected participants as compared with those who had never been infected.
Results The 12 year risk of endocarditis or venous thromboembolic disease was not increased among those who had been acutely infected. The 12 year risk of arterial disease was significantly higher among those who had been acutely infected (7%) as compared with those who had never been infected (4%) (relative risk 2.2, 95% confidence interval 1.4 to 3.6). Specifically, there was an increased risk of developing a cerebrovascular accident (relative risk 3.7, 1.6 to 8.4) and cardiac ischaemia (relative risk 1.9, 1.04 to 3.4). 12 year mortality was significantly higher among the 411 people who had been acutely infected in 1983 (9.7%; age adjusted relative risk 1.8, 1.2 to 2.6) when compared with the 1247 participants who had remained serologically negative in 1983 (7.0%).
Conclusions *Coxiella burnetii* infection may cause long term complications including vascular disease.

Introduction

Infectious agents that have been implicated as possible causes of atherosclerosis include herpesviruses[1] (mainly cytomegalovirus),[2] *Chlamydia pneumoniae*,[3–7] and *Helicobacter pylori*, which is less likely to be a cause.[8–12] It is important in understanding the connection between infection and atherosclerosis to determine whether arterial disease can result from inflammatory syndromes provoked by bacteria or viruses or whether infectious atherogenesis is specific to these agents.[13]

Coxiella burnetii is a plausible candidate since infection with this organism results in chronic infections of the heart valve and aortic grafts. It most commonly causes endocarditis.[14–17] Moreover, *C burnetii* belongs to the family of rickettsiae, as do the organisms that cause typhus. Rickettsiae were used in 1889 to successfully induce fatty sclerotic changes after inflicting slight mechanical injury to the arterial wall of the aorta of a rabbit.[18]

We have been able to study late (12 year) manifestations of infection with *C burnetii* in residents of Val de Bagnes, Switzerland, where the largest outbreak of Q fever occurred in 1983.[19]

Participants and methods

Study design and data collection

The study was confined to the six villages most affected by the outbreak of Q fever in Val de Bagnes. The results of serological testing from 1983 were available for 2355 people living in these villages.[19] Information on heart diseases, vascular disease, drug treatment, and symptoms of cardiovascular disease was obtained using a mailed, self administered questionnaire; assistance in completing the questionnaire or in clarifying the answers was provided by a participant's personal doctor if needed. By 1995, 208 people had died. The cause of death and any associated diseases were obtained from the Federal Statistics Office for 182 (88%) people; the rate of postmortem examinations in Switzerland is about 20%. A total of 285 participants were lost to follow up. We were thus able to obtain relevant follow up information on 87% (2044/2355) of the potential cohort.

Definition of exposure

In 1983, serological testing for infection with *C burnetii* was done with complement fixation and immunofluorescent antibody tests.[20] A fourfold or higher increase in titre between two serum samples, or a titre ⩾1:20 in specific IgM was considered diagnostic of acute *C burnetii* infection.[21] A titre ⩾1:20 in specific antiphase II IgG, without IgM, was considered diagnostic of an infection occurring before 1983. People classed as ever infected included those who were acutely infected and those who had been previously infected.

Definition of outcomes

The outcomes of interest were: endocarditis, venous thrombosis, cardiac ischaemia, cerebrovascular accident, arteriopathy of the lower extremities, and aortic dissection. Patients with cardiac ischaemia, cerebrovascular accident, arteriopathy of the lower extremities, or aortic dissection were classed as having arterial disease. A case was identified if the diagnosis was listed as a cause of death or as an associated disease on the death certificate, or cited as a medical problem in the questionnaire. In addition, questions about drug treatment and symptoms characteristic of a diagnosis were used to identify possible cases.

Data analysis

Data from all 2044 participants were used in the analysis of the association between *C burnetii* infection and various outcomes without regard to time sequence; analysis of 12 year risk (1983-95) was confined to the 1658 participants who were either acutely infected

(IgM positive) or not infected (negative IgG and IgM) in 1983. The 11 participants with any arterial disease diagnosed before 1983 were not considered to be at risk because a later disease event could have been caused by the same chronic pathology. Participants were not excluded if they had a history of endocarditis or venous thrombosis because a second episode occurring after 1983 could be unrelated to the first and not caused by progression of the disease. Because endocarditis can occur at any age, results are presented for data from the full sample. All analyses were also performed on a restricted sample of participants who were older than 25. Results in the restricted sample were virtually identical to those presented here.

Results

Characteristics of the 2044 participants included in the analysis are shown in table 1. Serological evidence of infection with *C burnetii* occurring before 1983 was more prevalent among those aged 50 and older (table 2). The 12 year risk of death was higher among participants who had been acutely infected compared with participants who had not been infected (adjusted relative risk 1.8, 95% confidence interval 1.2 to 2.6).

Infection and vascular disease

Of the 2044 participants, 18 had ever had endocarditis, 105 had ever had thromboembolic disease, and 117 had ever had arterial disease (table 1). The relative odds of ever having endocarditis were calculated using logistic regression while controlling for sex and age as a continuous variable. The relative odds were not higher among those who had ever been infected with *C burnetii* (7/797, 0.9%) when compared with people who had never been infected (11/1247, 0.9%); the relative odds adjusted for age and sex were 1.3 (95% confidence interval 0.5 to 3.4). Similarly, the relative odds were not significantly higher for thromboembolism (45/797 (5.6%) *v* 60/1247 (4.8%); adjusted relative odds 0.9, 0.6 to 1.4) or for arterial disease (61/797 (7.7%) *v* 56/1247 (4.5%); adjusted relative odds 1.3, 0.9 to 1.9).

12 year risk of vascular disease

Among the cohort of 1658 people who had been acutely infected or had never been infected, 12 cases of endocarditis and 45 cases of venous thrombosis occurred during follow up. The 12 year risk and the relative risk of endocarditis and of venous thromboembolism in participants who had been acutely infected as compared with participants who had never been infected is shown in table 3.

Among the cohort of 1647 people, which excluded those who had previously been infected and who had had an arterial disease diagnosed before 1983, 75 had one or more arterial diseases: 50 had cardiac ischaemia, 22 had had a cerebrovascular accident, 8 had arteriopathy of the lower limbs, and 5 had had aortic dissection. Table 4 shows that the risk of arterial disease, specifically cerebrovascular accident and cardiac ischaemia, was significantly higher among participants who had been infected with *C burnetii*.

Results were not stratified by sex because of the small number of participants and because exploratory analysis did not indicate that risks differed between men and women.

Table 1 Characteristics of people tested for serological evidence of *Coxiella burnetii* infection after an outbreak of Q fever in Val de Bagnes, Switzerland, 1983. Values are numbers (percentages) unless otherwise indicated

	All participants (n=2044)	Never infected (n=1247)	Acutely infected (n=411)	Previously infected (n=386)
Mean (SD) age in 1983	36 (21)	34 (21)	33 (19)	47 (19)
Male sex	1050 (51)	602 (48)	244 (59)	204 (53)
Dead at follow up in 1995	182 (8.9)	87 (7.0)	40 (9.7)	55 (14.3)
Developed:				
Endocarditis	18 (0.9)	11 (0.9)	3 (0.7)	4 (1)
Venous thromboembolism	105 (5.1)	60 (4.8)	20 (4.9)	25 (6.5)
Arterial disease	117 (5.7)	56 (4.5)	30 (7.3)	31 (8)

Table 2 Serological evidence of *Coxiella burnetii* infection in 1983 among 2044 residents of Val de Bagnes, Switzerland, by age

	Age (years)		
	<30	30-49	⩾50
Never infected	614	331	302
Acutely infected	200	126	85
Previously infected	85	114	187

Table 3 12 year risk and adjusted relative risk between 1983 and 1995 of developing endocarditis or venous thromboembolism by *Coxiella burnetii* infection among 1658 residents of Val de Bagnes, Switzerland*

	Never infected (n=1247)		Acutely infected (n=411)		Relative risk (95% CI)†
	No of cases	Risk (%)	No of cases	Risk (%)	
Endocarditis	9	0.7	3	0.7	1.0 (0.9 to 1.1)
Venous thromboembolism	30	2	15	4	1.8 (0.9 to 3.8)‡

*People with serological evidence of infection with *Coxiella burnetii* occurring before 1983 were excluded from this analysis. †Relative risk adjusted for age in 1983 and sex using Cox proportional hazard models. ‡P=0.10.

Table 4 12 year risk and adjusted relative risk of developing arteriovascular disease by *Coxiella burnetii* infection among 1647 residents of Val de Bagnes, Switzerland*

	Never infected (n=1238)		Acutely infected (n=409)		Relative risk (95% CI)†
	No of cases	Risk (%)	No of cases	Risk (%)	
Arterial disease‡:	47	4	28	7	2.2 (1.4 to 3.6)
Cerebrovascular accident	11	1	11	3	3.7 (1.6 to 8.4)
Cardiac ischaemia	33	3	17	4	1.9 (1.04 to 3.4)§
Arteriopathy	7	0.6	1	0.2	0.4 (0.1 to 3.5)
Aortic dissection	3	0.2	2	0.5	2.3 (0.4 to 13.9)

*People with serological evidence of infection with *Coxiella burnetii* occurring before 1983 were excluded as were those who had had an arterial disease diagnosed before 1983.
† Adjusted for age and sex using Cox proportional hazard models.
‡The sum of the individual arterial diagnoses is greater than the total number of participants with arterial disease because 10 people had more than one type of arteriovascular event. §P=0.04.

Discussion

This study found an increased 12 year risk of cerebrovascular accident and cardiac ischaemia and poorer survival from all causes in participants who had had Q fever. There was no association between Q fever infection and venous thromboembolism.

Although we did not find an increased risk of endocarditis among participants who had been infected, our results are consistent with the less than 1% long term risk for endocarditis postulated to occur after Q fever.[22] We cannot rule out the possibilities that our follow up period was insufficient to detect late cases (some cases have been documented as occurring as long as 20 years after infection[23]), that our study population was too young,[24] or that the strain of *C burnetii* involved in this outbreak was only weakly associated with chronic illness.[25–28]

Key messages

- The risk of developing venous or arterial disease after infection with *Coxiella burnetii* was assessed in a Swiss cohort of 2044 people exposed to the largest reported outbreak of Q fever
- Twelve year mortality was significantly higher among people who had been acutely infected in 1983
- The 12 year risk of arterial disease was significantly higher among those who had been acutely infected (7%) than among those who had not been infected (4%)
- Compared with those participants who tested negative, those who were acutely infected with *C burnetii* had an increased relative risk of having a cerebrovascular accident or cardiac ischaemia
- Infection with *C burnetii* may be responsible for the development of vascular diseases in addition to infection with *Chlamydia pneumoniae*, cytomegalovirus, and *Helicobacter pylori*

Infection with *C burnetii* was assessed only in 1983. People who tested negative for infection in 1983 may have become infected later since the disease is endemic in this area. The resulting misclassification of exposure status would have tended to obscure any real associations; our analysis defined a few participants as not infected who later became infected and whose risk of vascular disease may therefore have increased.

We did not observe an increased risk of vascular diseases in participants infected with *C burnetii* before 1983. However, this group may have a survival bias: some patients may have become sick or died as a result of being infected with *C burnetii* before 1983.

Information on established risk factors for vascular diseases had not been collected during the baseline survey in 1983. However, acute infection with *C burnetii* is transmitted by inhalation of aerosolised spores, consumption of contaminated milk or meat, or contact with infected blood.[29] These modes of transmission are unlikely to be associated with risk factors for cardiovascular disease. Moreover, the increased risk of developing arterial diseases, which was observed in other cohort studies of cytomegalovirus infection or *Chlamydia pneumoniae* infection, persisted after adjustment for risk factors for cardiovascular diseases.[2 4]

These results add evidence to the current research on the role of bacterial infections in causing vascular disease. Infection with *C burnetii* may also be a cause of arterial disease. It remains to be determined whether the organism has a non-specific inflammatory effect or whether, because *C burnetii* is a strictly intracellular pathogen capable of persisting and reappearing after a latency period, it has a unique mode of damaging the arterial wall.[30]

The results of this study were presented at the 31st annual meeting of the Society for Epidemiologic Research in Chicago, IL, June 1998.

Contributors: P-YL contributed to the conception of the study, designed the questionnaire, collected and validated the data, participated in the analysis and interpretation of the data, and wrote the paper. AM contributed to designing the study, conceived and supervised the analyses, presented the results, reviewed the paper, and rewrote sections of the paper. DB analysed the data, contributed to the writing of the first draft with P-YL, prepared the tables, and reviewed the final manuscript. OP and GD contributed to the conception and design of the study, collected data, performed the serological analysis in 1983, and helped revise the paper. JP initiated the project, discussed core ideas, participated in the design of the study, and revised the final paper. P-YL and AM will act as guarantors for the paper.

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