Lithium-ion capacitor safety assessment under electrical abuse tests based on ultrasound characterization and cell opening

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The sexual dimorphism of anticardiolipin autoantibodies in acute Q fever patients

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Abstract

Objectives : Q fever is a zoonotic disease caused by *C. burnetii* which affects men more than women (sex ratio men/women: 2.2). Acute Q fever complications are associated with elevation of anticardiolipin (aCL) antibodies. Here, we investigate the sexual dimorphism of aCL antibodies during acute *C. burnetii* infection.

Methods : IgG aCL antibodies were evaluated at the time of Q fever serological diagnosis with enzyme-linked immunosorbent assay. Results were analysed according to sex.

Results : Among the 1,323 patients with Q fever tested for aCL, 1,013 had acute Q fever (692 men/321 women) and 310 had persistent focalized infection (226 men/84 women). In case of acute Q fever, men presented a significantly higher proportion of positive aCL antibodies (351/692, 50.7%) than women (113/321, 35.2%) ($p<0.05$). In addition, men had significantly higher aCL antibodies levels than women ($p<0.0001$).

Conclusions : We highlight a relationship between sex and markers of autoimmunity during Q fever. Further investigations are necessary to better understand the mechanisms of this sexual dimorphism.

Key words: Q fever, *Coxiella burnetii*, anticardiolipin antibodies, sex, gender, autoimmunity

Introduction

Viral and bacterial infections have been reported to be associated with autoimmune clinico-biological manifestations [1]. The elevation of anticardiolipin (aCL) antibodies has been described in cases of human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, malaria, syphilis, leprosy, leptospirosis and Q fever [2]. In case of Q fever, the elevation of aCL antibodies has recently been reported as predictive for acute Q fever complications, such as acute Q fever endocarditis, haemophagocytic syndrome, alithiasic cholecystitis and thrombosis [3,4]. Interestingly, an unbalanced sex ratio has been described during *C. burnetii* infection, the disease affecting men more frequently than women (sex ratio men/women: 2.2). Here, we investigated the sexual dimorphism of autoantibodies during *C. burnetii* infection with a specific focus on aCL antibodies.

Methods

Between 1991 and 2016, 2,434 patients with *C. burnetii* infection were followed in the French national reference centre for Q fever. Acute Q fever was diagnosed by the association of acute clinical symptoms (fever, hepatitis and/or pneumonia) with the following serologic criteria: IgG titers representing phase II (200) and IgM titers representing phase II (50) or seroconversion within 3 months of the primary symptoms [5]. Persistent *C. burnetii* infection was defined by the persistence of clinical symptoms for more than 3 months in addition to a positive microbiological criteria and to the identification of an infectious focus [5].

1,323 patients were tested for IgG aCL antibodies assessed by enzyme-linked immunosorbent assay at first serological diagnosis. A cut-off threshold of 22 IgG anti-phospholipid-binding units (GPLU) was used to define positive samples.

The study was approved by the local ethics committee of the IHU (Institut Hospitalo-Universitaire)-Méditerranée Infection under the registration number 12-016 [4].

Statistical analyses were performed using Prism 6.0 (Graphpad Software Inc.) and SPSS 22 Statistics Software. Multivariate models were adjusted for sex and age at baseline [4]. P<0.05 was considered as significant.

Results

Among the 1,323 patients tested for aCL antibodies, 1,013 patients had acute Q fever and 310 had persistent *C. burnetii* focalized infection (Figure 1). Nine hundred and eighteen patients were men (sex ratio men/women: 2.26). The sexual dimorphism was more pronounced in cases of persistent focalized *C. burnetii* infection (sex ratio: 2.27) than in cases of acute Q fever (sex ratio: 2.16) (p=0.07). Eighty four patients with acute Q fever evolved towards a persistent *C. burnetii* infection, 70 were men (83.3%), 14 were women (16.7%), and the sex ratio was 5.

The aCL antibodies levels were significantly higher in cases of acute Q fever (mean 88.2 ± 14 GPLU and median 18 GPLU) than in cases of persistent *C. burnetii* infection (mean 14.2 ± 2.4 GPLU and median 7 GPLU) (Figure 2A, p<0.0001). In addition, the proportion of positive aCL antibodies were significantly higher in cases of acute Q fever (464/1,013, 45.8%) than in cases of persistent *C. burnetii* infection (32/310, 10.3%) (p<0.05). In cases of acute Q fever, men had significantly higher aCL antibodies levels (mean 113.3 ± 20.3 GPLU and median 24 GPLU) than women (mean 50 ± 7 GPLU and median 11 GPLU) (Figure 2B, p<0.0001) and men presented a significantly higher proportion of positive aCL antibodies (351/692, 50.7%) compared to women (113/321, 35.2%) (p<0.05) for all age groups (Figure 2C). In men, higher levels of aCL antibodies were observed in almost all age groups (Figure 2D). Being a male was associated with a significant risk of positive aCL antibodies, regardless of age (OR=1.6; [95% CI, 1.3-3.2], p<0.001) [4].

Acute Q fever hepatitis affected men more than women (p=0.007) and was associated with a significant increase in aCL in men (p=0.047). In case of acute Q fever, being male was a risk factor for acute Q fever to progress to persistent cardiovascular *C. burnetii* infection (OR=2.14; [95% CI, 1.17-3.91], p=0.013).

Discussion

Here, we report that aCL antibody levels are higher in men than in women with acute *C. burnetii* infection. This is distinct from the sexual dimorphism observed in the antiphospholipid syndrome (APS), in which women are more affected by the disease than men (sex ratio men/women: 1:5) [6]. In addition, the aCL antibodies sexual dimorphism observed in association with *C. burnetii* infection is different from that observed in association with HIV infection, in which aCL antibodies are described as significantly higher in women compared to men [7].

Our data support the possibility of a hormonal influence on the expression of autoantibodies in case of *C. burnetii* infection. It is known that women are described to be more prone to autoimmune diseases than men, and this increased susceptibility disappears after menopause [8]. A positive correlation has been shown between elevated aCL antibodies levels and high estradiol serum concentration in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis [9,10]. In addition, hyper-oestrogenic levels in premenopausal SLE women are associated with an increased risk of APS and cardiovascular manifestations [9]. In gonadoctemized or intact non-autoimmune male and female C57BL/6 mice, oestrogen treatment induces the expression of aCL autoantibodies [11]. It has been hypothetized that oestrogens act as enhancers of cell proliferation and stimulate humoral B cell response [12].

In addition, the influence of testosterone should not be neglected. While oestrogen increases the autoantibody production, androgens decrease it [12]. Men with hypogonadism

are at risk of developing autoimmune diseases of which the Klinefelter syndrome is a glaring example. This syndrome has been associated with SLE, progressive systemic sclerosis, polymyositis, mixed connective tissue disease and with an increased frequency of aCL antibody positivity [13]. Testosterone deficiency may promote autoantibody formation, however, in cases of *C. burnetii* infection, testosterone rather appears to favour aCL autoantibodies production [4].

Other mechanisms such as chromosomal influence could be involved. In transgenic SJL mice, the XX sex chromosome was compared with XY, and showed greater susceptibility to autoimmune encephalomyelitis and SLE [14]. Women with Turner's syndrome were at significantly increased risk of autoimmune thyroid diseases and type 1 diabetes mellitus [15].

As limitations of this study, we have no data on patient's hormonal serum levels, we have not studied the chromosomal influence on autoantibody secretion and we did not consider the gender impact, i.e. gender-related social habits that could influence the results.

In conclusion, we highlight a relationship between sex and markers of autoimmunity during Q fever. We noted that acute Q fever induces a higher autoimmune response in men compared to women. However, the mechanisms of sexual dimorphism are multifactorial and although age was taken into account, other factors such as hormone levels and chromosomal impact should be included in future analyses.

Transparency declaration

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Figure 1. Study Flowchart

Figure 2. (**A**) aCL antibodies levels in patients with acute Q fever and persistent *C. burnetii* focalized infection. (**B**) aCL antibodies levels in acute Q fever according to the sex of patients. (**C**) Percentage of patients with positive aCL antibodies in acute Q fever patients according to the age of patients in men and women. (**D**) aCL antibodies levels in acute Q fever patients according to the age of patients in men and women. The results are expressed as mean for each age group. Mann-Whitney U test were used *p<0.05, ****p<0.0001