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

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17 **Abstract**

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

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

24 **Results :** Among the 1,323 patients with Q fever tested for aCL, 1,013 had acute Q fever (692
25 men/321 women) and 310 had persistent focalized infection (226 men/84 women). In case of
26 acute Q fever, men presented a significantly higher proportion of positive aCL antibodies
27 (351/692, 50.7%) than women (113/321, 35.2%) ($p < 0.05$). In addition, men had significantly
28 higher aCL antibodies levels than women ($p < 0.0001$).

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

32

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

34

35 **Introduction**

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

46

47 **Methods**

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

55 1,323 patients were tested for IgG aCL antibodies assessed by enzyme-linked immunosorbent
56 assay at first serological diagnosis. A cut-off threshold of 22 IgG anti-phospholipid-binding
57 units (GPLU) was used to define positive samples.

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

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

63

64 **Results**

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

72 The aCL antibodies levels were significantly higher in cases of acute Q fever (mean 88.2 ± 14
73 GPLU and median 18 GPLU) than in cases of persistent *C. burnetii* infection (mean $14.2 \pm$
74 2.4 GPLU and median 7 GPLU) (Figure 2A, $p < 0.0001$). In addition, the proportion of
75 positive aCL antibodies were significantly higher in cases of acute Q fever (464/1,013,
76 45.8%) than in cases of persistent *C. burnetii* infection (32/310, 10.3%) ($p < 0.05$). In cases of
77 acute Q fever, men had significantly higher aCL antibodies levels (mean 113.3 ± 20.3 GPLU
78 and median 24 GPLU) than women (mean 50 ± 7 GPLU and median 11 GPLU) (Figure 2B,
79 $p < 0.0001$) and men presented a significantly higher proportion of positive aCL antibodies
80 (351/692, 50.7%) compared to women (113/321, 35.2%) ($p < 0.05$) for all age groups (Figure
81 2C). In men, higher levels of aCL antibodies were observed in almost all age groups (Figure
82 2D). Being a male was associated with a significant risk of positive aCL antibodies,
83 regardless of age (OR=1.6; [95% CI, 1.3-3.2], $p < 0.001$) [4].

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

88

89 **Discussion**

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

97 Our data support the possibility of a hormonal influence on the expression of
98 autoantibodies in case of *C. burnetii* infection. It is known that women are described to be
99 more prone to autoimmune diseases than men, and this increased susceptibility disappears
100 after menopause [8]. A positive correlation has been shown between elevated aCL antibodies
101 levels and high estradiol serum concentration in patients with systemic lupus erythematosus
102 (SLE) and rheumatoid arthritis [9,10]. In addition, hyper-oestrogenic levels in premenopausal
103 SLE women are associated with an increased risk of APS and cardiovascular manifestations
104 [9]. In gonadectomized or intact non-autoimmune male and female C57BL/6 mice, oestrogen
105 treatment induces the expression of aCL autoantibodies [11]. It has been hypothesized that
106 oestrogens act as enhancers of cell proliferation and stimulate humoral B cell response [12].

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

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

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

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

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

127

128 **Transparency declaration**

129

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131 **No relationship with industry**

132 **No conflict of interest**

133

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141

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- 186

187 **Figure 1.** Study Flowchart

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

194