Detailed analysis of health status of Q fever patients 1 year after the first Dutch outbreak: a case–control study

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Summary

Background: Q fever is a zoonosis caused by the obligate intracellular bacterium Coxiella burnetii. The two long-term complications, after primary infection, are chronic Q fever in ~1% of patients, and a chronic fatigue syndrome in 10–20%. However, the existence of a protracted decreased health status after Q fever remains controversial.

Aim: To determine the health status of the patients of the Q fever outbreak in The Netherlands in 2007, 1 year after primary infection.

Design: Cross-sectional case–control study.

Methods: Health status of the patients from the 2007 Dutch Q fever outbreak was compared to age-, sex- and geographically matched and Q fever seronegative controls. Health status of both patients and controls was assessed with the Nijmegen Clinical Screening Instrument (NCSI).

Results: Fifty-four Q fever patients provided 34 years of age- and sex-matched controls from the same neighbourhood. Eleven controls had positive Q fever serology and were excluded. Q fever patients had significantly more problems on the subdomains of symptoms and functional impairment. Overall quality of life was decreased in both patients and controls, 59% vs. 39%, respectively, ns). Severe fatigue levels were present in 52% of patients vs. 26% in controls (P < 0.05).

Conclusion: These data support a sustained decrease in many aspects of health status in Q fever patients in The Netherlands, 1 year after primary infection.

Introduction

Q fever is a zoonosis caused by the obligate intracellular bacterium Coxiella burnetii. In its acute form, Q fever generally presents as a mild flu-like syndrome, atypical pneumonia or hepatitis. After primary infection, ~1% of patients develop chronic Q fever, mainly as endocarditis in patients with pre-existing cardiac valvulopathies. In recent years, research groups have drawn attention to another, less known, chronic sequel to primary Q fever, which takes the form of a debilitating chronic fatigue syndrome lasting >6 months in up to circa 20% of patients. However, despite these
reports on post Q fever fatigue, the existence of a ‘post Q fever fatigue syndrome’ or QFS as a distinct clinicopathological entity remains controversial, especially in France and the USA.\(^1\),\(^10\) In 2007, a goat farming-related Q fever outbreak of 73 cases was identified in the rural town of Herpen, the Netherlands.\(^1\) Since then, an ongoing Q fever epidemic has produced the Dutch province of North-Brabant as the currently most hyperendemic region in the world with more than 3000 acute Q fever cases in 2008 and 2009.\(^12\),\(^13\) No data exist on the impact on the long-term impact on health status after acute Q fever in The Netherlands. The aim of the present study was to determine the health status of the patients of the Q fever outbreak in The Netherlands in 2007, 1 year after primary Q fever infection.

**Methods**

**Patients**

All patients from the Q fever outbreak cluster in Herpen (\(n = 73\)) were asked to participate. A case of acute Q fever was defined as any inhabitant of the outbreak cluster area who presented with compatible clinical symptoms and a positive serology defined by immunofluorescence assay (IFA) (Focus diagnostics). Positive serology was defined as both anti-phase II IgM and anti-phase II IgG antibodies with a 1:64 or greater dilution or a seroconversion consisting of a 4-fold increase of anti-Phase II IgG titer during follow-up. All Q fever patients were followed up serologically for a period of 1 year for antibodies against both Phases I and II antigens, to exclude progression to chronic infection. As controls, Q fever patients were asked to bring along an age- and sex-matched control subject from their neighbourhood without a history of Q fever. Control subjects had to be age (\(\pm 10\) years) and sex matched to the patient. Control subjects were serologically tested for \(C.\) burnetii antibodies using IFA. Positive serological findings of Q fever excluded controls from the primary analysis. Documentation on actual significant comorbidity was available for all participants. All patients provided written informed consent. The study was approved by the local Ethical Board for Human Research. (Commissie Mensgebonden Onderzoek file-nr.: 2008/192, ABR nr.: NL24404.091.08).

**Study design**

The health status of the patients from the 2007 Q fever outbreak was compared to age-, sex- and geographically matched controls. Health status of both patients and controls was assessed with the Nijmegen Clinical Screening Instrument (NCSI) 1 year after the initial Q fever infection.

**The NCSI**

In the literature, health status is defined as covering physiological functioning, symptoms, functional impairment in daily life and quality of life (QoL) as main domains.\(^14\),\(^15\) These domains were shown empirically to be subdivided into many independent subdomains.\(^16\) The NCSI is an empirically composed battery of well validated instruments that enable a detailed measurement of these subdomains of health status.\(^17\) See Table 1 for the tests and instruments by which the subdomains of health status were measured. In the present study, the NCSI covers eight subdomains of the main domains ‘symptoms’, ‘functional impairment’ and ‘quality of life’. The clinical meaning of these main domains is given hereafter.

**Main domain subjective symptoms**

The subdomain subjective symptoms represent the patient’s overall burden of dyspnea and experienced dyspnea during activities. The subdomain Dyspnea Emotions embodies the level of frustration and anxiety a person experiences when dyspnoeic.

**Main domain functional impairment**

The subdomain behavioural impairment represents the extent to which a person cannot perform specific and concrete activities, with respect to ambulation and activities at home, as a result of having the disease. The subdomain subjective impairment represents the experienced degree of impairment.

**Main domain QoL**

The subdomain general QoL covers mood and satisfaction with life as a whole. The subdomain HRQoL represents satisfaction with physical functioning and confidence in the future. The subdomain satisfaction relations represents the satisfaction with (or absence of) the relationships with spouse and others.

The NCSI provides normative data for each subdomain; increasing scores indicating normal functioning, mild problems or severe problems.

**Statistical analysis**

All quantitative data are presented as mean ± SE if normally distributed, otherwise median values (with range) are reported. Testing for differences between patients and controls was performed by Pearson’s \(x^2\) or Mann–Whitney test when appropriate.
Statistical significance is set at a $P < 0.05$. Data were analyzed with SPSS 14.

**Results**

A total of 54 of the 73 (74%) Q fever patients from the 2007 Herpen outbreak agreed to participate. Thirty-four of these patients provided an age- and sex-matched control from the same neighbourhood. Eleven of these controls had positive Q fever serology and were excluded, leaving 23 seronegative controls for comparison. Characteristics of the study and seronegative control subjects are given in Table 2. Patients and controls proved to be well matched for age, sex, pre-existing comorbidity and smoking status. Results on the subdomains of the NCSI on a group level are provided in Table 3. Q fever patients had significantly higher scores on all subdomains of ‘symptoms’ (subjective pulmonary symptoms, dyspnea emotions, fatigue), ‘functional impairment’ (subjective impairment, behavioural impairment) and ‘satisfaction with relations’. With respect to the main domain ‘quality of life’, there was a non-significant trend towards more problematic (i.e. higher) scores on the subdomains ‘general quality of life’ ($P = 0.09$) and ‘health-related quality of life’ ($P = 0.073$). In Figure 1, results are presented on an individual level by the percentages of patients and controls scoring in the range of normal, mild or severe problems. Fatigue scores of Q fever patients were abnormal (score: mild or severe) in 74% vs. 48% in controls. Severe fatigue levels were present in 52% of patients vs. 26% in controls. Overall QoL was decreased in a substantial number of patients and controls, but not significantly different between the two groups (Q fever patients 59% vs. controls 39%, ns). In Figure 2, the percentage of patients and controls (y-axis) is given as a function of the number of subdomains in which these patients and controls experience severe problems (x-axis). In addition to the primary data analysis, we compared NCSI scores of the excluded seropositive controls ($n = 11$) with the scores of seronegative control subjects ($n = 23$). The NCSI scores of seropositive and seronegative controls were not statistically different in all eight measured subdomains of health status ($P > 0.05$ for all subdomains).

**Discussion**

One year after primary infection, Q fever patients from the 2007 Herpen outbreak had a significantly lower health status in many subdomains of the main
domains ‘symptoms’ and ‘functional impairment’, when compared to age-, sex- and geographically matched controls. Overall QoL and health-related QoL were significantly decreased in both patients and controls. Furthermore, on an individual level, patients had severe problems in more subdomains than controls. Our findings lend support to the notion of a protracted reconvalescence phase after Q fever associated with decreased health status in many aspects.

We found remarkably high clinically relevant (=severe) fatigue levels in roughly half (52%) of the Q fever patients 1 year after infection. In two separate case–control studies published as letters, the editor in the Lancet in 1996, Marmion et al.\textsuperscript{4} and Ayres et al.\textsuperscript{5} reported a syndrome of protracted fatigue and debility in Q fever patients for >5 years after primary infection with similar fatigue levels [67% (n = 39) and 66% (n = 71) respectively]. Five- and 10-year follow-up of the large Q fever outbreak in the West Midlands, UK, also showed similar levels of chronic fatigue.\textsuperscript{6,7} Dubbed the post Q fever fatigue syndrome (QFS), this protracted fatigue state shares common features with the chronic fatigue syndromes following other (viral) pathogens such as Epstein–Barr virus and Ross River virus.\textsuperscript{9}

Although there was a significantly higher fatigue level in Q fever patients, the abnormally high-fatigue level and low overall QoL and health-related QoL of the control group is striking. We postulate two explanations for this. First, the level of

### Table 3 NCSI scores on all subdomains (the higher the score, the more problematic) (Mann–Whitney test)

<table>
<thead>
<tr>
<th>Main domain</th>
<th>Subdomain</th>
<th>Minimum–maximum</th>
<th>Patient Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Subjective symptoms</td>
<td>2–20</td>
<td>7.26 (4.85)</td>
<td>4.57 (4.92)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Dyspnea emotions</td>
<td>6–24</td>
<td>9.85 (4.36)</td>
<td>7.39 (3.16)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>8–56</td>
<td>34.35 (13.87)</td>
<td>23.87 (14.08)</td>
<td>0.004</td>
</tr>
<tr>
<td>Functional impairment</td>
<td>Behavioral impairment</td>
<td>0–135.5</td>
<td>8.21 (11.65)</td>
<td>3.13 (6.37)</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td>Subjective impairment</td>
<td>4–28</td>
<td>9.70 (5.55)</td>
<td>6.00 (3.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quality of life</td>
<td>General QoL</td>
<td>1–101.6</td>
<td>19.52 (17.84)</td>
<td>11.96 (9.98)</td>
<td>Ns</td>
</tr>
<tr>
<td></td>
<td>HRQoL</td>
<td>2–10</td>
<td>4.26 (2.04)</td>
<td>3.35 (1.40)</td>
<td>Ns</td>
</tr>
<tr>
<td></td>
<td>Satisfaction relations</td>
<td>2–10</td>
<td>3.72 (2.08)</td>
<td>2.70 (1.29)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Ns = not significant.

![Figure 1. Percentages of mild and severe problems for each subdomain of the NCSI for the patient and control group (*P < 0.05).](image-url)
co-morbidity in this study is ~40%, which could partly account for the overall high scores on the NCSI subdomains. Second, the original normal values for NCSI subdomain scores were derived from healthy control subjects with normal pulmonary function tests. As these tests were not available in the present study and given the significant smoking history equally present in patients and controls, undocumented pre-existing pulmonary morbidity may also have increased NCSI subdomain scores in both groups.

Remarkably, NCSI scores from controls without a clinical history of Q fever but with serological evidence of exposure to C. burnetii (and thus excluded from the primary analysis), were not statistically different from seronegative controls, suggesting that clinical expression of acute Q fever infection is an essential factor in the subsequent sustained decrease in health status. Severity of initial illness previously indeed has been shown to be the best predictor of subsequent development of a post-infective fatigue syndrome in both viral and non-viral pathogens, including Q fever.9 Moreover, the same genetic polymorphisms in cytokine genes with critical roles in the inflammatory response to infection, underpin both the severity of the acute sickness and the average time to recovery across varied infections, including Q fever.19

There are obvious difficulties with the credibility of QFS as a distinct clinico-pathological entity, as confounding factors such as financial compensation or insurance benefits following the acute sickness can be held responsible for the symptomatology and associated reduced QoL. However, both the West Midlands outbreak mentioned earlier and the currently described Dutch outbreak were non-occupational and no litigation for financial compensation was pursued. A QFS diagnosis relies solely on the patient’s own account of symptoms. In clinical practice, QFS patients remain indistinguishable from patients with a complete recovery after primary infection with C. burnetii, as they do not meet the criteria for chronic Q fever infection; anti-phase I IgG titers are less than 800 and appropriate cultures of the patients blood or tissues show no viable bacteria. Recently, an elegant new paradigm of persistence of Coxiella antigenic non-viable cell residues after primary infection in interaction with immunogenetic polymorphisms in the host has been put forward to better explain the chronic sequelae of acute Q fever, including QFS.20 The importance of genetic host factors in QFS is supported by research done by Kerr et al.21,22 in the UK. They found significant differences in expression of 88 human genes, notably with a high proportion of genes involved in the immune response and infection, between patients with idiopathic chronic fatigue syndrome and normal controls. Remarkably, QFS patients were found to have similar patterns of gene expression to patients with idiopathic chronic fatigue syndrome.

Although our data support a decrease in many aspects of health status in many Q fever patients, some considerations have to be taken into account. First of all, patient numbers are small. However, Q fever patients were optimally matched including serological testing in the controls. Furthermore, despite the small numbers, a statistically significant difference was found in six of the eight tested subdomains of the NCSI, supporting the notion of a rather large difference in health status between patients and controls. Second, the NCSI has proved to be a useful tool in assessing health status for use in research and care, but has mostly been applied in COPD patients. We used the NCSI in the setting of post-infectious health status assessment for the first time. Nevertheless, the various (parts of) questionnaires used to compile the NCSI function in their original and unaltered form. These generic questionnaires are not specified to assess only pulmonary disease and assess the different subdomains of health status in the exact same way these

![Figure 2. Frequency distribution of numbers of subdomains with severe problems in patients and controls.](image-url)
In conclusion, these data support a sustained decrease in health status in Q fever patients in The Netherlands, 1 year after primary infection. With more than 3000 new Q fever patients in the last 2 years in the setting of the ongoing Dutch Q fever epidemic, these are the first clinical data indicating a major long-term burden of the disease in the years to come.

Conflict of interest: None declared.

References