Correlation Between Acute and Chronic Inflammatory States, a Case Control Study

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Abstract

Fever is the hallmark of efficient acute inflammatory response, which may be disrupted in chronic inflammatory conditions. “The Continuum Theory” proposes that the return of acute inflammatory states with high fever herald improvement in chronic diseases during treatment. Our objective was to investigate if a correlation exists between chronic inflammation and efficient acute inflammation.

In a case control study, the reports of patients diagnosed with chronic inflammatory conditions with at least 6 months of follow up under homeopathic treatment were retrospectively sampled from homeopathic medical practitioners from Greece, India, Romania, and Russia. 20 patients who improved under homeopathic treatment and 20 age matched controls of those who did not improve were selected. The occurrence of common acute infectious diseases with fever during the follow up period was investigated.

The Odds Ratio of improving with respect to development of acute infectious diseases was calculated and graphs were plotted to study the pattern in each case.

The average age of the cases and controls was 28.4 and 27.9 years respectively. 18/20 cases and 4/20 controls developed common infectious diseases with fever respectively. Odds Ratio of improving with respect to development of acute infectious diseases was 36 (95%, CI: 5.7973 to 223.5513), z statistic: 3.846 (p = 0.0001).

In this case control study, appearance of common acute infectious diseases with fever was strongly associated with improvement in the chronic inflammatory conditions.

Background

Fever, a non-specific response, is a cardinal feature of acute inflammation (1). Immunological studies have demonstrated the necessity and the importance of fever in efficient acute inflammatory response against pathogens (2). Many studies indicate that the initial response, including fever are necessary for the downstream resolution to occur as well (3–6). In states of compromised immunity or when the acute inflammation is excessive or deficient, the fever component seems to be missing or downplayed (7–11). Many times, hypothermia seems to be the defensive response in such cases (12). Vithoulkas et al. proposed the continuum theory, where they recapitulate the importance of high fever as a hallmark of an efficient immune system and go further to propose the absence or downplaying of this reaction as a sign of chronic inflammatory disease (13). They also state that when chronic diseases begin to improve under homeopathic treatment, the return of simple acute diseases with high fever is a favourable prognostic indicator. This implies the return of the ability to mount an efficient inflammatory response by the organism, which they claim is lost during chronic inflammatory state. This phenomenon was earlier observed in cases under homeopathic treatment (14, 15). Many other studies have reported the absence of fever associated with chronic inflammatory diseases such as multiple sclerosis and cancer (16–18).
Based on these studies and theories, we hypothesised that chronic inflammatory disease is associated with reduction in occurrence of common infectious diseases with fever, and a return of such infection and fever during treatment heralds improvement in the chronic disease.

Our objective was to investigate if there is a correlation between chronic inflammatory state and ability to mount an efficient acute inflammatory response and whether improvement in chronic inflammatory state is associated with increase in efficient acute inflammatory response with fever.

**Methods**

We designed a case control study, involving case records from multiple homeopathic medical practices, including 3 centres in India, 2 in Russia and one each in Greece and Romania. Cases were defined as patients diagnosed of chronic inflammatory diseases, who had improved considerably under homeopathic treatment with at least 6 months of follow up. Age matched controls were selected from patients with chronic inflammatory diseases, who had not improved with homeopathic treatment with at least 6 months’ follow up.

We collected data regarding the age, sex, main diagnosis, comorbidities, follow up period, improvement status in the chronic condition, measure used to assess improvement, occurrence of any acute infectious diseases during follow up with details regarding fever temperature for each of the cases and controls.

Statistical analysis: We drafted graph for severity of disease, assessed either by standardised measures or clinical signs and symptoms as applicable, against the occurrence of common acute infectious diseases during the follow up period. We also calculated the odds ratio for occurrence of common acute infections with fever and improvement in the chronic inflammatory disease.

**Results**

The Table 1 provides the characteristics of participants, both cases and controls. The detailed data of individual cases is available at the data repository.

The average age of the cases and controls were 28.4 and 27.9 years respectively. Among cases improving under homeopathic treatment, 18/20 patients had common infectious diseases with fever during the follow up period, while 4/20 patients among the controls developed common infectious diseases with fever (Fig. 1). The odds ratio for acute infectious disease with fever occurrence in correlation with improvement in the chronic disease was 36 (95%, CI: 5.7973 to 223.5513), z statistic: 3.846 and significance level was p = 0.0001.

The graphs for individual cases were plotted for clinical presentation at follow ups and occurrence of acute infections. The graphs showed a distinct pattern of improvement in the chronic condition following any acute infections with fever (Fig. 2 and Fig. 3). These are presented in detail as supplementary material.
Discussion

Our hypothesis was that chronic inflammatory condition precludes the ability to mount an efficient acute inflammatory response characterised by high fever, and that the return of such an ability is associated with improvement in the chronic condition. The results of this case control study add evidence to this hypothesis. Many studies have indicated that the susceptibility to common pathogens is associated with a healthier immune system than those susceptible to opportunistic and resistant pathogens (20–22). They also indicate that healthy immune systems are capable of mounting a robust response to neutralise the pathogen and re-establish tissue harmony (9). Compromised immune systems are not capable of such a reaction. There may be reduced or aggressive response, causing increased viral load and hyper inflammation, which may even lead to death of the host, the evidence to which was abundant during the pandemic of COVID 19. It was seen that people with chronic inflammatory diseases tended to react aggressively, causing a cytokine storm, detrimental to the host (23–26). However, this wasn’t the case in most people who did not have chronic diseases. Wrotek and colleagues have proposed and investigated the idea that the ability to raise fever is dependent on the glutathione level in the tissues. They demonstrate that higher and lower glutathione, implying minimal and excessive oxidative stress in the body respectively, are associated with no fever generation during acute inflammation. It is only in the moderate levels of glutathione that the organism is capable of producing fever (27, 28). Therefore, in a chronically inflamed system, with excessive oxidative stress with altered glutathione levels (29), one may not appreciate the development of fever during infections. However, with the resolution of the chronic inflammation, this ability may return (14, 15). Our intention was to investigate this immunological finding at the level of clinical cases. We found that the chronic inflammatory disease patients were able to put up acute inflammatory response with fever only around the time they showed clinical improvement in their chronic condition. The cases that did not improve, rarely showed any acute inflammatory response with fever. This phenomenon was visually impressive on graphs (supplementary material).

This brings to the fore, a pertinent question that needs deeper scientific investigation to guide clinical practice. What is the role of acute inflammatory response in preserving the efficiency of the immune system? And whether we are compromising the efficiency by tampering with the acute response during infections. Many investigators have asked the same question especially in the context of resolution of inflammation (30). The process of acute inflammation is a tightly orchestrated one and many factors that are activated in the initial part, including the cytokines, cox and lox enzymes have a role to play later in resolving the inflammation and establishing homeostasis (2–5, 31, 32). Fever, especially, has been shown to be necessary for all these components to be activated and the question is raised whether interrupting with febrile response inadvertently hampers resolution, perpetuating chronic inflammation (2, 32). With this study, we were able to appreciate the association of resolution of chronic inflammation with the return of the ability to raise fever and acute inflammatory response. However, whether the opposite is true, that the loss of acute inflammatory response ability is a sign of development of chronic inflammation, remains to be investigated.
There are a few limitations in our study. Our study was a small one, as the inclusion criteria and the details available in the records made selection of participants stringent. We did not consider one single chronic disease as the number of cases would be even more restricted in niche practices such as the homeopathic. Further, we acknowledge that there may be a selection bias as the patients were only from homeopathic medical practices. It would be interesting to see if patients improving under conventional medicine also presented this pattern. This study was a preliminary exploration into this pattern of exclusivity of acute and chronic inflammatory conditions and generalisability is limited as the study does not have sufficient power. However, this study indicates that the correlation between acute and chronic inflammation needs to be investigated further with sufficiently powered studies to inform clinical practice and policy making.

Conclusions

In this case control study, occurrence of common acute infectious diseases with fever was strongly associated with improvement in the chronic inflammatory disease. This correlation between acute and chronic inflammatory conditions requires investigations with larger studies to be established.

Declarations

Funding: Nil

Conflicts of interest: authors declare there are none.

Availability of data and material: The datasets generated and/or analysed during the current study are available in the Figshare repository, accessible at: https://doi.org/10.6084/m9.figshare.16912573.v1

Code availability: Not applicable

Authors' contributions: SM, MM, VV, VS, ES, NK, DC, DT, LJ and AJ were the primary physicians. They collected and analysed the data, SM wrote the manuscript and obtained the references. GV is the approver and guarantor of the work.

Ethics approval: All experiments were performed in accordance with Helsinki declaration. Informed oral consent was obtained from patients at the time of treatment. The scientific committee consisting of representatives of International Academy of Classical Homeopathy Alonissos, Greece and Centre For Classical Homeopathy Bangalore, India deemed a separate ethical approval as not necessary as the dataset was anonymised with no individual recognisable information whatsoever.

Consent to participate: Not applicable.

Consent for publication: Informed oral consent was obtained during the time of treatment.
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References


Table 1

Table 1. Characteristics of participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Average age</td>
<td>28.4 years</td>
<td>27.9 years</td>
</tr>
<tr>
<td>Males: Females</td>
<td>8:12</td>
<td>10:10</td>
</tr>
<tr>
<td>Improvement status</td>
<td>Improved</td>
<td>Not improved</td>
</tr>
<tr>
<td>Common acute infections during follow up</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Fever during infection</td>
<td>18</td>
<td>4</td>
</tr>
</tbody>
</table>

Figures
Figure 1

Comparison of occurrence of common acute infections with fever during follow ups of Cases and Controls.
(Cases improved considerably under homeopathic treatment in their chronic inflammatory diseases and Controls did not.)
Figure 2

Examples of graphical representation of Cases’ follow up
Fig. 3. Examples of graphical representation of Controls’ follow up

Figure 3

Examples of graphical representation of Controls’ follow up

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterialcasesandcontrolsgraphs.pdf