




Association between Acute and Chronic Inflammatory States: A Case-Control Study

Seema Mahesh¹ Mahesh Mallappa¹ Vitalie Vacaras² Viraj Shah³ Elena Serzhantova⁴
Nadezhda Kubasheva⁵ Dmitriy Chabanov⁴ Dionysios Tsintzas⁶ Latika Jaggi⁷ Atul Jaggi⁷
George Vithoulkas⁸

¹ Centre for Classical Homeopathy, Bangalore, Karnataka, India

² Department of Neurosciences, “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania

³ Shah Homeopathic Clinic, Vastrapur, Ahmedabad, India

⁴ Novosibirsk Centre of Classical Homeopathy, Novosibirsk, Russia

⁵ Clinic of Nadezhda Kubasheva, Moscow, Russia

⁶ Department of Orthopaedics, General Hospital of Aitolokarnania, Agrinion, Greece

⁷ H3 Centre of Classical Homeopathy, Nashik, Maharashtra, India

⁸ Department of Homeopathy, University of the Aegean, Syros, Greece

Address for correspondence Seema Mahesh, MD, Centre for Classical Homeopathy, No 10, 6th Cross Road, Chandra Layout, Vijayanagar, Bangalore 560040, Karnataka, India
(e-mail: bhatseema@hotmail.com; cfchmahesh@gmail.com).

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Abstract

Background 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 predicts improvement in chronic diseases during treatment. Our objective was to investigate the observation made, during classical homeopathic treatment, that such an association exists between chronic inflammation and efficient acute inflammation.

Methods 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 practices from Greece, India, Romania and Russia. Twenty 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.

Results The average age of the cases and controls was 28.4 (SD: 16.64) and 27.9 (SD: 17.19) years respectively. 18/20 cases and 4/20 controls developed common infectious diseases with fever. Cramer’s V co-efficient value was found to be 0.551 ($p < 0.01$), indicating that improvement was more in patients with fever than without. Odds ratio of improving with respect to development of acute infectious diseases was 36.0 (95% CI: 5.8 to 223.5). The binary logistic regression model indicated significant contribution of occurrence of acute infections with fever as a predictor for improvement in chronic inflammatory disease.

Keywords

- ▶ inflammation
- ▶ fever
- ▶ homeopathy

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Conclusions Classical homeopathic clinical observations indicate an association between chronic inflammatory status in the body and the ability to mount efficient acute inflammation. In this case-control study, the occurrence of common infections with fever during treatment heralded improvement in chronic inflammatory disease. Further powered studies are necessary to substantiate this finding.

Introduction

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, is necessary for the downstream resolution to occur.³⁻⁶ In states of compromised immunity, or when acute inflammation is excessive or deficient, the fever component seems to be missing or downplayed.⁷⁻¹¹ Often, hypothermia seems to be a defensive response in such cases.¹² 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 both 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 at moderate levels of glutathione that the organism is capable of producing fever.^{13,14} Therefore, in a chronically inflamed system experiencing excessive oxidative stress with altered glutathione levels,¹⁵ fever may not develop during infections. However, with the resolution of chronic inflammation, this ability may return.¹⁶⁻¹⁸

Vithoulkas and Carlino proposed the “continuum theory”, where they emphasise the importance of high fever as the hallmark of an efficient immune system. They propose the absence or downplaying of this reaction as a sign of chronic inflammatory disease.¹⁹ They also state that when chronic diseases begin to improve under homeopathic treatment, the return of simple acute diseases with high fever is a favorable prognostic indicator. This implies a return of the ability to mount an efficient inflammatory response, which they claim is lost during chronic inflammatory state.

This phenomenon was indeed observed in cases under homeopathic treatment.^{16,17} In a case series involving atopic dermatitis under homeopathic treatment, the skin clearance was strongly associated with reappearance of acute infections with fever, which had been absent since the onset of atopic dermatitis. The controls (atopic dermatitis cases not responding to homeopathy) showed no occurrence of acute infections with fever.¹⁶ Further, in a case of anti-neutrophil cytoplasmic antibodies-negative glomerulonephritis, the patient was able to stop dialysis under homeopathic therapy. This improvement was associated with return of respiratory infection with fever, which was absent since the onset of renal failure.¹⁷ A detailed exposition of a juvenile rheumatoid arthritis case with 17 years' follow-up showed that the patient had recurrent acute infections typical of childhood before the onset of rheumatoid

arthritis. The timeline shows absence of any such acute diseases with fever until the patient started to improve under individualised classical homeopathy. There was no relapse in the long follow-up period.¹⁸ Some other previously published studies have reported the absence of fever associated with chronic inflammatory diseases such as multiple sclerosis and cancer.²⁰⁻²²

Based on these studies and theories, we intended to investigate this immunological finding at the level of clinical cases: that the onset of chronic inflammatory disease is associated with reduction in occurrence of common infectious diseases with fever. We hypothesised that a return of such infection and fever during treatment heralds improvement in the chronic disease.

The objective of this study was to investigate if such an association exists between chronic inflammatory state (chronic disease) and the ability to mount an efficient acute inflammatory response during infections, and whether improvement in chronic inflammatory state (chronic disease) is associated with increase in efficient acute inflammatory response with fever, as observed during classical homeopathic practice thus far.

Methods

We designed a case-control study, involving case records from multiple homeopathic medical practices, including three centres in India, two in Russia and one each in Greece and Romania. ‘Cases’ were defined as patients diagnosed of chronic inflammatory diseases, who had improved considerably compared with first intake assessment (as per clinical assessment or laboratory/radiological reports, as the case may be) under homeopathic treatment with at least 6 months of follow-up. From the same clinical database, patients diagnosed with chronic inflammatory diseases and who did not respond to homeopathic treatment, with at least 6 months follow-up, were separately sorted by age. From this latter list, an age-matched control was randomly selected for each of 20 improved cases from the respective age range.

The inclusion criteria were broad because the previous studies observed this phenomenon in most chronic inflammatory diseases. The included cases were deep chronic inflammatory diseases (neuropsychiatric, musculoskeletal, rheumatic, hormonal and metabolic disorders/diseases) with improvement status measured either by respective laboratory or radiological reports or, as in most cases, clinically through symptom severity and the general condition of the patient.

We collected data regarding the age, sex, main diagnosis, co-morbidities, follow-up period, improvement status of the

chronic condition, and occurrence of any acute infectious diseases during follow-up, with details regarding high temperature for each of the cases and controls.

Statistical Analysis

The odds ratio was calculated to study the association of occurrence of common acute infections with fever and improvement in the chronic inflammatory disease (though this should not be interpreted as a causal factor for the return of acute infections). Correlational statistics were performed for the same association, and a binary logistic regression model was developed to check the contribution of acute infections with fever to the improvement status in chronic inflammatory disease.

Ethics

The original study was approved by the Centre for Classical Homeopathy's Research Ethics Committee, Bengaluru, India, with waiver of patient consent. The approval number is PP/AS/01/19-20. The later smaller study from the same data, as reported in the present paper, did not require additional ethical approval.

Results

Data were collected from 40 patients, with 20 cases and 20 controls. The primary variable of focus was the status of improvement of the patients in relation to the occurrence of acute infections with fever during the follow-up period.

The characteristics of cases and controls are provided in ► **Table 1**. The mean age of the cases and controls was 28.4 (standard deviation [SD]: 16.64) and 27.9 (SD: 17.19) years respectively. The mean age of the total sample was 28.15 years (SD: 16.76).

In comparing improvement and non-improvement with respect to the occurrence of fever and non-occurrence of fever (► **Table 2**), it was seen that of the 20 patients who we selected as showing improvement, 90% ($N=18$) had fever during the follow-up period, whereas 10% ($N=2$) did not develop fever. With respect to the patients in the control group, 80% ($N=16$) had no fever and only 20% ($N=4$) had fever. The Pearson chi-square value was found to be significant (19.798; $p < 0.01$), indicating observation of fever differed significantly across improvement and non-improvement.

The odds ratio for improvement with the occurrence of acute infections with fever was calculated and was found to be 36.0 (95% confidence interval [CI]: 5.8 to 223.5), indicating a strong association between improvement in chronic inflammatory states and return of acute infections with fever.

Correlational statistics were calculated for the status of improvement of the patients and the occurrence of acute infections with fever during follow-up (► **Supplementary Table S1**, available online only). Cramer's V co-efficient value was found to be 0.551 ($p < 0.01$), indicating that there exists a significant moderate positive relationship between the status of improvement and observation of fever during follow-up. This implies that improvement was slightly more among patients with fever than the patients without fever.

Table 1 Characteristics of participants

Characteristics	Cases	Controls
Number of patients	20	20
Mean age	28.4 y (SD: 16.64)	27.9 y (SD: 17.19)
Males: Females	8:12	10:10
Improvement status	Improved	Not improved
Common acute infections during follow-up	18	4
Fever during infection	18	4

Abbreviation: SD, standard deviation.

Table 2 Cross-tabulation between improvement status and occurrence of fever during follow-up

Improvement status	Fever occurrence during follow-up		Total
	Occurrence	Non-occurrence	
Not improved	4 (20%) Residual = -2.1	16 (80%) Residual = 2.3	20 (100%)
Improved	18 (90%) Residual = 2.1	2 (10%) Residual = -2.3	20 (100%)
Total ($N=40$)	22 (55%)	18 (45%)	40 (100%)
Pearson chi square	Value = 19.798	df = 1	$p < 0.01$

Note: Cross-tabulations of two levels of improvement (not improved and improved) against two levels of observations of fever during the follow-up (occurrence and non-occurrence). The Pearson chi-square value is found to be significant (value = 19.798; $p < 0.01$) indicating that the distribution of cases is significantly different across improvement status and observation of fever. df, degree of freedom.

A binary logistic regression model was performed, with the improvement status as the dependent variable and the occurrence of acute infection with fever as a predictor (– **Supplementary Table S2**, available online only). The Cox and Snell R-square value was found to be 0.424, and the Nagelkerke R-square value was found to be 0.565, indicating that 42.4% to 56.6% variation in the improvement status can be explained by observations of fever.

The overall percentage accuracy in the classification of improvement status after the addition of fever as the explanatory variable was found to be 85%, which is higher compared with the expected 50% from the null model (– **Supplementary Table S3**, available online only).

Discussion

Observations from classical homeopathic practice were the basis for our hypothesis. We investigated if chronic inflammatory disease is associated with reduction in occurrence of common infectious diseases with fever, and if a return of such infection and fever during treatment indicated improvement in the said chronic disease. The results of this case-control study add evidence in support of this hypothesis. Previously published studies have indicated that susceptibility to common pathogens is associated with a healthier immune system than those susceptible to opportunistic and resistant pathogens.^{23–26} 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, recent evidence for which was abundant during the pandemic of coronavirus disease 2019. It was seen that people with chronic inflammatory diseases tended to react aggressively, causing a cytokine storm, detrimental to the host.^{27–29} However, this was not the case in most people who did not have chronic diseases. This is in keeping with the findings by Wrotek and colleagues: that it is in the range of moderate oxidative stress (measured by the amount of glutathione) that the organism raises fever. They found that in an environment of excessive oxidative stress, as in chronic inflammatory disease, fever is detrimental to the host and the tendency is to not raise a fever.^{13,14} Hypothermia as a defense mechanism is favoured by the organism in such a case.^{12–14}

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 raises 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 are we 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 cytokines and the 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 febrile response inadvertently hampers resolution, perpetuating chronic inflammation.^{2,32} With this study, we are able to strengthen the association between the resolution of chronic inflammation and the return of 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 to our study, the main one being the lack of disease matching between cases and controls. The cases were mostly rare neuropsychiatric/musculoskeletal disorders, whose match was difficult to find as controls. Therefore, we included chronic inflammatory diseases in age-matched patients as controls. This may affect the response interpretation to some extent. However, the objective was a very broad one, including all chronic inflammation as the main phenomenon and its association with efficient acute inflammation. Therefore, the bias arising out of lack of disease match is negligible. 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 since the number of cases would be even more restricted in niche practices such as homeopathy. Further, we acknowledge that there may be a selection bias, as the patients were from homeopathic medical practices only. It would be interesting to see if patients improving under conventional medicine also presented this pattern.

This study is 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, our findings provide strong grounds to investigate this association between acute and chronic inflammation further, to inform clinical practice and policy making.

Conclusions

The classical homeopathic clinical observation that there exists an association between the chronic inflammatory status in the body and the ability to mount an acute inflammatory defense with high fever during common infections was investigated. In this case-control study, a return of common infections with fever during treatment heralded improvement in the chronic inflammatory disease. Confirmation of this association between acute and chronic inflammatory conditions will require investigations with larger sample size.

Highlights

- 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 heralds improvement in chronic diseases during treatment.

- In a case-control study, patients diagnosed with chronic inflammatory diseases with at least 6 months of follow-up under homeopathic treatment were retrospectively sampled.
- 20 patients who improved under homeopathic treatment and 20 age-matched controls of those who did not improve were investigated for occurrence of common acute infectious diseases with fever.
- The odds ratio of improving with respect to development of acute infectious diseases was calculated and correlational analysis was performed. A binary logistic regression model was also developed to understand the occurrence of fever as a predictor of improvement.
- In this case-control study, appearance of common acute infectious diseases with fever during follow-up under individualised homeopathic treatment was associated with improvement in the chronic inflammatory condition.

Preprint

Initial ethical clearance for data collection was for a larger retrospective analysis of a clinical database including 11,800 cases, as described in a preprint publication: <https://doi.org/10.22541/au.160269741.18547290/v1>

The present study utilised data from the above repository for a different study design (case-control study) and its preprint is available online: <https://doi.org/10.21203/rs.3.rs-2083679/v1>, posted on November 22nd, 2022. The later alteration to the study's data analysis did not require specific additional ethical approval. Changes made to the current manuscript compared with the preprint were as follows: The title was changed from "Correlation" to "Association" between Acute and Chronic Inflammatory States, a Case-control Study. The abstract is structured and the homeopathic paradigm was added to the hypothesis. Further clarification on inclusion/exclusion criteria, including clarity on the meaning of "chronic inflammatory state", was added. Ethical clearance statements were clarified to reflect the nature of the original approval. The graphs in the Results section of the 20 cases and controls were removed as they did not add to the understanding of the findings. Statistical analysis was enhanced, along with the calculation of odds ratio, Pearson's chi square was calculated and correlational statistical analysis was performed. A binary logistic regression model was also developed and described in Results. The context of homeopathy was added to conclusions.

Supplementary Material

Supplementary Table S1. Correlation between status of improvement and occurrence of acute infections with fever during follow-up.

Supplementary Table S2. Model summary.

Supplementary Table S3. Classification table.

Availability of Data and Material

The datasets generated and/or analysed during the current study may be requested by writing to the authors.

Authors' Contributions

S.M., M.M., V.V., V.S., E.S., N.K., D.C., D.T., L.J., and A.J. were the primary physicians who collected and analysed the data. S.M. wrote the manuscript and attended to the referencing. G.V. is the approver and guarantor of the work. All authors read the final version of the manuscript and approved its submission to the journal.

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Conflicts of Interest

None declared.

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References

- 1 Rather LJ. Disturbance of function (functio laesa): the legendary fifth cardinal sign of inflammation, added by Galen to the four cardinal signs of Celsus. *Bull N Y Acad Med* 1971;47:303–322
- 2 Evans SS, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: the immune system feels the heat. *Nat Rev Immunol* 2015;15:335–349
- 3 Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. *Nat Immunol* 2005;6:1191–1197
- 4 Panigrahy D, Gilligan MM, Huang S, et al. Inflammation resolution: a dual-pronged approach to averting cytokine storms in COVID-19? *Cancer Metastasis Rev* 2020;39:337–340
- 5 Serhan CN. Treating inflammation and infection in the 21st century: new hints from decoding resolution mediators and mechanisms. *FASEB J* 2017;31:1273–1288
- 6 Blatteis CM. Fever: pathological or physiological, injurious or beneficial? *J Therm Biol* 2003;28:1–13
- 7 Shimazui T, Nakada TA, Walley KR, et al. Significance of body temperature in elderly patients with sepsis. *Crit Care* 2020;24:387
- 8 Martín S, Pérez A, Aldecoa C. Sepsis and immunosenescence in the elderly patient: a review. *Front Med (Lausanne)* 2017;4:20
- 9 Wrotek S, LeGrand EK, Dzialuk A, Alcock J. Let fever do its job: the meaning of fever in the pandemic era. *Evol Med Public Health* 2020;9:26–35
- 10 Bhavani SV, Huang ES, Verhoef PA, Churpek MM. Novel temperature trajectory subphenotypes in COVID-19. *Chest* 2020;158:2436–2439
- 11 Smith BJ, Price DJ, Johnson D, et al. Influenza with and without fever: clinical predictors and impact on outcomes in patients requiring hospitalization. *Open Forum Infect Dis* 2020;7:ofaa268
- 12 Liu E, Lewis K, Al-Saffar H, et al. Naturally occurring hypothermia is more advantageous than fever in severe forms of lipopolysaccharide- and Escherichia coli-induced systemic inflammation. *Am J Physiol Regul Integr Comp Physiol* 2012;302:R1372–R1383
- 13 Wrotek S, Sobocińska J, Kozłowski HM, Pawlikowska M, Jędrzejewski T, Dzialuk A. New insights into the role of glutathione in the mechanism of fever. *Int J Mol Sci* 2020;21:1393
- 14 Wrotek S, Jędrzejewski T, Nowakowska A, Kozak W. Glutathione deficiency attenuates endotoxin fever in rats. *Int J Hyperthermia* 2015;31:793–799

- 15 Perricone C, De Carolis C, Perricone R. Glutathione: a key player in autoimmunity. *Autoimmun Rev* 2009;8:697–701
- 16 Mahesh S, Mallappa M, Habchi O, et al. Appearance of acute inflammatory state indicates improvement in atopic dermatitis cases under classical homeopathic treatment: a case series. *Clin Med Insights Case Rep* 2021;14:1179547621994103
- 17 Mahesh S, Jaggi L, Jaggi A, Tsintzas D, Vithoukias G. Individualised homeopathic therapy in ANCA-negative rapidly progressive necrotising crescentic glomerulonephritis with severe renal insufficiency—a case report. *J Med Life* 2019;12:49–55
- 18 Chabanov D, Tsintzas D, Vithoukias G. Levels of health theory with the example of a case of juvenile rheumatoid arthritis. *J Evid Based Integr Med* 2018;23:X18777995
- 19 Vithoukias G, Carlino S. The “continuum” of a unified theory of diseases. *Med Sci Monit* 2010;16:SR7–SR15
- 20 Wrotek S, Kamecki K, Kwiatkowski S, Kozak W. Cancer patients report a history of fewer fevers during infections than healthy controls. *J Pre Clin Res* 2009;3:31–35
- 21 Donati D. Viral infections and multiple sclerosis. *Drug Discov Today Dis Models* 2020;32:27–33
- 22 Mastrangelo G, Fadda E, Milan G. Cancer increased after a reduction of infections in the first half of this century in Italy: etiologic and preventive implications. *Eur J Epidemiol* 1998;14:749–754
- 23 Witkin SS, Linhares I, Giraldo P, Jeremias J, Ledger WJ. Individual immunity and susceptibility to female genital tract infection. *Am J Obstet Gynecol* 2000;183:252–256
- 24 Luebke RW, Parks C, Luster MI. Suppression of immune function and susceptibility to infections in humans: association of immune function with clinical disease. *J Immunotoxicol* 2004;1:15–24
- 25 Pana ZD, Farmaki E, Roilides E. Host genetics and opportunistic fungal infections. *Clin Microbiol Infect* 2014;20:1254–1264
- 26 Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? *Aging (Albany NY)* 2020;12:9959–9981
- 27 Bajaj V, Gadi N, Spihlman AP, Wu SC, Choi CH, Moulton VR. Aging, immunity, and COVID-19: how age influences the host immune response to coronavirus infections? *Front Physiol* 2021;11:571416
- 28 Schmitt BD, Offit PA. Could fever improve COVID-19 outcomes? *Contemp Pediatr* 2020;37:8–9
- 29 Chiappetta S, Sharma AM, Bottino V, Stier C. COVID-19 and the role of chronic inflammation in patients with obesity. *Int J Obes* 2020;44:1790–1792
- 30 Rajakariar R, Yaqoob MM, Gilroy DW. COX-2 in inflammation and resolution. *Mol Interv* 2006;6:199–207
- 31 Wang X, Ni L, Wan S, et al. Febrile temperature critically controls the differentiation and pathogenicity of T helper 17 cells. *Immunity* 2020;52:328–341.e5
- 32 Fisher DT, Vardam TD, Muhitch JB, Evans SS. Fine-tuning immune surveillance by fever-range thermal stress. *Immunol Res* 2010;46:177–188