REVIEW ARTICLE

WHEN QUARTAN FEVER RELIEVED DEPRESSION: THE INCEPTION OF PYRETOTHERAPY IN THE GRECO-ROMAN ANTIQUITY

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Christos Tsagkaris[1], Ivan Romash[2], Oksana Kukhta[2], Rehab A. Rayan[3], Vasyl Neyko[2], Marios Papadakis[4], Constantinos Trompoukis[5]

[1]UNIVERSITY OF CRETE, FACULTY OF MEDICINE, HERACLION, GREECE
[2]IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE
[3]HIGH INSTITUTE OF PUBLIC HEALTH, ALEXANDRIA, EGYPT
[4]UNIVERSITY WITTEN-HERDECKE, WUPPERTAL, GERMANY
[5]DEPARTMENT OF HISTORY OF MEDICINE, UNIVERSITY OF IOANNINA, IOANNINA, GREECE

ABSTRACT

The aim: This paper explores the documentation of the effect of quartan fever on, the ancient Greek equivalent of conditions falling nowadays under the spectrum of depression, in Greco-Roman medical sources.

Materials and methods: The authors searched original medical texts written in Greek by physicians who lived and practiced Medicine in the broader Mediterranean region from the 5th century BC to the 7th century AD for records related to quartan fever and neuropsychiatric diseases.

Conclusions: Quartan fever was used as a treatment for neuropsychiatric conditions until the middle of the 20th century. Although malaria can have severe neuropsychiatric sequelae, the neuroimmunological underpinnings of the effect of fever and heat on depression warrant further investigation.

KEY WORDS: Depression, mental health, malaria, quartan fever, fever, Hippocrates, Galen, Oribasius, Stephanus

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INTRODUCTION

Ancient Greek and Roman physicians had limited knowledge about the anatomy, the physiology and the pathophysiology of the nervous system. Their understanding of neurological and psychiatric conditions was based on the humoral theory, a cosmological and philosophical model that defined human health (eucrasia) as an equilibrium of four distinct humors, blood, phlegm, yellow and black bile. Diseases were associated with an increase in or a deficit of one or more humors (dyscrasia). The names of the definitions of mental disorders would frequently reflect the hypothesized pathophysiology. For instance, cholericus, literally derived from yellow bile, was used to describe aggressive behaviors and depression spectrum disorders were coined as melancholia implying an increased concentration (plethora) of black (melaena) bile (cholḗ) [1]. With the quantitative analogy of humors being unique for each person (idiosyncrasia), sadness, fear and behaviors associated with negligence and withdrawal from social activities would indicate that the individual acceptable threshold of black bile was surpassed and the person suffered from melancholy [1, 2].

In this frame the treatment of melancholia was challenging. Etiological treatment would necessitate a reinstatement of the humoral equilibrium. This would be achieved with bloodletting, medical herbs, change of nutrition or change of residence [3]. Nevertheless, due to the apparent lack of a widely effective treatment, ancient physicians would resort to the keen observation of patients with melancholia in their effort to identify factors that caused, exacerbated or relieved the disease. Notably, infection and particularly fever was also considered as a factor capable of alleviating or even treating melancholia.

THE AIM

This paper presents excerpts from ancient Greek and Roman medical treatises describing the beneficial effects of fever on melancholia. The authors further discuss the reception of fever and high temperatures as treatment modalities in psychiatry during the 20th century and nowadays.

MATERIALS AND METHODS

The authors searched original medical texts written in Greek by physicians who lived and practiced Medicine in the broader Mediterranean region and Greco-Roman culture from the 5th century BC to the 7th century AD. The search focused on excerpts including possible references to melancholia and the effect of infection and fever in the course of the disease. The selection of authors was made on the following criteria: 1) the recognition of the authors' credibility and scientific integrity by their peers at that time; 2) the survival of the whole or the greatest part of their work, enabling

contemporary researchers to reach safe conclusions about the range of conditions that they studied; 3) the medical orientation and focus of these authors' treatises – texts related to philosophy, theology and arts were not examined; and, 4) the location of their activities at successive chronological order during the above mentioned period and region. Citations were taken from respected modern editions that are easily available in well-stocked libraries, some of which also include translations of the original Greek text into modern European languages, for those who wish to read further.

REVIEW AND DISCUSSION

Passages documenting the effect of infection and fever on melancholia have been detected in the works of Hippocrates (c. 460 – 370 AD), Galen (c. 129 – 216 AD), Oribasius of Pergamon (c. 325 – 403 AD) and Stephanus of Athens (c. 540–680 AD).

Hippocrates appears to be the first to touch upon the matter in his treatises De morbis popularibus (About Infectious Diseases) and Aphorisms. Although he does not refer specifically to melancholia, he states that quartan fever (*τεταρταῖος*) not only has a favorable prognosis, but is also capable of curing other severe diseases [4]. In the remaining relevant passages, Hippocrates emphasizes the beneficial effect of quartan fever on the so called major or sacred disease (*μεγάλη νόσος*), a term that he frequently used to describe epilepsy. It becomes evident that in his experience people suffering from quartan fever were cured from epilepsy and related neuropsychological sequelae [5]. Moreover, it appears that a history of quartan fever significantly decreased the risk of developing seizures later [6]. Although Hippocrates did not explicitly refer to melancholia, he was the first to report the potential connection between fever and neuropsychological diseases. Subsequent medical treatises shifted the focus from epilepsy to melancholia.

Galen, commented twice on Hippocrates's views, asserting that quartan fever can result in the cure of severe diseases, while posing little to no harm to the patient [7, 8]. Galen also provided a lengthy pathophysiological interpretation of the effect on fever – induced high temperature on the black bile, the supposed causative agent of melancholia. He argued that quartan fever suppresses the black bile and helps its excretion. The latter would be further explained by Oribasius and Stephanus.

Oribasius claimed that both melancholia and quartan fever are characterized by an increased concentration of black bile. Despite this seemingly synergistic pathophysiology, he noted that quartan fever cures melancholia [9]. The interpretation of Stephanus sheds light to this paradox. An important part of Stephanus's work deals with uroscopy, the medical observation of urine and the subsequent assessment of conditions affecting the urinary tract, the kidneys and the blood, to the extent that its contents are excreted through the urine [10]. Therefore, Stephanus approached the connection between quartan fever and melancholia through the uroscopic features of these diseases. According to his account, the dark and thick composition of urine at the resolution of quartan fever implies the excretion of black bile through the urine. The subsequent reduction of the remaining black bile in the body cures melancholia [11].

Hippocrates observed and documented the curative effect of quartan fever on neuropsychiatric disorders. Galen attempted a pathophysiological explanation that shifted attention to black bile and melancholia. Oribasius and Stephanus confirmed this observation and elaborated further on its potential pathophysiology trying to strengthen the argument with clinical findings. These observations were usually transferred from physician to physician in the form of teaching. A number of physicians would also leave a written record of their experience and observations.

The written collections of Hippocrates (460 – 370 BC) and Galen (129 – 216 AD) are the most well – known sources of medical knowledge in the antiquity. The authorship of these works, each of whom included tens of books covering diagnostics, therapeutics and medical ethics, is disputed. It is believed that several unnamed physicians, disciples of major figures such as Hippocrates and Galen, attributed their treatises to the names of their mentors out of respect or seeking more visibility among their colleagues. Eminent physicians and medical writers such as Aretaios of Cappadocia (80-130 AD), Oreibasios of Pergamon (325 – 403 AD) and Aetius of Amida (mid-5th century to mid-6th century AD) further contributed to the written medical scholarship, oftentimes commenting on or comparing their findings with previous works. Therefore, it cannot be asserted whether Hippocrates and Galen or some unnamed disciples made the claims presented [12]. However, it is reasonable to assume that disciples of Hippocrates and Galen attempted to further document the teachings of these eminent physicians in their own clinical practice.

The work of Hippocrates and Galen was influential in the broader Mediterranean region and in Europe for centuries, at least until the Renaissance (15th – early 17th century AD). To the authors' best knowledge these claims were not further discussed in the accessible literature of the time, until the early 20th century. At that time, the Austrian neuropsychiatrist Wagner Jauregg reported that febrile episodes in the context of malaria could cure paralytic dementia. Jauregg, who later earned a Nobel Prize, compared several artificial methods of fever induction (malaria, tuberculin, streptococci). Artificial fever was widely used against tertiary syphilis (neurosyphilis) until the middle of the 20th century. At that point fever therapy, also known as pretotherapy or pyrotherapy, was gradually abandoned due to the increased use and effectiveness of antibiotics in treating syphilis [13, 14].

What is yet to be explained is how quartan fever, a manifestation of malaria, or malaria per se were capable of affecting the brain. Nowadays, it is established that malaria rarely poses a threat to the central nervous system. Nevertheless, cerebral malaria is one of the most severe forms of the disease leading to coma and death. Evidently Hippocrates and his disciples must have encountered uncomplicated cases of malaria before reporting quartan fever as a benign and even beneficial disease. Experience gained from epidemics of malaria during the 1st World War and the Vietnam War confirmed that cerebral malaria can cause severe neuropsychiatric symptoms and discouraged the so – called malariotherapy. The latter was solely used in patients with tertiary syphilis, because this disease was not sufficiently curable then and because these patients could receive treatment from malaria few days after the onset of the artificial disease [15]. Heat, on the other hand has a documented potential to alleviate major depression. A number of studies have initially

reported the remission of depressive symptoms during febrile episodes, while other have assessed alternative practices, such as physical activity in a heated room, as a means of treatment for major depression [16]. The same studies point the activation of the immune system as the missing link between malaria, fever, depression and neuropsychiatric disorders' treatment.

The present study is subject to a number of limitations. The authors were able to access medical literature archived in the Thesaurus Linguae Graecae database in ancient Greek. Records in Latin or other languages together with non-indexed records were not evaluated. From a historical perspective, future research should seek similar records in the Latin medical scholarship or in medical texts published in languages other than Greek and Latin, particularly after Renaissance. Folk medicine records, such as Iatrosophia, might provide relevant information from the observations of less known or non – erudite physicians [17], who tended to treat underprivileged patients oftentimes exposed to the bad conditions of life that are associated with the transmission of malaria. From a biomedical point of view, future research delving into the neuroimmunological underpinnings of depression has a major potential to translate this knowledge in treatment targets for depression, whose burden still constitutes a considerable challenge [18].

CONCLUSIONS

Quartan fever was observed to have a beneficial effect on patients with neuropsychiatric diseases for centuries. Although inducing quartan fever would be unsafe in the context of contemporary neuropsychiatry, researching further the neuroimmunological connection between heat and mental health and translating this knowledge into safe and effective therapeutic practices is worthwhile.

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ORCID and contributionship:

Christos Tsagkaris: 0000-0002-4250-574X[A,B,D]
Ivan R. Romash: 0000-0002-6591-6613[E,F]
Oksana Kukhta: 0000-0003-3533-8450[E,F]
Rehab A. Rayan: 0000-0003-3852-5710[B,F]
Vasyl E. Neyko: 0000-0002-6033-2387[E,F]
Marios Papadakis: 0000-0002-9020-874X[E,F]
Constantinos Trompoukis: 0000-0001-8723-3621[E,F]

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The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Christos Tsagkaris
University of Crete
2770 NSW, Heraclion, Greece
tel: +306980513072
e-mail: chriss20x@gmail.com

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