Letter

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Healing with malaria: a brief historical review of malariotherapy for neurosyphilis, mental disorders and other infectious diseases

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Dear Editor,

Ten years ago, two articles about malariotherapy in Chinese human immunodeficiency virus (HIV) patients once again raised ethical issues about this widely used treatment for infectious and mental diseases. Malariotherapy was born in a context where bioethics was not recognized as we do now, and evidence-based medicine was not yet established.

During the pre-penicillin era, there was no efficient treatment for syphilis. During the natural evolution of the disease, patients sometimes developed neurosyphilis 10 to 25 years after the initial infection. The most severe form of neurosyphilis is general paralysis of the insane (GPI)[1], which is fatal in almost all cases because of a progressive degeneration of the nervous system. Physically, GPI is characterized by seizures, ataxia, speech deficits and general paralysis. Mentally, it causes mania, depression, paranoia, violent behavior, delirium, memory loss, disorientation and apathy[2].

The curative effect of fevers has been reported since Hippocrates' time. The Physician of Kos wrote that during and after the intermittent fever, as malaria was then called, patients with mental insanities improved and their aggressiveness was reduced. Reports from the Middle Ages describe improvement in patients in asylums stricken by cholera. In the 15th century, Ruy Diaz de Isla was the first to report that fever had a beneficial effect on syphilis[3]. However, 350 years later, Wagner-Jauregg, the father of malariotherapy, described in detail experiments with induced fever in GPI patients.

General paralysis of the insane was the main cause of institutionalization in asylums and psychiatric hospitals from the end of 19th century until the 1940s. The prevalence of GPI at that time ranged from 10% to 45% in psychiatric hospitals worldwide[1,2].

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Julius Wagner von Jauregg (1857-1940) studied medicine in Vienna, and his interest in psychiatry, especially in psychoses[4], was soon aroused. He started his experiments with induced fever in 1894 by injecting tuberculin, erysipelas streptococci and typhoid vaccine in patients with psychoses[3]. However, in 1887, Wagner-Jauregg observed that GPI patients who had febrile diseases presented a significant improvement in their mental status. General paralysis of the insane was not a known consequence of syphilis until 1905, when Landsteiner published that high fever killed the spirochetes of syphilis, and 1913, when Hideo Noguchi demonstrated that GPI was caused by *Treponema pallidum*. Consequently, Wagner-Jauregg tested malariotherapy in GPI patients and published his findings in 1919 under the title, *On the impact of malaria on the Paralysis of the Insane*[5]. The results were encouraging: three of nine patients recovered completely, three presented a *good improvement*, two reported no changes and one died of malaria.

The news on the *efficacy* of malariotherapy in GPI spread across the world. Detailed descriptions of the experiments, protocols and adverse events can be found in several scientific articles[6,7]. An international review of 2,460 cases showed that 27.5% of patients subjected to malariotherapy showed great improvement and 25.6% presented mild improvement[5]. For a disease whose prognosis was death within 5 years, this alternative brought hope to the patients' families, and in 1927, Wagner-Jauregg won the Nobel Prize in Medicine for this discovery. He was the first and only psychiatrist to be awarded this prize[4].

Malariotherapy became a medical research area, and countless studies were carried out. Malariotherapy was used by hospitals for other mental diseases such as schizophrenia, manic-depressive psychosis, psychomotor cortical irritation syndromes, post-Parkinson's encephalitis and psychoses of epilepsy[8,9]. Hospitals continuously maintained the malaria cycle in hospitalized patients, termed source patients. Studies were made to preserve plasmodium in frozen or cooled blood samples, and hospitals established *Anopheles gambiae* farms to avoid source patients. The most suitable plasmodium was *Plasmodium vivax* due to its benign characteristic and high and regular cycles of fever that were necessary, as believed, for the treatment.

The real efficacy of malariotherapy for GPI or other mental diseases has never been analyzed under modern clinical epidemiology studies[3]. However, the dissemination of the therapy among physicians and institutions was considered a guarantee that GPI patients, who used to be sentenced to death, would present a *significant* improvement or at least live longer. On the other hand, the *primum non nocere* precept (non-maleficence) was clearly ignored because the reports of deaths caused by malaria reached 5% to 13%[1,5]. Nevertheless, it is important to highlight that at the time of Wagner-Jauregg, GPI was terrible and incurable and the notion that *desperate maladies justify desperate remedies* was an acceptable idea up to the end of the 2nd World War[4]. With the development of bioethics and the establishment of ethical parameters for research involving human beings, the principle of non-maleficence started to be considered and required.

After the introduction of penicillin, malariotherapy fell into disuse for GPI. In the early 1980s however, another *desperate malady* affected the human population: acquired immunodeficiency syndrome (AIDS) started its devastating course. Similar to what occurred with GPI, there was no available treatment and patients usually died within 2 years of the diagnosis. azidothymidine (AZT), the first medication for AIDS was approved in 1987. In spite of this and other antiviral drug advances in the following years, experiments using malariotherapy in HIV infected patients were carried out in the 1990s and 2000s in China with the participation of North American scientists and institutions.

The first study was published in 1997[10] and was titled *Malariotherapy for HIV patients*. Using data from scientific papers about malariotherapy in patients with neurosyphilis, the authors justified the method by arguing that the therapy was widely used, safe, and did not cause resistance to HIV. The authors reported an increase in the number of cluster of differentiation 4 (CD4) cells in two of eight patients after 2 years of follow-up. Two other papers reported similar results, also with Chinese patients[11,12], which included 12 and 20 patients in each study. The authors described the methodology in detail, such as the fact that the plasmodium inoculation used 10ml of heparinized whole blood from a malaria patient and that HIV patients were subjected to 10 cycles of fever. Viral load measurements, CD4 counts and plasma cytokine concentrations were presented. Because the pre-clinical or clinical evidence justifying the research was not shown, these studies are comparable to the malariotherapy studies from the beginning of the 20th century. Furthermore, it is known that HIV patients infected with plasmodium have worse outcomes compared to individuals without the co-infection.

Henry Judah Heimlich, the North American researcher who authored the first study mentioned above, had already been the object of another polemic in 1990 when he published a letter in the New England Journal of Medicine defending the use of malariotherapy in the treatment of patients with Lyme disease. In fact, in 1990 and 1991, the Morbidity and Mortality Weekly Report published two articles about cases of induced malaria in New Jersey and Texas (USA) after a group of patients with late Lyme disease went to Mexico to undergo malariotherapy.

To conclude, malariotherapy was widely used from 1917 to 1950 in the treatment of GPI and other mental diseases. Recent attempts have included the use of malariotherapy in Lyme disease and AIDS. No randomized controlled studies have been conducted to assess the true efficacy of this treatment, which is required in modern clinical epidemiology.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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