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Review Article

Malariotherapy: The Old-Renewed Immunotherapeutic Candidate for Systemic Lupus Erythematosus

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ABSTRACT

Therapeutic options for Autoimmune Diseases (ADS) are very limited with no real curable value. The etiology of this category of diseases is not clear however; environmental factors are well known to participate in the development of ADs. Infectious agents like malaria parasites have historically been positively linked with psychiatric and ADs. Jauregg J Wagner has noticed an obvious amelioration in the neurological abnormalities associated with general paralysis of the insane (GPI) when some of his patients have encounter malaria infection and subsequently the term malariotherapy has been introduced. Many years later, Greenwood has noted a lower prevalence of the autoimmune condition, rheumatoid arthritis (RA) in West Nigerian population and concluded that this low incidence may be a result of immunological modulation resulting from recurrent exposure to *Plasmodium* sp. He could also report a suppressed spontaneous autoimmune activity in BWF1 lupus mice infected with *Plasmodium berghei*. Additionally, a lower prevalence of autoimmune allergic diseases has been observed in native populations in Northern Canada compared to other populations. These results augment the immunotherapeutic value of malaria infection in ADs. The current review will focus on this therapeutic value of malarial infection both in human and experimental animal models.

Keywords: Autoimmune diseases; Hygiene hypothesis; Immunotherapy; Malaria; Malariotherapy; Psychiatric diseases

MALARIA AS A LETHAL DISEASE

Malaria is considered as one of the most dangerous life-threatening diseases that can be transmitted to human through the bites of infected female Anopheles mosquitoes [1]. According to the 2017 World Malaria Report, there were two hundred and sixteen million cases of malaria in 2016, up from two hundred and eleven million cases in 2015. This has resulted in a number of deaths reached approximately four hundred and forty-five thousand in 2016 [2]. The parasite species that are able to cause malaria infection in humans are five, and two of these species *P. falciparum* and *P. vivax* pose the greatest threat [3]. The time period between the infective mosquito bite and the appearance of symptoms in a non-immune individual, is usually ranging from ten to fifteen days. Unfortunately, early malaria symptoms like – fever, headache and chills may be misdiagnosed and subsequently delay the treatment regimen [4]. The most aggressive one, *P. falciparum* if not treated within twenty-four hours, the infection can progress to severe illness, and ultimately to death [5]. It is noteworthy that Partial immunity against malaria infection is developed over years of exposure, and despite it never provides complete protection, it can reduce the disease severity [6]. For this reason, the majority of malaria deaths in Africa occur in young children, whereas in areas with less transmission, all age groups are at equivalent grade of risk [7]. Antimalarial medicines still having a huge problem due to the drug resistance and the evolution of drug-resistant genes in malaria parasites is still challenging issue [8]. Mosquirix–is an injectable vaccine that offers partial protection against malaria infection in young children. It has been evaluated in many parts of Africa as a complementary malaria control tool that could be added to the WHO-recommended preventive and treatment measures. [9]. Indeed, the war between malaria parasites and the host immune system is multifactorial and highly sophisticated.

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That's why some chronic infections end with death and others have been abrogated. Even after the malaria recovery, Post-malaria neurological syndrome (PMNS) could arise which is a complication that has been reported after recovery from a severe *Plasmodium falciparum* attack [10]. Autoimmune haemolytic anaemia due to *P. vivax* malaria or following its treatment with artesunate was also recorded [11,12]. Hemograms from some malaria-infected patients have showed deep thrombocytopenia and macrocytic normochrome anemia [13]. Also, acute pancreatitis and subdural haematoma were presented in a patient with severe falciparum malaria [14]. Meanwhile, there is another point of view which deals with this war as a positive event from which the host can gain benefits. Surprisingly, when some patients suffering from general paralysis of the insane (GPI) or paralytic dementia have been treated with malaria, they have expressed a significant amelioration in their neurological abnormalities and hence the term malariotherapy has been introduced [15].

THE OTHER FACE: MALARIOTHERAPY OF PSYCHIATRIC DISEASES

Malaria infection was historically associated with reductions in aggressiveness of symptoms among the patients suffering from mental illness who have recurrent malaria infection [16]. The malaria-associated psychiatric effects, have introduced it as proposed therapeutic candidate in the treatment of neurosyphillis [17] a debilitating condition then is now commonly known as "general paresis of the insane" (GPI) for which no effective treatments were available [18]. According to the first published description of the practical application of the malariotherapy, for which its author has win the Nobel Prize in medicine [19], GPI patients were intentionally inoculated with the blood-stage of malaria benign forms, allowing approximately ten cycles of intermittent fever prior to treatment of the infection with available anti-malarial drugs [20]. Later on, this approach was applied on a larger number of GPI patients and pronounced improvements in psychiatric symptoms including aggression, mania, reduced irritability, psychosis, amnesia, confusion, and disorientation following this malaria treatment was reported [21,22]. Although remissions in up to a third of patients were documented by some authors [23], it still represents a surprising effect in the remaining patients. On the other hand, some reports claimed that the risk behind malaria infection may exceed the beneficial effects associated with it and the success rates are not satisfactory [24-29]. In spite of the fact that mosquito inoculation is associated with a higher risk than blood-stage inoculation, [30], the growing popularity of malariotherapy for the treatment of non-syphilitic psychiatric patients, together with the possibility of cross-contamination with Treponema pallidum, led to increasing use of direct mosquito inoculation for the purpose [31]. Indeed, the clinical outcomes of malariotherapy for neuropsychiatric disorders are controversial. Despite the results of treatment of some psychiatric disorders (including chronic "dementia praecox" or schizophrenia, as well as manic-depressive psychosis) perceived as less successful [32], a group of diseases have been also suggested to be significantly improved by applying malariotherapy [33-36]

THE CURRENT MALARIOTHERAPY FOR AUTOIMMUNE DISEASES

After the first introduction of the term malariotherapy by the Austrian psychiatrist Julius Wagner-Jauregg, there was a debate about the concept that lethal parasites could have beneficial effects to their hosts. No any attempts were done to investigate the mechanisms behind the malaria- associated neurocurable effects after Wagner innovation. At 1969, Greenwood has noticed that there is a low incidence of the autoimmune disease, rheumatoid arthritis, in western Nigeria where malaria infection is frequent [37]. Afterwards, his group has showed suppressed spontaneous autoimmune disease in BWF1 mice that have been infected with plasmodium berghei [38]. Similar results were obtained when Gerrard et al. [39] have observed a lower prevalence of allergy in native populations in Northern Canada compared to other populations. Later on, Strachan [40] has postulated what's called "Hygiene Hypothesis" according to which the increase in the autoimmune diseases (ADs) in industrialized world is directly associated with the lack of recurrent infections and the hygienic conditions in these countries. Conversely, as greenwood has noticed, low incidence of ADs is associated with poor countries where infections especially malaria are endemic [41]. Similarly, Matricardi et al. [42] have correlated exposure to childhood infections with the reduced risk of atopy later in life. As another face of the hygiene hypothesis, the "old-friend hypothesis" has been introduced by Graham Rook [43] when he suggested that Mycobacteria and other environmental organisms can act as immunomodulators for immunoregulatory disorders. The "ole friend hypothesis" and its supporting, "microflora hypothesis" have attracted investigators later on to discover such surprising relationship between harmful infections and aggressive ADs. Ege et al. [44] have reported a wider range of microbial exposures and lower prevalence of asthma and atopy in children growing up on farms. Two years later, our group have tried the story in experimental models of ADs rather than humans. We have infected the animal model of human lupus, female BWF1 mice with plasmodium chabaudi- infected erythrocytes and investigated the consequences of infection on the disease parameters. We have found that malaria infection has altered the redox state in kidney and liver tissues and confers protection against lupus nephritis [45]. After that, we have investigated the mechanism through which malaria infection could ameliorate the lupus- associated pathology. It was interesting that malaria infection attenuated B-Cell auotreactivity through modulating the CXCL12/CXCR4 Axis and its downstream Signals PI3K/AKT, NFκB and ERK [46]. The infection has also diminished plasma immune complexes and ameliorated the histopathological alterations in different organs of female BWF1 lupus mice [47]. In the renal tissue of lupus mice, the malaria infection has increased the rate of renal immune complexes deposition [48] with concomitant increased total antioxidant capacity [49]. Conversely, malaria infection has increased oxidative stress and apoptosis in splenic tissue of lupus-prone (NZB/NZW) F1 mice [50]. The detailed mechanism behind this surprising phenomenon still been unresolved and the results obtained are still controversial but this situation has attracted many research groups around the world to deeply study this

mysterious relationship. Many neurologists have focused on the malariotherapy for neurosyphillis and other mental disorders and sometimes they called it as pyro therapy or fever therapy [51-56]

CONCLUSION

The term malariotherapy, despite being old and forgotten since nearly eighty years returns to the scientific world potentially after both the human and the animal experimental data that supports it. This term may be the key for the solution of the problematic greatly mysterious in curable category of diseases named autoimmune diseases. This surprising relationship between malaria infection and the autoimmune condition, SLE returns back the postulation that parasitic infections could be double edged swards having both positive and negative consequences.

REFERENCES

1. Barreaux AMG, Oumbouke WA, Tia IZ, Brou N, Koffi AA, Guessan NR, et al. Semi-field evaluation of the cumulative effects of a "Lethal House Lure" on malaria mosquito mortality. Malar J. 2019;18(1):1-9.
2. Barber BE, Rajahram GS, Grigg MJ, William T, Anstey NM. World malaria report: Time to acknowledge Plasmodium knowlesi malaria. Malar J. 2017;16(1):135.
3. Cowman AF, Tonkin CJ, Tham WH, Duraisingh MT. The molecular basis of erythrocyte invasion by malaria parasites. Cell Host Microbe. 2017;22(2):232-245.
4. Demissie Y, Ketema T. Complicated malaria symptoms associated with *Plasmodium vivax* among patients visiting health facilities in Mendi town, Northwest Ethiopia. BMC Infect Dis. 2016;16(1):1-8.
5. Wahlgren M, Goel S, Akhouri RR. Variant surface antigens of Plasmodium falciparum and their roles in severe malaria. Nat Rev Microbiol. 2017;15(8):479-491.
6. Priest JW, Plucinski MM, Huber CS, Rogier E, Mao B, Gregory CJ, et al. Specificity of the IgG antibody response to *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale* MSP119 subunit proteins in multiplexed serologic assays. Malar J. 2018;17(1):1-20.
7. Schumacher RF, Spinelli E. Malaria in children. Mediterr J Hematol Infect Dis. 2012;4(1):e2012073.
8. Oboh MA, Singh US, Antony HA, Ndiaye D, Badiane AS, Ali NA, et al. Molecular epidemiology and evolution of drug-resistant genes in the malaria parasite *Plasmodium falciparum* in southwestern Nigeria. Infect Genet Evol. 2018;66:222-228.
9. Morrison C. Landmark green light for Mosquirix malaria vaccine. Nat Biotechnol. 2015;33(10):1015-1016.
10. Poulet A, Bou Ali H, Savini H, Kaphan E, Parola P. Post-malaria neurological syndrome: Imported case series and literature review to unscramble the auto-immune hypothesis. Travel Med Infect Dis. 2019;29:16-20.
11. Ghosh A, Sharma S, Choudhury J. Autoimmune Hemolytic Anemia in Plasmodium vivax Malaria. Indian J Pediatr. 2017;84(6):483-484.
12. Taneja S, Agarwal N. Autoimmune haemolytic anaemia associated with *P. vivax* malaria. Trop Doct. 2019;49(1):54-55.
13. Miloudi M, Sbaai M, Fatihi J. Immune thrombocytopenia associated with malaria: A case report. Ann Biol Clin. 2017;75(5): 569-571.
14. Seshadri P, Dev AV, Viggeswarpu S, Sathyendra S, Peter JV. Acute pancreatitis and subdural haematoma in a patient with severe falciparum malaria: Case report and review of literature. Malar J. 2008;7:1-8.
15. Kaplan RM. Malariotherapy at Mont Park: The earliest surviving movie of psychiatric treatment in Australia. Australas Psychiatry. 2013;21(1):73-75.
16. Freitas DR, Santos JB, Castro CN. Healing with malaria: A brief historical review of malariotherapy for neurosyphilis, mental disorders and other infectious diseases. Rev Soc Bras Med Trop. 2014;47(2):260-261.
17. Morison lectures. Treatment of mental disease. BMJ. 1929.
18. Chernin E. The malariatherapy of neurosyphilis. J Parasitol. 1984;70(5):611-617.
19. Gartlehner G, Stepper K. Julius Wagner-Jauregg: Pyrotherapy, simultan methode, and 'racial hygiene'. J R Soc Med. 2012;105(8): 357-359.
20. Jauregg JW. The treatment of general paresis by inoculation of malaria. J Nerv Ment Dis. 1922;55:369–375.
21. Delgado HF. The treatment of paresis by inoculation with malaria. J Ment Sci. 1923;69(284):126–127.
22. Scripture EW. Treatment of general paralysis by malaria. Br Med J. 1922;2:1197.
23. Pool A. Dementia Paralytica: Therapeutic measures and results. J Neurol Psychopathol. 1929;10:21–32.
24. Grant AR. Treatment of general paralysis by malaria. Br Med J. 1923;1:995.
25. Yorke W. The malaria treatment of general paralysis. Nature. 1924;114:615–616.
26. Drought CW, Beccle HC. The treatment of general paralysis of the insane by Malarial Infection. Br Med J.1923;2:1256–1257.
27. Lees R. Treatment of general paralysis of the insane by induced malaria: Note on fifty cases. Br Med J. 1931;2:336–339.
28. Nicol WD. Treatment of G.P.I. Br Med J. 1938;2:1012.
29. Crawford CM. Treatment of paretic neurosyphilis by malaria and tryparsamide. Can J Public Health. 1940;31:99–105.
30. Clark RM. Treatment of general paralysis by malaria. BMJ. 1925;1:600.
31. Mayne B. The injection of mosquito sporozoites in malaria therapy. Public Health Rep. 1933;48(31):909–916.
32. Rudolf GDM. Recent advances in therapeutic (induced) malaria. J Neurol Psychopathol. 1936;16(63):239–255.
33. Greentree LB. Malariotherapy and cancer. Med Hypotheses. 1981;7(1):43-49.
34. Heimlich HJ. Should we try malariotherapy for Lyme disease? N Engl J Med. 1990;322(17):1234-1235.
35. Chen X, Heimlich HJ, Xiao B, Liu S, Lu Y, Rao J, et al. Phase-1 studies of malariotherapy for HIV infecton. Chin Med Sci J. 1999;14(4):224-228.
36. Austin SC, Stolley PD, Lasky T. The history of malariotherapy for neurosyphilis. Modern parallels. JAMA. 1992;268(4):516-519.
37. Greenwood BM. Polyarthritis in Western Nigeria. I. Rheumatoid arthritis. Ann Rheum Dis. 1969;28(5):488–496.
38. Greenwood BM, Herrick EM, Voller A. Suppression of autoimmune disease in NZB and (NZB x NZW) F1 hybrid mice by infection with malaria. Nature. 1970;226(5242):266–267.
39. Gerrard JW, Geddes CA, Reggin PL, Gerrard CD, Horne S. Serum IgE levels in white and metis communities in Saskatchewan. Ann Allergy. 1976;37(2):91–100.
40. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989;299(6710):1259–1260.

41. Strachan DP, Taylor EM, Carpenter RG. Family structure, neonatal infection, and hay fever in adolescence. Arch Dis Child. 1996;74(5): 422–426.

42. Matricardi PM, Rosmini F, Riondino S, Fortini M, Ferrigno L, Rapicetta M, et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: Epidemiological study. BMJ. 2000;320(7232):412–417.

43. Rook GA, Adams V, Hunt J, Palmer R, Martinelli R, Brunet LR.. Mycobacteria and other environmental organisms as immunomodulators for immunoregulatory disorders. Springer Semin Immunopathol. 2004;25(3–4):237–255.

44. Ege MJ, Mayer M, Normand AC, Genuneit J, Cookson WO, Braun-Fahrländer C, et al. Exposure to environmental microorganisms and childhood asthma. N Engl J Med. 2011;364(8):701–709.

45. Al-Quraishy S, Abdel-Maksoud MA, El-Amir A, Abdel-Ghaffar FA, Badr G. Malarial infection of female BWF1 lupus mice alters the redox state in kidney and liver tissues and confers protection against lupus nephritis. Oxid Med Cell Longev. 2013:1-10.

46. Badr G, Sayed A, Abdel-Maksoud MA, Mohamed AO, El-Amir A, Abdel-Ghaffar FA, et al. Infection of Female BWF1 Lupus Mice with Malaria Parasite Attenuates B Cell Autoreactivity by Modulating the CXCL12/CXCR4 Axis and Its Downstream Signals PI3K/AKT, NFκB and ERK. PLoS One. 2015;10(4): e0125340.

47. Abdel-Maksoud MA, Abdel-Ghaffar FA, El-Amir A, Al-Quraishy S, Badr G. Infection with Plasmodium chabaudi diminishes plasma immune complexes and ameliorates the histopathological alterations in different organs of female BWF1 lupus mice. Eur Rev Med Pharmacol Sci. 2016;20(4):733-744.

48. Abdel-Maksoud MA, Abdel-Ghaffar FA, El-Amir A, Al-Quraishy S, Badr G. Altered renal immune complexes deposition in female BWF1 lupus mice following *Plasmodium chabaudi* infection. Saudi J Biol Sci. 2018;25(8) :1609-1616.

49. Abdel-Maksoud MA, Abdel-Ghaffar FA, El-Amir A, Al-Quraishy S, Badr G. Increased total antioxidant capacity in renal tissue of female BWF1 mice infected with *Plasmodium chabaudi*. Indian J Anim. Res. 2017:1-5.

50. Abdel-Maksoud MA, Abdel-Ghaffar FA, El-Amir A, Badr G, Al-Quraishy S. Increased oxidative stress and apoptosis in splenic tissue of lupus-prone (NZB/NZW) F1 mice infected with live but not gamma irradiated. Pakistan J Zool. 2017;49(1):331-336.

51. Zuschlag ZD, Lalich CJ, Short EB, Hamner M, Kahn DA. Pyrotherapy for the Treatment of Psychosis in the 21st Century: A case report and literature review. J Psychiatr Pract. 2016;22(5): 410-415.

52. Vogel G. Malaria as lifesaving therapy. Science. 2013;342(6159): 686.

53. Jelencsik I. Therapy of neurosyphilis. 1876. Orv Hetil. 2001;142(20):1069-1071.

54. Karamanou M, Liappas I, Antoniou Ch, Androutsos G, Lykouras E. Julius Wagner-Jauregg (1857-1940): Introducing fever therapy in the treatment of neurosyphilis. Psychiatriki. 2013;24(3):208-212.

55. Castor B, Nettelbladt P. The Nobel laureate who wanted to cure neurosyphilis with malaria. Lakartidningen. 2016;113:pii: DXR3.

56. Raju TN. Hot brains: Manipulating body heat to save the brain. Pediatrics. 2006;117(2):320-321.