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CAUGHT A FLU IN THE TROPICS? IT MIGHT BE MALARIA

Jelmer Raaijmakers¹

¹ Master Student Biomedical Sciences, Radboud university medical center, Nijmegen, the Netherlands.

Abstract

Review

Background: Malaria (*Plasmodium spp.*) and influenza viruses both cast a significant burden of disease on the world's population. Since *Plasmodium spp.* remains endemic in many countries, it can infect many people on a global scale while influenza infects many patients during each influenza season. Malaria and influenza overlap in terms of clinical symptoms. Since malaria is deadly when untreated, misdiagnosis as influenza should be prevented in order for correct treatment to be initiated on time.

Objective: This review sets out to compare malaria with influenza in terms of clinical presentation, diagnosis and treatment.

Clinical presentation: Malaria and influenza show similar symptoms. However, both diseases have their own distinct symptoms due to their disease-causing pathogens. Infection with *Plasmodium spp.* Results in the possibility of regular fever peaks as a result of the multiplication-release-invasion cycle of the parasite. Symptoms that are seen during an influenza infection and not during a *Plasmodium spp.* infection are severe respiratory symptoms.

Diagnosis: Since the pathogens differ from each other in terms of replication, size and endemic areas, the diagnosis of the pathogens also differ. Diagnosis of malaria is based on case history, clinical observations and diagnostic tests. Influenza does not always need a diagnosis unless the patient is hospitalised, severely ill or at risk for severe infections for correct treatment. Influenza can be diagnosed using antibody tests, cell culture tests or reverse-transcriptase polymerase chain reaction, of which the latter is most frequently performed.

Treatment: Malaria can be treated using a combination of artemether and a drug that inhibits the formation of 'hemozoin' so that the toxic 'heme' accumulates in the parasitic vacuole, such as mefloquine. Influenza can be treated using different antiviral drugs. Currently, there is an ongoing discussion on the value of the treatment of viral infections, since resistance against antiviral medication can occur.

Conclusion: The disease causing pathogens *Plasmodium spp.* and influenza viruses differ a lot in terms of disease-causing pathogen and epidemiology. The diagnosis differs based on this information, such as case history and blood examination for malaria. The treatment of both diseases differ due to the causes of disease. Since malaria is deadly when untreated, physicians should be aware of the disease if a patient's case history does not rule out malaria.

KEYWORDS: plasmodium, misdiagnosis, symptoms, flu

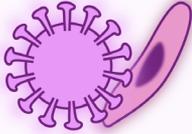
Introduction

Both malaria and influenza cast a major burden of disease on humanity. According to the World Health Organization, roughly half of the world population is at risk of a malaria infection, which is caused by *Plasmodium* species parasites and transmitted by *Anopheles* species mosquitoes [1]. It should be kept in mind that the disease we know as 'malaria' is caused by a group of *Plasmodium* parasites, with each of those varying in severity of disease and where the parasite is endemic [2]. Malaria causes an estimated 1.2 million deaths each year, based on World Health Organization reports [2]. Although in many temperate zones near- or complete elimination of malaria has been established, this does not count for influenza [2]. Furthermore, the near- or complete elimination of malaria is expected to be reversed due to climate change [3]. Influenza viruses continue to be a season-dependent threat on a global scale to both humans and animals [4]. Humans and many animals of all age groups can get infected with these highly contagious viruses and severe disease states can occur [4]. Highly pathogenic strains of Influenza have emerged while this was not predicted, such as the 'Spanish flu', which killed globally 20 to 40 million people [4]. Early diagnosis of malaria is essential for adequate treatment, as well as effective disease management [5]. However, misdiagnosis of influenza might occur due to the overlapping symptoms of

malaria and influenza and physicians might not think of malaria due to the (near-) complete elimination of malaria in their country, which might cause misdiagnosis of malaria [5, 6]. This review sets out to compare malaria to influenza in terms of clinical presentation, diagnosis and treatment.

Clinical presentation

Malaria is caused mainly by four species of *Plasmodium*: *P. falciparum*, *P. ovale*, *P. vivax* and *P. malariae*. Once the parasite gets into the bloodstream after a replication cycle in the liver, it infects red blood cells for replication, which spread across the body and the organs [2]. Symptoms can develop between six to eight days after the bite of an infected mosquito. Once the parasites have replicated in the red blood cells, this will result in cell lysis. The parasites released in the blood will subsequently infect other red blood cells. As a result of this multiplication-release-invasion cycle, sharp increases in body temperature are seen [2]. Since parasite-infected blood cells accumulate in various organs, such as the heart, brain, lungs and kidneys, a variety of other symptoms are frequently seen. The symptoms typically experienced are very flu-like: Fever, shivering, cough, pain in the joints, headache, diarrhoea, vomiting and convulsions [2]. Due to several pathogenic processes, such as jaundice, kidney failure and severe anaemia, this disease is severe and often fatal [2].

		
<i>Plasmodium spp.</i>	<i>Influenza virus</i>	<i>Plasmodium & Influenza</i>
Regional	Seasonal	Cough
Fever peaks	Rhinitis	Fever
Treatment necessary	Often no treatment necessary	Shivering
Fatal	Lasts 7-10 days	Vomiting
		Diarrhoea
		Joint pain

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Figure 1: Characteristics and symptoms of Plasmodium and influenza

In contrast to malaria, influenza is not caused by a parasite infection and does not cause periodic fever spikes. Influenza viruses usually cause respiratory disease and are transmitted by aerosol droplets. The replication of the viruses in epithelial cells and enhanced mucus production causes a runny nose and a cough. The onset of systemic symptoms is seen much earlier than in malaria: after an incubation time of approximately two days [4]. During the incubation period, the virus can already be transmitted to another host. Influenza infection is typically recognised by the systemic symptoms, such as fever, myalgia, headaches and severe malaise, as well as respiratory symptoms: coughing, sore throat and rhinitis, which can last for seven to ten days. Coughing and overall malaise can persist for up to two weeks [4]. The symptoms of malaria and flu can thus be very alike, but the incubation periods and specific symptoms (such as periodic fever peaks) differ between the two pathogens. The most crucial difference in quick diagnosis is that a malaria infection occurs in endemic areas and that influenza infections occur during the influenza season. Therefore, the case history of a patient is essential to rule out malaria quickly.

Diagnosis

The diagnosis of malaria and influenza differ since there is a difference in pathogens, replication methods, size and endemic areas [2]. Malaria is diagnosed using case history (whether the patient has been in a malaria-endemic area), clinical observations and diagnostic tests [2]. These diagnostic tests include microscopic examination of blood and polymerase chain reaction (to demonstrate the presence of parasite DNA) [2]. The blood for microscopic examination is ideally collected when the patient's temperature is rising, as that is when the highest number of parasites are likely to be found. Thick blood drops are used for routine diagnosis due to the high sensitivity [2]. Influenza is diagnosed using accurate and rapid tests, as this is essential for effective management of disease, such as isolation measures and exclusion of a bacterial infection [4]. Antibody tests on serum, cell culture tests or reverse-transcriptase polymerase chain reaction can be used, of which the latter can be used for strain typing [4]. These tests should be done within days after onset of symptoms since the virus replication and illness progresses rapidly [4]. Malaria diagnosis is important in every infected individual due to the severity of the disease. Influenza does not cause severe disease states in many patients and is, therefore, not always diagnosed using the pre-mentioned tests. Only people who are at risk of developing severe disease states are usually diagnosed in such manners, such as hospitalized patients.

Treatment

The different species of *Plasmodium* differ in drug response and diagnosing the right pathogen is important [2]. Prevention of infected mosquito bites is the first step of malaria prevention. If one is nonetheless infected, several treatment options are available [3]. Uncomplicated infections are mainly treated with a combination of artemether (inhibits DNA and protein synthesis of the parasite) and a drug, such as mefloquine, that inhibits the formation of 'hemozoin' so that the toxic 'heme' accumulates in the parasitic vacuole [3]. These drugs can be ingested orally. When severe malaria occurs, intravenous or intramuscular artesunate for at least 24 hours can be administered. When oral ingestion is tolerated again, this treatment is followed up by three days of artemisinin-based combination therapy [3].

Four different antiviral drugs are recommended for the treatment of influenza: oseltamivir, zanamivir, peramivir and baloxavir [7]. Although these drugs should be administered early to prevent disease progression, the efficacy is sometimes limited [7]. These drugs can either be used as a treatment to inhibit viral replication while they can also be used as chemoprophylaxis (prophylaxis in the form of medication) [7]. Each year, there are three strains predicted to emerge, and a vaccine is prepared for these three strains. People at risk can receive this vaccine, although this vaccine is not always effective if a strain emerges different than the predicted strains [7].

Conclusion

Malaria and influenza both infect many people and can cause severe disease states. However, the disease outcomes differ between the two diseases when untreated. Treatment is always necessary for malaria, whereas this is not always the case for influenza infections. The pathogens are diagnosed in a different manner due to the epidemiological, replication, and species differences. One key difference in symptoms is the periodic fever spikes seen with malaria and the continuous fever that is present with influenza. For this reason, an important question that physicians should ask when a patient presents with flu-like symptoms is whether the patient has been in a malaria-endemic area, to exclude malaria as a possible cause of symptoms.

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References

1. World Health Organization. World malaria report 2016, (World Health Organization, Geneva, 2016).
2. Tuteja R. Malaria - an overview. *The FEBS journal* 2007; **274**(18): 4670-9.
3. Anonymous. *WHO Guidelines Approved by the Guidelines Review Committee*. in *Guidelines for the Treatment of Malaria*, (ed. 3) World Health Organization 2015., Geneva, 2015).
4. Pleschka S. Overview of influenza viruses. *Current topics in microbiology and immunology* 2013; **370**: 1-20.
5. Mahdavi, S.A., et al. Malaria or flu? A case report of misdiagnosis. *Asian Pacific journal of tropical biomedicine* **4**, 556-58 (2014).
6. Ali, M.S., et al. A case of misdiagnose of malaria infection. *Asian Pacific journal of tropical biomedicine* **3**, 748-750 (2013).
7. Prevention, C.F.D.C.A. *Influenza Antiviral Medications: Summary for Clinicians*. in, Vol. 2019 (ed. ^)(eds. (CDC, 2019).