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Treatment Strategies for Monkey Malaria: An overview

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ABSTRACT

After Swine Flu, another disease that is making news these days is Monkey Malaria. . Several questions on public health impact have arisen from the discovery of a large focus of the simian malaria parasite, Plasmodium knowlesi, in the human population. It is not newly emergent but was overlooked until molecular tools to distinguish between P. knowlesi and the morphologically similar Plasmodium malariae became available. Information on knowlesi malaria should be included in medical and public health guidelines to encourage the accurate diagnosis and treatment of patients, and monitor the incidence and distribution of cases. Since the parasites reproduce every 24 hours, even a short delay in accurate diagnosis and treatment could lead to the rapid onset of complications, including liver and kidney failure, and death. . Malaria case management remains a vital component of the malaria control strategies. Malaria control requires an integrate approach, including prevention (primarily vector control) and prompt treatment with effective antimalarials. A complete emergence of P. knowlesi into the human population could be overwhelming and, although exigent, the prevention of this situation deserves serious concern.

Key words: Monkey Malaria, Plasmodium knowlesi, treatment

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INTRODUCTION

Malaria parasites were first reported in 1908 in Peninsular Malaysian monkeys, but only gained prominence after the accidental discovery [1] that Plasmodium cynomolgi could be transmitted to humans through mosquito bites in the laboratory in 1960's [2]. From early in the 1930's a pyretic treatment of P. knowlesi was given in patients with neurosyphillis. Plasmodium knowlesi was first recognized as a lethal infection of long tailed macaques in 1931. In 1932, it was revealed that these parasites could also infect humans by inoculation experiment using human blood [3]. The first case of knowlesi malaria (naturally occurring infection) in human was reported in American man after he visited peninsular Malaysia [4]. It was confirmed to be P. knowlesi after the infected blood was used to inoculate Rhesus monkeys [2] which were initially identified as P. falciparum, and later P.malariae. In 1971 second natural infection of P.knowlesi [2] was reported in Malaysia. But there have been an increased number of cases P. knowlesi among humans in South East Asia since 2004.

There are mainly four Plasmodium species which cause malaria that is Plasmodium falciparum, plasmodium vivax, Plasmodium ovale, and Plasmodium malariae. In addition to these species another species, Plasmodium knowlesi, is aprimate malaria that causes malaria in long tailed macaques (Macaca fascicularis).It is also called as Crab eating Macaque, Cynomolgus Monkey, Philippine Monkey [5] or Long-tailed Macaque. This is an emerging infection that was reported for the first time in humans in 1965[6]. Majority of malaria cases are seen in South East Asia where it is mostly found. P.knowlesi infection is a parasite of long tailed (Macaca fascicularis) and pig tailed (Macaca nemestrina). Macaques[7],[8] is mostly found in South East Asian countries particularly in Borneo, Malaysia, Myanmar, Philippines, Singapore, Thailand and neighboring countries. Since West African blacks lack the duffy antigen-a protein on the surface or red blood cell that the parasite uses to invade thus plasmodium knowlesi is less prevalent in Africa [5] .Due to increasing popularity of deforestation and development efforts in South East Asia, macaques are now coming in direct and close contact with humans [7]. Hence more and more infection of knowlesi malaria was seen in people living in semi urban areas.

MODE OF TRANSMISSION

Monkey malaria transmitted mainly through:

- infected monkey to another monkey
- infected monkey to a human
- infected human to another human
- infected humans back to monkey

Known vectors belong to: genus-Anopheles; subgenus-Cellia; series-Neomyzomyia; group-leucosphyrus.Anopheles crucens is considered as an efficient vector of Plasmodium knowlesi because it contains as many as 1,000 sporozoits [7].

Anopheles latens is attracted to monkeys in canopy and humans on ground suggesting that both humans and monkeys could be exposed to infection from each other. It is mainly a forest breeding mosquito associated with dense jungle and forest fringes [9], [10].Thus Plasmodium knowlesi, a zoonotic parasite is transmitted to both Macaques and humans by Anopheles latens. In 1960, Anopheles leucosphyrus group suggested a link between humans and monkeys. Simian malaria is transmitted to man in nature, and is likely to be in area where these mosquitoes are common [11]. Anopheles hackeri is considered to be a main vector of Plasmodium knowlesi within monkey population in Peninsular Malaysia, can transmit malaria to humans[12] also, but since it is not attracted to humans it is not an important vector for transmission to humans[13].

Life Cycle

Plasmodium knowlesi parasite replicates and complete its blood stage cycle in 24 hour cycles [14] thus in very short time high loads of parasite densities are produced. P.knowlesi is unprecedented among the malaria parasites of humans and non human primates as it reproduces every 24 hours and has high no. of infected red blood cells in the patients. Even a short delay in correct diagnosis and treatment could lead to rapid complications including liver, kidney failure and death [15].

Life cycle shows merozoite → schizont → trophozoites. Microscopically it is similar to P.malariae. The following mosquito stages are observed in life cycle [16]: gametocyte → (microgamete or macrogamete) → zygote → ookinete → oocyst → sporozoites. Gametocytes, which have been formed in the mammalian host, are ingested by the mosquito. These can be either macrogametocytes (which give rise to female gametocytes) or microgametocytes (which give rise to male gametocytes). These gametocytes mature into macrogametes and microgametes respectively, and results in formation of zygotes within the midgut of the mosquito by fertilization. These zygotes then mature into ookinetes, then into oocysts. Lastly, the oocysts mature into sporozoites which move to salivary gland of the mosquito [fig 1].

In Man: sporozoites → schizonts → merozoites. It is called as exoerythrocytic stage which occurs in the liver [16] .The sporozoites present in the mosquito are injected into the humans through their bites. These injected sporozoites then travel to the liver through blood stream and undergo asexual reproduction to become merozoites through schizonts in the liver cell. No Hypnozoites was seen in the liver.

In Man: Merozoite → trophozoite → schizont → merozoites. This is called as erythrocytic stage which occurs in the blood [16] . In the blood stream merozoites are unleashed to infect into the erythrocytes constituting one asexual cycle of infection of the erythrocytes. Some merozoites become microgametocytes or macrogametocytes after infection of the erythrocytes. These are ingested by the mosquito from the blood.

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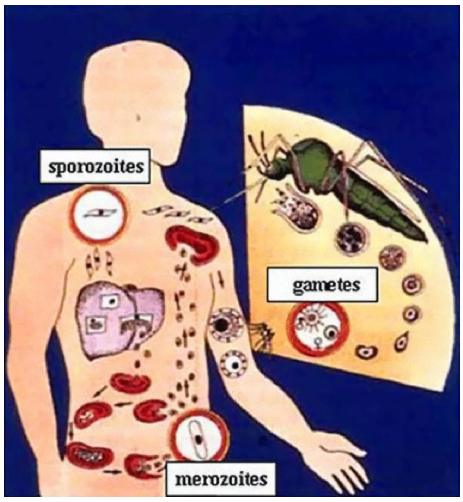

Fig: 1 malarial life cycle

Incubation Period:

Incubation period for P.knowlesi is about 12 days [17]. P.knowlesi has a 24 hour asexual cycle and shortest known malarias that can infect humans and primates [14].

Diagnostic Characteristics:

P. knowlesi infection is diagnosed by examining thick and thin blood films. The appearance of P. knowlesi is similar to that of P. malariae and is unlikely to be correctly diagnosed except by using molecular detection assays [2] in a malaria reference laboratory. PCR assay and molecular characterization are the most reliable methods for detecting and diagnosing P. knowlesi infection [18]. PCR identifies the parasite protein but is considered to be slow, expensive and require very specialized equipment [2] therefore cannot be used for routine identification. P. knowlesi is very specific, so rapid diagnostic tests kits may or may not recognize the parasite.

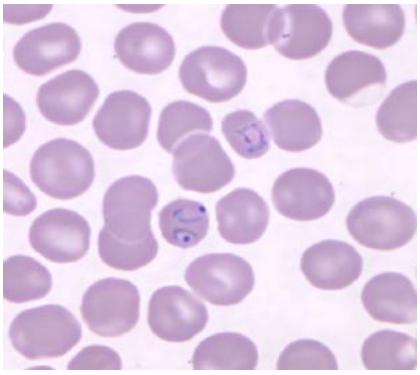

Fig: 2 Ring-form trophozoites of P. knowlesi in a Giemsa-stained thin blood smear from a human patient that traveled to the Philippines. Note a multiply-infected RBC.

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CLINICAL MANIFESTATIONS

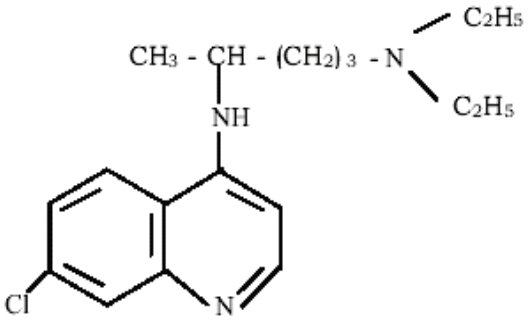
Symptoms may appear approximately 11 days after an infected mosquito bites a person and parasites can be seen in the blood between 10-12 days [18]. Symptoms of Plasmodium knowlesi in humans include headache, nausea and flu like signs, same as human malaria. Patients also have low platelet count (characteristic of monkey malaria) which worsens condition quickly. Mortality rate was found to be 2% [19].Thus infection is not serious but life threatening complications like abnormal liver function including jaundice, renal failure and respiratory distress or even death may occur in minority of cases.

TREATMENT

Early treatment is adviced as Plasmodium knowlesi has very high parasite density and thus prove fatal in humans [2] due to only 24 hour required to complete its life cycle.

Chloroquine

Chloroquine and Primaquine [2] are commonly used in its treatment. For uncomplicated infections [14] Chloroquine is the choice of treatment.



Chloroquine

Pharmacokinetics:

Chloroquine diffuses into body's adipose tissue resulting in very high volume of distribution. Retinal toxicity, blurred vision and blindness are seen with higher doses and longer time frames. Chloroquine accumulates in the lysosomes of the cells of the body. This lysosomotropic character is responsible for antimalarial activity as it interferes with essential process and accumulation of drug in the acidic food vacuole of the parasite. The pKa for the quinoline nitrogen of chloroquine is 8.5, i.e at physiological pH ~10% deprotonated as calculated by the Henderson-Hasselbalch equation. This decreases to ~0.2% at a lysosomal pH of 4.6. The deprotonated form of chloroquine is more membrane-permeable than the protonated form, resulting in quantitative "trapping" of the compound in lysosomes.

Clinical applications associated with chloroquine

Antimalarial Activity:

Malarial parasite in order to construct its own protein and for energy metabolism must degrade hemoglobin inside red blood cells to acquire essential amino acids. Digestion takes place inside a vacuole of the parasite cell. Toxic and soluble molecule heme consisting of a porphyrin ring called Fe (II)-protoporphyrin IX (FP) is produced by the parasite during this process. This heme biocrystallizes to form hemozoin, a non-toxic molecule produced by the parasite to avoid the destruction of this molecule. Hemozoin then collects in the digestive vacuole as insoluble crystals. Chloroquine after entering the red blood cell inhibits parasite cell and digestive vacuole by simple diffusion. As the digestive vacuole is known to be acidic (pH 4.7); Chloroquine becomes protonated (to CQ2+) so that it cannot leave by diffusion. Capping of hemozoin molecules by chloroquine further reduces biocrystallization of heme, resulting in heme buildup. FP-Chloroquine complex is formed by binding of Chloroquine with heme (FP). This complex is highly toxic to the cell and interferes membrane function resulting in cell lysis and ultimately parasite cell autodigestion. In other words, the parasite cell drowns in its own metabolic products.[20]

Popular drugs based on chloroquine on chloroquine phosphate (called as Nivaquine), Resochin and Dawaquin. Other antimalarials for chloroquine resistance P.falciparum include mefloquine or atovaquone. Combination of chloroquine with proguanil is more effective against Plasmodium species than chloroquine alone. But due to availability of more effective combinations [21] .It is no longer recommended by CDC (Centre for Disease Control and Prevention) for children of 14 years or below.

Antiviral Activity:

It interferes the completion of viral life cycle by inhibiting processes occurring within intracellular organelles. In HIV-1, chloroquine inhibits the glycosylation of the viral envelope glycoprotein gp120, which occurs within the Golgi apparatus. Thus it is antiretroviral in humans with HIV-1/AIDS and as a potential antiviral agent against chikungunya fever.[22]

Antitumor Activity:

The radiosensitizing effects through lysosome permeation and chemosensitizing of chloroquine effects through inhibition of drug efflux pumps(ATP-binding cassette transporters) are utilized in anticancer strategies in humans.[23] [24]

Antirheumatoid activity:

As chloroquine mildly suppresses the immune system by inhibiting lymphocyte proliferation, phospholipase A, release of enzymes from lysosomes, release of reactive oxygen

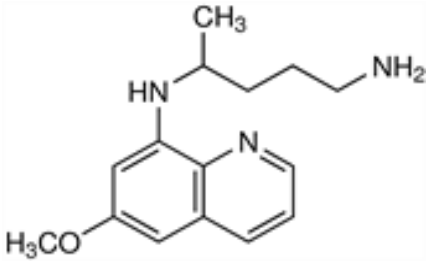
species from macrophages, and production of IL-1, it is used in the treatment of some autoimmune disorders, such as rheumatoid arthritis and lupus erythematosus.

Adverse effects with chloroquine:

The most common side effects observed with chloroquine are stomach ache, itch, headache, and vision. Toxicity in the eye (central serous retinopathy) is a rare side effect and thus regular monitoring is required[25].On higher doses depression, anxiety, changes in moods occurs due to small therapeutic index[26].Overuse leads to development of specific strain of E.Coli that is resistant to powerful antibiotic Ciprofloxacin[27].

Primaquine

Primaquine (or primaquine phosphate) is used in the treatment of malaria and Pneumocystis pneumonia. It is a class of 8-aminoquinoline derivatives and includes tafenoquine and pamaquine.



Primaquine

More therapeutic effects were observed when Primaquine is used in combination of quinine/chloroquine [28].The cure rate is only 21% when primaquine is administered alone.

Adverse reactions

Side effects of primaquine include nausea, vomiting and stomach cramps. Other known adverse effects that occasionally occur are headache, visual disturbances and intense itching. Methemoglobinemia is caused in patients who administer primaquine (levels of up to 18% are reported, normal level is <1%), but this seldom causes symptoms and is always self-limiting.[29] Patients with glucose-6-phosphate dehydrogenase deficiency have dangerous levels of Methemoglobinemia[30][31].

Contraindications

Primaquine should not be administered to anyone with Glucose-6-phosphate dehydrogenase deficiency as it can cause hemolytic anemia. It should be contraindicated in pregnancy, because the G-6-PD status of the fetus would be unknown. Primaquine should not be given to patients with NADH methemoglobin reductase deficiency.[30] [31].

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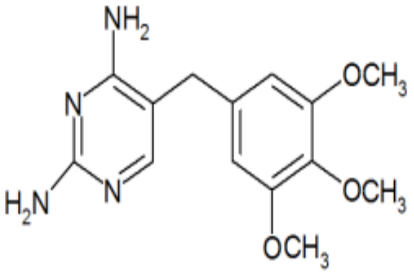
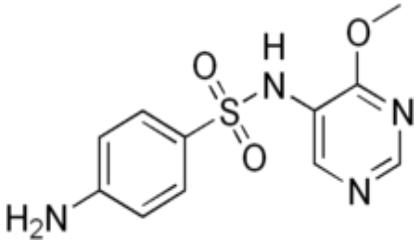
Trimethoprim and Sulfalene

Rhesus monkeys with trophozoite-induced P. knowlesi infections can be treated with Trimethoprim and Sulfalene [32], alone or in combination, and followed clinically for 65 days. Anti malarial drugs should not be taken on empty stomach.



Trimethoprim



Sulfalene

Preventive measures for Monkey malaria [33]

- Avoiding exposure to mosquitos
- Wear appropriate clothing
- Use mosquito's repellents or mosquitos nets while sleeping.

Herbs used in Monkey Malaria

There are some immunity building herbs which are very effective against monkey malaria.

- A wonder herb named Giloy (Tinospora cordofolia) is widely used against monkey malaria. Giloy juice which is a mixture of Giloy herb and Tulsi leaves increases body resistance upto 3 times and powerful counter of Plasmodium virus attacks. Giloy plant on the neem tree (called as Neem Giloy popularly) if found is therapeutically much more powerful.

- Decoction of fennel seeds soaked in warm water is excellent for body building resistant against all kinds of malaria.

- As malaria is a liver infection Bhunimanala which is a juice taken from the plant and Ghritkumari are effective herbal remedies used in the treatment of malaria. The Ghritkumari is a cactus rich in aloe and other vital revitalizing produce. All these remedies will help mend the liver and make it more robust to see off the malaria carrying parasites. [34]

- Tea made from papaya leaves is consumed in some countries as protection against monkey malaria.

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CONCLUDING REMARKS

Knowlesi malaria is zoonotic, not newly emergent, and potentially fatal which is widely distributed in Southeast Asia. Recognition that P. knowlesi is one of the five species of Plasmodium that causes human disease is considered very important. Recently, descriptions of knowlesi malaria have been included in two text books [35, 36], and these descriptions should be included in revised editions of other medical texts and in government and WHO guidelines on malaria diagnosis and treatment. Zoonotic knowlesi malaria will, therefore, continue to be a problem for malaria control, and it poses a threat to the renewed efforts directed at the eradication of malaria [37]. The situation is being monitored in Sarawak, and monitoring should be extended to other areas of Southeast Asia. The importance of early detection and repression of human-to-human knowlesi transmission in the event of a complete emergence into the human population should be encouraged.

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