SHORT REPORT

MANAGEMENT OF *PLASMODIUM KNOWLESI* MALARIA WITHOUT PCR CONFIRMATION

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Abstract. *Plasmodium knowlesi* morphologically resembles *P. malariae*; PCR assays are able to differentiate between the 2 species correctly. However, PCR is not available in many hospitals in *P. knowlesi* endemic areas, particularly in Southeast Asia. In places where PCR is not available, anti-malarial drugs for *P. malariae* or other non-*P. falciparum* or *P. falciparum* species are effective against *P. knowlesi*. Even with a wrong diagnosis of another malaria species by light microscopy instead of *P. knowlesi*, the antimalarial drugs given are still effective for treating *P. knowlesi* infection.

Key words: *Plasmodium knowlesi*, management, PCR

Plasmodium knowlesi, a fifth known cause of human malaria, naturally occurs among long-tailed and pig-tailed Southeast Asian monkeys. There have been many cases reported from Malaysian Borneo (Singh *et al*, 2004), and reports of human cases from Myanmar, the Philippines, Singapore, and Thailand (Jongwutiwes *et al*, 2004). Cox-Singh *et al* (2008) showed that by using PCR, *P. knowlesi* was misdiagnosed by light microscopy to be *P. malaraie, P. falciparum*, and *P. vivax* in 69% (216/312 cases), 5% (11/216 cases), and 4% (16/428 cases), respectively. For the 4 human malaria species (*P. falciparum, P. vivax, P. ovale*, and *P. malariae*) light microscopy is the gold standard for diagnosis of malaria species but light microscopy results in a high rate of misdiagnosis for *P. knowlesi*.

White (2008) determined some factors for the diagnosis of *P. knowlesi*: (1) febrile patients with travel history to a *P. knowlesi* endemic area, such as Southeast Asia or Borneo; (2) a blood smear showing early trophozoites, similar to *P. falciparum* and late trophozoites, similar *to P. malariae*; (3) *P. malariae* multiplies every 3 days (quartan cycle) and never reaches hyperparasitemia, whereas *P. knowlesi* has a daily (quotidian) cycle and can rapidly reach potentially lethal densities. In clinical practice, hyperparsitemic *P. malariae* is unusual and life-threatening *P. malariae* is rare.

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Therefore, if light microscopy morphologically appears to show *P. malariae* in a patient with an unusual clinical presentation of *P. malariae*, or a patient with morphologically appearing *P. malariae* on blood smear has severe malaria, then the correct diagnosis is most likely *P. knowlesi* rather than *P. malariae*.

Molecular techniques, such as PCR, are useful in confirming the diagnosis of *P. knowlesi* for epidemiological reasons and in characterizing mixed infection. Recently, a rapid diagnostic test using pLDH was positive for *P. falciparum, P. vivax* and *P. knowlesi* (McCutchan *et al*, 2008). Whether commercially available rapid diagnostic test can detect *P. knowlesi* infections in larger patient samples remains to be determined.

P. knowlesi is sensitive to chloroquine, quinine, mefloquine and other conventional antimalarials (Singh *et al*, 2004; Bronner *et al*, 2009). Primaquine is not necessary for treatment since *P. knowlesi* has no hypnozoite. Therefore, the treatment of uncomplicated *P. knowlesi* infection is similar to *P. malariae* (*eg*, chlorquine without primaquine). In severe infections due to *P. knowlesi*, the treatment is quinine. Intravenous quinine cleared *P. knowlesi* parasitemia in 2.4±0.97 days (range 1-5 days) (Singh *et al*, 2004). Although there have been no clinical studies of the use of parenteral artemisinin derivatives for the management of severe *P. knowlesi* malaria in humans, a previous study found artemisinin derivatives had antimalarial activity against *P. knowlesi* in rhesus monkeys (Li *et al*, 2003).

PCR is not a rapid detection method and is not available option for diagnosis in many hospitals in Southeast Asia. Confirmation of all suspected *P. malariae* cases by PCR may not be possible in many malaria endemic areas. Studies of the use of a rapid diagnostic test specific for *P. knowlesi* have been limited and are not widely available. Light microscopy is more available than PCR. However, light microscopy in *P. knowlesi* infection may lead to a misdiagnosed of *P. malariae* or another malaria species, and treatment may be given accordingly: chloroquine for *P. malariae,* chloroquine plus primaquine for *P. vivax*, or quinine plus doxycycline or artesunate plus mefloquine for *P. falciparum*. *P. knowlesi* is sensitive to those antimalarial drugs even with a wrong diagnosis of non-*P. knowlesi* species. Therefore, even with a misdiagnosis by light microscopy, treatment is still effective against *P. knowlesi.*

In conclusion, although a confirmative diagnosis of *P. knowlesi* by PCR is often not available, the treatment of uncomplicated *P. knowlesi* with anti-malarial regimens against *P. malariae*, other non-*P. falciparum* malaria or uncomplicated *P. falciparum* malaria is effective; the treatment of severe *P. knowlesi* with the antimalarial regimens against severe *P. falciparum* malaria (such as with intravenous quinine) is also effective.

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