Plasmodium knowlesi: The Fifth Human Malaria Parasite

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In 1952, when Knowles and Das Gupta [1] succeeded in transmitting to humans the monkey malaria they had discovered, it appeared that a new agent for malaria therapy had been discovered. Since the Nobel Prize–winning research of Julius Wagner-Jauregg, malaria therapy had become widely used for the treatment of general paralysis of the insane (neurosyphilis), one of the main reasons for admission to psychiatric institutions. But it soon became apparent that this infection could rapidly become uncontrollable, and after several fatalities, its use was largely discontinued in favor of the less virulent human parasite Plasmodium vivax. Malaria parasites are generally rather choosy, both about their mammalian, avian, or reptilian hosts and their respective mosquito vectors. Transmission of Plasmodium knowlesi, for malaria therapy, from human to human was by blood passage. So initially, it was uncertain whether natural infection could take place and, thus, whether this could be a zoonosis. In 1960, Eyles et al. [2] demonstrated the first experimental mosquito transmission of a simian malaria organism to humans (Plasmodium cynomolgi), and in 1967, Chin et al. [3] showed that P. knowlesi could also be transmitted from monkeys to humans. The mosquitoes used were Anopheles balabacensis (part of the Anopheles leucosphyrus group, which has undergone extensive taxonomic revision in recent years). This is an important vector of human malaria in forested areas of Southeast Asia, where the natural hosts of P. knowlesi—the long-tailed and pig-tailed macaques (Macaca fascicularis and Macaca nemestrina, respectively)—normally live. But the zoonotic potential of P. knowlesi has, until recently, seemed limited, with only sporadic case reports of human infection.

The studies of the Kuching group, led by Balbir Singh and Janet Cox-Singh [4], have changed this view radically. Investigating what appeared initially to be an unusually high incidence of Plasmodium malariae infection, they have shown conclusively that P. knowlesi is a major cause of malaria in Malaysia—particularly on the island of Borneo. Younger stages of these 2 parasites appear very similar under light microscopy, but, although P. malariae multiplies every 3 days (quartan) and never reaches dangerously high densities in the blood, P. knowlesi has a daily (quotidian) cycle and, unchecked, can rapidly reach potentially lethal densities. In this issue, the Kuching group retrospectively reviews the recent Malaysian experience with P. knowlesi infection and describes 4 fatal cases. There are several important practical lessons from this experience. Humans can and do acquire some monkey malarias if they share the same habitat (the reverse is also true). Molecular techniques are very useful in identifying the infection, in describing the epidemiology, and in characterizing mixed infections, which are otherwise underreported. This discovery resulted from good clinical and laboratory investigation, combined with an efficient malaria-control program. Presumably, these P. knowlesi infections were acquired from their natural reservoirs, forest-dwelling macaques—but it remains possible that some may have derived from other human infection. If so, Ciuca’s observation [5], from his malaria therapy practice in Romania, that serial passage of P. knowlesi enhanced virulence may be relevant. There are also potential insights into pathological processes of relevance to severe Plasmodium falciparum malaria. P. knowlesi does not sequester significantly in the microcirculation, but once high parasite densities have been reached, P. knowlesi is rapidly and predictably lethal in the Rhesus monkey (Macaca mulatta). This has been among the most studied of animal models. A fatal outcome in the monkey is associated with very high parasite loads and rapid development of anemia, jaundice, and renal failure—all of which are features of severe P. falciparum malaria in adults, although the clinical picture is unlike cerebral malaria. This unique clini-
copathological syndrome seems specific to severe *P. falciparum* malaria. Terminally ill monkeys are obtunded but not comatose. Thus, although there is no satisfactory animal model of human cerebral malaria, severe *P. knowlesi* infection in the Rhesus monkey and in humans may have important similarities. Although details in this retrospective study are limited, there are several interesting features of the 4 fatal cases reported, in this issue of *Clinical Infectious Diseases*, by Cox-Singh et al. [4]. The patients were relatively old (age, 39–69 years), and each presented with abdominal pain and fever. Two patients were not anemic despite high parasite counts, although they may have been dehydrated and hemoconcentrated (patient 2 had a perforated gastric ulcer); each had renal impairment and jaundice, which are ominous signs in severe *P. falciparum* malaria. All had platelet counts <30,000 platelets/μL, and 3 patients had leukocytosis. This small series raises many questions. How similar is severe disease in humans and Rhesus monkeys (in which the pathophysiology has been investigated extensively)? Do the abdominal symptoms reflect gut ischemia? What is the relationship between parasite biomass and disease severity? Additional studies of severe *P. knowlesi* malaria in humans to assess metabolic acidosis, exclude concomitant bacteremia, and assess the response to antimarial treatment would be informative. Microcirculatory studies in Rhesus monkeys conducted >60 years ago showed sludging of RBCs in the capillaries and venules, so there is clearly more to learn about microvascular dysfunction. Cox-Singh et al. [4] provide important advice; in Asia, high parasite loads with what appears to be *P. malariae* should be regarded as the potentially lethal *P. knowlesi* malaria and should be managed carefully to prevent a fatal outcome. Despite its simian preference, it is legitimate to claim *P. knowlesi* to be the fifth human malaria parasite.

**Acknowledgments**

*Potential conflicts of interest.* N.J.W.: no conflicts.

**References**

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