REVIEW

Expert Review of Evidence Bases for Managing Monkey Bites in Travelers

Nicholas J. Riesland, MD* and Henry Wilde, MD[†]

*Lake Forest Park, Seattle, WA, USA; [†]Department of Infectious Diseases, Chulalongkorn University Faculty of Medicine, Bangkok, Thailand

The clinical problem discussed in this case report involves the management of an adolescent traveler bitten by a non-captive monkey in Southeast Asia. Treatment decisions and the state of evidence for or against are discussed. To assure successful clinical management of travelers who suffer injuries inflicted by non-human primates, clinicians should acquaint themselves with the potential threats and discuss current published recommendations with their patients prior to arriving at a treatment plan.

Scenario

Your patient is a 14-year-old high school student who just returned from a school-sponsored trip to Ko Phi-Phi, in Thailand. She is in your clinic because of a bite to her right hand by a crab-eating macaque monkey inflicted 2 days earlier near Monkey Beach. The bite broke the skin, but she immediately irrigated the wound under a nearby faucet for about 5 minutes. The wound does not look infected. She can move her hand normally and sensation is intact. She is afebrile and otherwise feels fine. She received three doses of rabies vaccine 2 years earlier, prior to moving to Thailand. What is your advice?

Rabies

A recent review from France looked at rabies transmission from nonhuman primates (NHPs) to humans.[1] The report cites 159 rabies cases that occurred in NHPs, documented from 1960 to 2013 and 25 human rabies cases following NHP-caused injuries. The review cited data from 14 surveys and studies involving a total of 2000 travelers seeking care for rabies post-exposure prophylaxis (PEP). Nearly one third had been injured by monkeys. If representative of the experience of travelers, this high number of monkey injuries may differ from what occurs in local resident populations. For instance, in Thailand, a large Asian country with high rabies prevalence in feral and stray dogs, Bangkok's Thai Red Cross Animal Bite Clinic collected common animal bite statistics between 2008 and 2014 in the city's urban local population, with the following mean annual numbers: dogs 657, cats 324, and only 11 from monkeys (H. Wilde, unpublished data, September 2014). In contrast to these numbers, the French data suggest that among foreign tourists, while dogs are usually considered to be the most frequent exposure sources for rabies, NHPs ranked second overall and first in incidents occurring in Southeast Asia. The authors suggest that rabies PEP should be indicated for any NHP wounds that occur in rabies-enzootic regions. Their recommendation for rabies PEP following monkey bites covers a large number of countries in Asia and is consistent with advice on the US Centers for Disease Control (CDC) website.[2] Although the risk of rabies from monkey exposures is acknowledged by the authors of this French study to be extremely low, a nearly 100% mortality rate drives this and the CDC's PEP recommendation.

B Virus

Assuming that the data from Paris are correct and that monkey bites among travelers to Asia are not rare occurrences, there is another unlikely but potentially catastrophic infection associated with NHP injuries that also bears consideration. This infection may not readily come to mind in the differential diagnosis of risk by many medical providers who find themselves treating overseas travelers. Cercopithecine herpesvirus

Corresponding Author: Nicholas J. Riesland, MD, Lake Forest Park, 3404 NE 163rd Street, Lake Forest Park, Seattle, WA 98155, USA. E-mail: nickriesland@gmail.com

1 (CeHV-1) or Simian herpes B virus is enzootic in the commonly encountered Asian monkeys of the genus Macaca, among other monkey species. The virus was first identified by Drs Sabin and White in 1933. They reported a case in which a medical investigator was bitten on a finger by an "apparently normal" *Macacus rhesus* monkey.[3] He died 13 days later from respiratory paralysis caused by an ascending transverse myelitis. Since then, additional cases have confirmed the deadly potential that this virus brings to anyone thus infected, with mortality rates from encephalitis cited as high as 80% by some investigators.[4]

CeHV-1, or B virus, is a double-stranded DNA virus with similarities to herpes simplex virus (HSV)-1 and HSV-2. In monkeys, the normal course of a B virus infection resembles what humans experience with HSV 1 and 2 infections, wherein initial viral replication occurs at the mucosal infection site, inducing an immune response. The virus then enters the axons and is transported to the sensory ganglia where it becomes latent, held in check by the primate's immune response. In rare cases, latency does not occur and the virus disseminates with fatal consequences for the macaque. Similar to humans with HSV, B virus seropositivity in monkeys increases with age, with rates reaching 80% to 100% in captive populations.[5] In the vast majority of seropositive monkeys, however, recurrent infections involve asymptomatic viral shedding. Thus, any injury from a captive macaque is of concern although the monkey does not need to have appeared sick.

Over the past 80 years since Sabin's initial report, nearly 50 human B virus infections resulting from monkey exposures are known to have occurred,[6] approximately one third the number of known monkey-to-human rabies cases chronicled during the past 53 years cited in the above French study. Human B virus infection is now well described and usually occurs within a month of exposure, though symptoms have occurred after less than 1 week or, rarely, months later. The picture, according to a US CDC website, includes herpetic skin lesions and sensory changes near the exposure site, fever and nonspecific flulike myalgias and headaches, fatigue, and progressive neurologic impairment, including dyspnea. Once the central nervous system is involved, the outcome is invariably fatal. But with the deployment of antiviral therapy, both for prophylaxis and treatment, cases are now infrequent and deaths are rare, although they have occurred.

Death usually results from encephalomyelitis after transport of the virus from the peripheral nerves to the spinal cord and then to the brain. Nearly all known infections in humans have been occupational and resulted from direct or indirect exposure to rhesus macaques by biomedical research employees. Although PEP with antiviral agents has not been proven to be effective in humans, due to the obvious difficulty of conducting randomized controlled trials, PEP is shown to prevent disease in otherwise vulnerable rabbits that have been inoculated with B virus. Acyclovir, approved by

the FDA in 1982, began to be used for B virus exposures by the mid-1980s, but was advocated only after symptoms appeared. Within a few years, experts began urging the use of Valacyclovir and acyclovir for prophylaxis prior to the appearance of signs and symptoms. The last update by the CDC's B Virus Working Group in the recommendations referred to on the CDC website was published in 2002.[7] With the availability of antiviral drugs, the outlook for exposures is quite favorable, if care providers consider the diagnosis and implement PEP, especially within 72 hours of exposure.[7]

How likely is a monkey bite to transmit B virus? Among laboratories where macaques are used in research, workers are thought to incur frequent exposures, yet they incur very few infections. Only 2% of macaques in a typical captive population will be shedding B virus at any given time giving estimates that 1-in-50 to 1-in-250 monkey contacts will result in human exposure to contaminated material.[7]

Bites, scratches, needlestick injuries, contamination of cuts with infected material, and splashing of infected fluid into the eyes may cause and have resulted in human infections. Occupational exposures generally occur in a setting where post-exposure protocols are enforced and available health professionals are well informed and ready to provide appropriate care, usually at no cost to the worker-patient. Feral and pet macaque injuries, on the other hand, might be considered to be higher risk due to inadequate wound care, delay in seeking medical care, and/or available medical providers being unfamiliar with the dangerous potential posed by B virus and neglecting to prescribe the appropriate protection. Despite this more hazardous picture, reports of nonoccupational infections are nearly nonexistent.

Whether injuries from macaques outside of laboratory populations pose the same risks as from those in captivity remains uncertain. Apparently not all non-captive macaque populations are equally infected by B virus. For example, there was a complete absence of seroreactivity in 79 macaque monkeys studied in Gibralter[8] and only 15% of Indonesian performance macaques tested positive.[9] Temples in Asia, however, that are inhabited by monkeys and frequented by human visitors, often tourists, probably represent one of the more likely opportunities for B virus exposure. Antibody seroprevalence in the macaque population at one temple in Kathmandu, Nepal, was reported to be almost 65%.[10] Another study performed in 2002 looked at monkeys in Balinese temples.[11] More than 80% of the monkeys tested positive for B virus antibodies, a prevalence similar to that seen in captive populations. The authors reported that nearly half of 105 locals who worked in the temple vicinity had been either bitten or scratched by a macaque. They cite another report where 40% of visitors to the temple sites in this part of Bali are reportedly bitten. The investigators estimated the annual number of injuries inflicted by macaques to both locals and visitors at this particular temple to be in the thousands. This is just one of a myriad of Balinese

temple complexes attracting tourists. Yet, no cases of B virus have ever been reported from any of these encounters. The same holds for India and Nepal where feral macaques frequently come into contact with humans.

One explanation given for the absence of reports of monkey-related encephalitis cases is that monkeys shed B virus infrequently, thus minimizing the opportunity for infection. But none of the countries that are home to indigenous macaque populations have conducted simian herpesvirus surveillance programs among undiagnosed encephalitis cases, raising the possibility that B virus cases are being missed. One recent report states that 50% of encephalitis cases investigated by second-generation molecular biology remain undiagnosed today.[12] Among foreign travelers, however, it seems less likely that such cases would not eventually be identified, even if the diagnosis of B virus encephalitis did not initially occur to clinicians in their home countries when presented with a history of a monkey bite and symptoms suggesting CeHV-1 infection. Could infection be occurring without disease? Among monkey handlers in clinical laboratories and zoological gardens, there is no significant documentation of asymptomatic infection,[7] yet one review cites unpublished results from 2007 (Jones-Engel and Eberle) in which serologic analysis of monkey temple workers indicates that infection without disease may occur.[13] Allowing that indigenous populations might enjoy a resistance to B virus, this would not be expected to hold for visitors. The lack of more extensive data on outcomes from NHP injuries that occur outside of the occupational setting paints a picture that is far from complete and remains somewhat enigmatic.

In the absence of reports of B virus infections among travelers and given that human infection is thus far known to have occurred only in research employees handling captive monkeys, we seem to be left with the question of whether the risk in exposed travelers is zero or close enough to it to decline making any treatment recommendations. Given the unknowns that are likely to persist surrounding this issue and because of the remote possibility of a catastrophic infection should PEP be neglected, the consensus among experts allows that when practitioners are confronted with travelers injured by macaques, they should think of the possibility of infection, however unlikely, and in all candor discuss treatment options with their patients and allow this discussion to dictate implementation of therapy.[14]

Additional Threats

Monkey bites pose a tetanus risk for which the CDC website[14] recommends standard vaccination according to Advisory Committee on Immunization (ACIP) guidelines. Monkey bites may also share a risk profile for bacterial infection similar to human bites.[15] Using human bites as a guide, evidence favors antibiotic treatment for those with contaminated wounds, puncture wounds, bites on the hands, or those involving subepidermal structures.[16] Antibiotics should give broad coverage, including Streptococcus, Staphylococcus, and Eikenella. Amoxicillin clavulanate and moxifloxicin offer reasonable coverage and should be continued orally for 3 to 5 days, whether or not a parenteral first dose is administered.

Our Patient

Returning to our 14-year-old patient, what should be done? Given that Thailand is classified as "high risk" by the World Health Organization for rabies, protection should come to mind. This patient has had the pre-exposure vaccination series, so immunoglobulin is not indicated, although she will require two additional doses of rabies vaccine. Verification of tetanus status and administration of antimicrobial therapy effective against primate oral flora should be considered, such as amoxicillin clavulanate; although it is now 2 days since the bite and with no sign of infection, some may opt for close observation. As for CeHV-1, the conundrum alluded to above is that in injuries from macaques, B virus infection is rare and treatment, therefore, is usually unnecessary. But if infection occurs, as in rabies, the risk of death is high. And, for antiviral therapy to be most effective, it should be administered prior to the development of neurological symptoms. Whether adequate and timely wound cleansing (advised for 15 minutes) had occurred is difficult to consider reliably as a criterion for antiviral therapy. It did not, in the case of our patient. Thus, as the context here is that of broken skin, there is a good case for initiating PEP with an antiviral drug such as valacyclovir (CDC: 1 g by mouth every 8 hours for 14 days), which has a more reasonable dosing schedule than acyclovir (CDC: 800 mg by mouth five times daily for 14 days), an alternative drug. This course of action is consistent with current CDC guidelines already cited. Parenteral ganciclovir (CDC: 5 mg/kg intravenously every 12 hours) is reserved for treatment of infection with central nervous system symptoms. If adequate wound cleansing occurred shortly after the bite, a specimen for PCR testing might have been taken, but only after, not before, adequate cleansing. Because B virus is classified as a biosafety level 4 pathogen, culturing requires a specialized facility, which is often not available.

Given the French report cited above, monkey injuries among travelers may not be rare. Until more data are available, there may be few alterations in the existing guidelines on CeHV-1 exposure in humans. Due to the infrequency of human infections, new data will be difficult to obtain. In the interim, despite the lingering questions, one key feature of managing monkey bites successfully will be for the clinician to consider B virus exposure, discuss interventions with their patient, and then act in concert with current guidelines. When engaged in pre-travel counseling, medical providers should take into account the availability and proximity

of reliable medical care that dispense trustworthy pharmaceuticals.

Declaration of Interests

Both authors state that they have no conflicts of interest to declare.

References

1. Gautret P, Blanton J, Dacheux L, et al. Rabies in nonhuman primates and potential for transmission to humans: a literature review and examination of selected French national data. PLoS Negl Trop Dis 2014; 8:e2863.
2. Centers for Disease Control and Prevention. Travelers' health. Chapter 3: Infectious diseases related to travel: rabies. 2013. Available at: http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/rabies. (Accessed 2015 May)
3. Sabin AB, Wright AM. Acute ascending myelitis following a monkey bite, with the isolation of a virus capable of reproducing the disease. J Exp Med 1933; 59:115–139.
4. Hilliard J, Monkey B. Virus, Chapter 57. In: Human herpesviruses: biology, therapy, and immunoprophylaxis. New York, NY: Cambridge University Press, 2007 online edition.
5. Huff JL, Barry PA. B-virus (Cercopithecine herpesvirus 1) infection in humans and macaques: potential for zoonotic disease. Emerg Infect Dis 2003; 9:246–250.
6. Jensen K, Alvarado-Ramy F, Gonzalez-Martinez J, Kraiselburd E, Rullan J. B-virus and free-ranging macaques, Puerto Rico. Emerg Infect Dis 2004; 10:494–496.
7. Cohen JI, Davenport DS, Stewart JA, et al. Recommendations for prevention of and therapy for exposure to B virus (Cercopithecine herpesvirus 1). Clin Infect Dis 2002; 35:1191–1203.
8. Engel GA, Pizarro M, Shaw E, et al. Unique pattern of enzootic primate viruses in Gibraltar macaques. Emerg Infect Dis 2008; 14:1112–1115.
9. Schillaci MA, Jones-Engel L, Engel GA, et al. Prevalence of enzootic simian viruses among urban performance monkeys in Indonesia. Trop Med Int Health 2005; 10:1305–1314.
10. Jones-Engel L, Engel GA, Heidrich J, et al. Temple monkeys and health implications of commensalism, Kathmandu, Nepal. Emerg Infect Dis 2006; 12:900–906.
11. Engel GA, Jones-Engel L, Schillaci MA, et al. Human exposure to herpesvirus B–seropositive macaques, Bali, Indonesia. Emerg Infect Dis 2002; 8:789–795.
12. Saraya A, Mahavihakanont A, Shuangshoti S, et al. Autoimmune causes of encephalitis syndrome in Thailand: prospective study of 103 patients. BMC Neurol 2013; 13:150.
13. Elmore D, Eberle R. Monkey B virus (Cercopithecine herpesvirus 1). Comp Med 2008; 58:11–21.
14. Centers for Disease Control and Prevention. Travelers' health. Chapter 2: The pre-travel consultation: animal-associated hazards. 2013. Available at: http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-2-the-pre-travel-consultation/animal-associated-hazards. (Accessed 2015 May)
15. Abrahamian FM, Goldstein EJC. Microbiology of animal bite wound infections. Clin Microbiol Rev 2011; 24:231–246.
16. Patil PD, Panchabhai TS, Galwankar SC. Managing human bites. J Emerg Trauma Shock 2009; 2:186–190.