

## Recovery from Rabies

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Worldwide, some 55,000 people die every year from rabies, mostly in Asian and African countries where canine rabies is endemic. Children are frequently the victims of rabies. In the United States, indigenous cases of rabies in humans usually occur through transmission of rabies virus from wildlife vectors, and molecular characterization of the variants indicates that the majority of these cases originate from insect-eating bats.

In this issue of the *Journal*, Willoughby et al.<sup>1</sup> report the case of a young patient in whom rabies developed after a clear history of having been bitten by a bat. Most of the cases of rabies in the United States do not have such a history, and many of the patients do not even have a known exposure to bats, which makes the diagnosis of rabies very challenging for physicians. Most human cases are associated with a rabies-virus variant found in small silver-haired or eastern pipistrelle bats,<sup>2</sup> and transmission probably occurs as a result of unrecognized bat bites. After a bat bite or a situation in which an unrecognized bite may have occurred (e.g., in an unattended infant found in a room with a bat), the bat should be tested for the presence of rabies-virus antigen. If rabies cannot be ruled out and the patient has not received previous immunization, postexposure rabies prophylaxis should be initiated with the administration of five doses of rabies vaccine and of human rabies immune globulin.

In 2003, a group of physicians and researchers with expertise in rabies reached a consensus on the management of human rabies.<sup>3</sup> At that time, there had been only five well-documented survivors of the disease,<sup>3</sup> and all these patients had received rabies vaccine before the onset of symptoms. At least one of the survivors had a good neurologic outcome. The group said that rabies vaccine, human rabies immune globulin, ribavirin, interferon alfa, and ketamine should be considered when an aggressive approach is desirable. They also noted that combination therapy might be promising, since it had proven efficacy in other viral and nonviral diseases.

An immune response is essential for recovery from rabies, although vaccine would not need to be given if—at the time of diagnosis—a patient had rabies virus-specific antibody, as in the case report by Willoughby et al. Rabies vaccination would be reasonable at presentation when the rabies virus-

antibody status of the patient is unknown, especially since all previous survivors of rabies had received rabies vaccine. Antibodies have a very limited ability to cross an intact blood-brain barrier, and the therapeutic usefulness of human rabies immune globulin (which is available for rabies prophylaxis) in rabies encephalitis is probably limited unless the delivery to the central nervous system can be improved. Ribavirin and interferon alfa failed to show efficacy in rabies in a previous report.<sup>4</sup> However, these drugs may still be useful, especially in combination with other agents.

Amantadine, as discussed by Willoughby et al. in the case report, has received less attention, and ketamine (also discussed) is a dissociative anesthetic agent that is a noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist. There has been recent speculation that the NMDA receptor may be one of the rabies virus receptors.<sup>5</sup> Tsiang and co-workers reported that ketamine inhibited the genome transcription of rabies virus and restricted viral spread in an experimental rat model of rabies virus infection.<sup>6,7</sup> In contrast to what has been shown in experimental Sindbis virus encephalomyelitis in mice,<sup>8,9</sup> neuronal injury that is mediated by excitatory amino acids has not yet been shown in rabies. Although there is strong experimental evidence that excitotoxicity is important in animal models of stroke and other neurologic diseases, clinical trials of neuroprotective agents in humans have had disappointing results.<sup>10</sup>

Our understanding of exactly why humans die of rabies is incomplete. In human rabies, many neurons are infected by rabies virus, but the neuropathological findings are quite mild, with inflammatory changes and few cells showing evidence of neuronal death, as compared with those in herpes simplex encephalitis, for example. For this reason, it is felt that rabies virus infection produces neuronal dysfunction rather than neuronal death, but the fundamental cause of this dysfunction is not yet well understood, despite a number of research studies of a variety of neurotransmitters and endogenous neurotoxins in animal models.<sup>11</sup> When aggressive treatment is undertaken in critical care units, patients usually die from medical complications or multisystem organ failure.<sup>12</sup>

Since we do not know exactly why most patients

die of rabies, it is difficult to speculate why the patient survived in the report by Willoughby et al. What role did the drug therapy play in her survival? One possibility, mentioned by the authors, is that she may have been infected by an attenuated variant of bat rabies virus, perhaps one never yet isolated, and that the specific therapeutic agents she received may have played an insignificant or only a minor role in the outcome. It is not clear whether induction of coma per se played a role in her recovery. The desired pharmacologic effects of drugs may be associated with depression of the level of consciousness that is not the primary goal of therapy. For example, coma may occur as a result of therapy with antiepileptic medications for control of status epilepticus, in which the goal is to suppress clinical and electroencephalographic seizures. Induction of coma is not known to have beneficial therapeutic effects in rabies or in other infections of the central nervous system. In the future, induction of coma will probably not be shown to be an effective therapeutic approach to the management of rabies or viral encephalitis due to other causes. However, it is probable that the patient's pharmacologic therapy, especially ketamine and ribavirin, produced beneficial antiviral and maybe even neuroprotective effects.

Future research efforts will be needed to assess further the efficacy of the drugs used to treat this patient. The approach taken may also have helped to prevent autonomic complications that may occur in rabies and may lead to death. The success of Willoughby and his clinical colleagues in ensuring the survival of this young patient with rabies should be applauded. The case provides hope that therapeutic approaches can be successful in rabies and that such treatments may become even better in the future. Early diagnosis and prompt initiation

of therapy before laboratory confirmation of the diagnosis will be important for future efforts in the management of rabies in humans. An improved understanding of the pathogenesis and mechanisms of neuronal injury and the identification of good therapeutic agents on the basis of both in vitro studies and studies in animals are obviously important steps in combating one of the most deadly neurologic diseases affecting humans.

Dr. Jackson reports having received consulting fees from Chiron.

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