

Rabies

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Rabies remains an important public health problem in developing countries, and the indigenous threat of rabies continues in developed countries because of wildlife reservoirs. A diagnosis of rabies is often not considered by physicians until late in the clinical course or after death in North America and Europe, even with typical clinical presentations. Transmission of rabies virus has occurred in association with transplantation of tissues and also recently with organs. In 2004 a young patient survived rabies in Wisconsin, but the reasons for this favorable outcome remain elusive. This article reviews current information and developments on a variety of neurologic aspects of rabies.

Pathogenesis

Rabies virus is usually transmitted in the saliva from the bite of a rabid animal; however, rare human cases have been transmitted by aerosols in laboratory accidents [1], and in a cave containing millions of bats [2,3], and also by transplantation of tissues and organs [4]. After a bite exposure, saliva containing infectious rabies virus is deposited in muscle and subcutaneous tissues. The virus remains close to the site of exposure for the majority of the long incubation period, which usually lasts from 20 to 90 days (Fig. 1). Rarely, the incubation period may last for over 1 year [5]. Rabies virus binds to the nicotinic acetylcholine receptor in muscle [6], which is expressed on the postsynaptic membrane of the neuromuscular junction. Differences in the susceptibility of different species for rabies may be related, in part, to the quantity of nicotinic acetylcholine receptors in muscle, and a marked difference has been reported in muscle of foxes (high content

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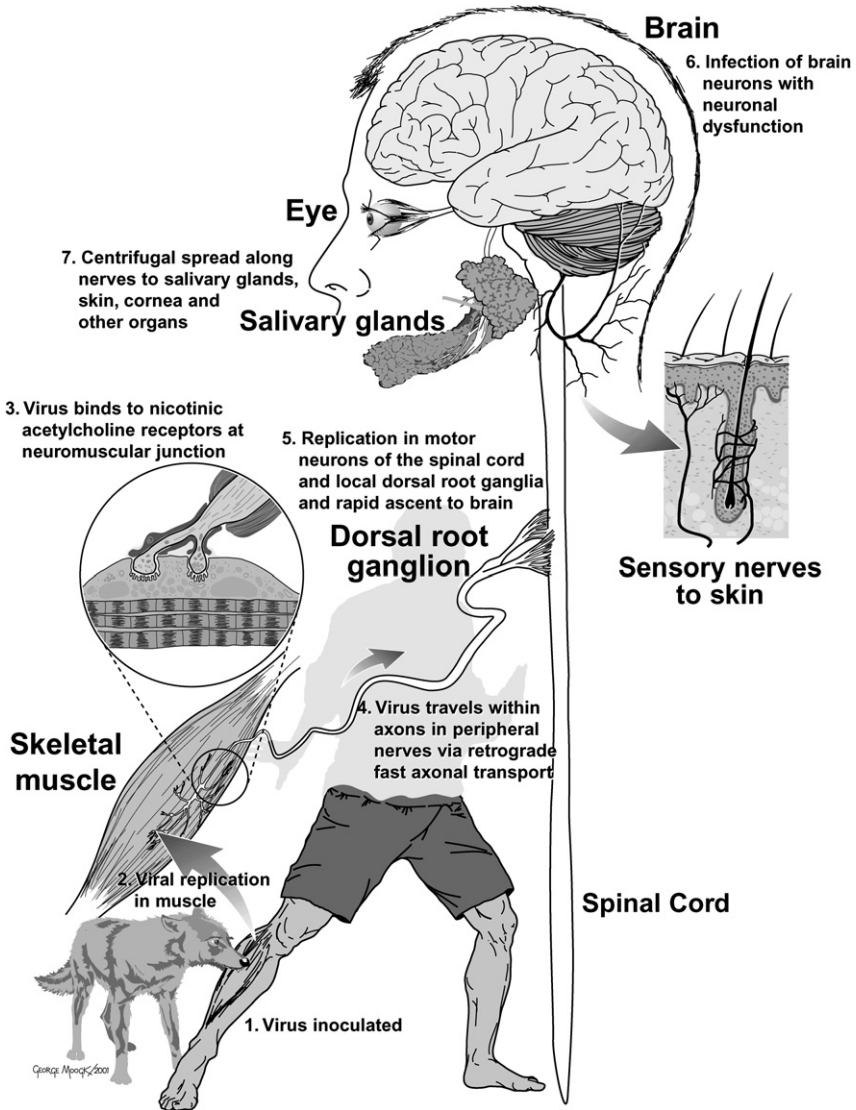


Fig. 1. Schematic diagram showing the sequential steps in the pathogenesis of rabies after an animal bite. (Reproduced from Jackson AC. Pathogenesis. In: Jackson AC, Wunner WH, editors. Rabies. San Diego: Academic Press; 2002; with permission.)

and high susceptibility) and opossums (low content and low susceptibility) [7]. After crossing the neuromuscular junction, the virus spreads within axons in peripheral nerves by retrograde fast axonal transport [8]. Once the virus reaches the central nervous system (CNS), widespread dissemination occurs by axonal transport along neuroanatomical connections [9]. The bases for behavioral changes in rabies vectors is unclear, but studies in

a skunk model of rabies indicate that impaired serotonin neurotransmission caused by infection of raphe nuclei in the brainstem may play a role [10,11]. There are inflammatory changes in the brain, but neurodegenerative changes are quite mild, which gives rise to the concept that neuronal dysfunction, rather than neuronal death, explains the severe clinical disease with a fatal outcome [11,12]. The virus spreads from the CNS to multiple organs along autonomic and sensory neurons, which results the salivary gland infection in rabies vectors and, consequently, infectious virus is secreted in the saliva. There is involvement of nerves in close proximity to hair follicles, which is the basis for a skin biopsy as a diagnostic test for rabies in humans [13], and cardiac involvement may sometimes be associated with a myocarditis. There is infection of nerve plexuses in other organs and of the adrenal medulla [14].

Epidemiology

Globally, there are about 55,000 fatal human cases of rabies each year [15]. Because rabies often occurs in children, when the years of life lost are factored into an analysis, rabies is the seventh most important infectious disease [16]. The main problem resulting in the majority of human cases worldwide is endemic dog rabies in developing countries with dog-to-dog rabies virus transmission. In developed countries, rabies in wildlife is the main threat for indigenous cases. In the United States rabies is present in bats, raccoons, skunks, and foxes, and bat rabies is present in all states except Hawaii [17]. Bat rabies viruses are responsible for most human cases in the United States and Canada. Transmission can occur without awareness of either a bat bite or exposure to a bat. Bat rabies virus variants associated with silver-haired and eastern pipistrelle bats, and, less commonly, with Brazilian (Mexican) free-tailed bats are responsible for the majority of human deaths in the United States. Raccoon rabies is present throughout the eastern United States, but only a single known case of human rabies was associated with the raccoon rabies virus variant [18]. Imported cases may also occur, typically caused by dog exposures in developing countries.

Clinical features

Most cases of rabies can be diagnosed, or at least strongly suspected, on clinical grounds. Human rabies is often misdiagnosed or only recognized relatively late in the clinical course in developed countries because physicians are not familiar with the disease. Delayed diagnosis often leads to many exposures in health care workers, with a requirement for postexposure prophylaxis (see below). Prodromal symptoms include malaise, headache, fever, anxiety, and agitation. Pain, paresthesias, or pruritus may occur at the site of the exposure, at which time the wound has often healed, likely because of involvement of local sensory ganglia (eg, dorsal root ganglia).

There are two clinical forms of rabies: encephalitic (furious) rabies in about 80% of cases, and paralytic (dumb) rabies in about 20%. In encephalitic rabies there are episodes of generalized arousal or hyperexcitability that occur separated by lucid intervals, autonomic dysfunction, including hypersalivation, gooseflesh, cardiac arrhythmias, priapism, and hydrophobia. Hydrophobia, from the Latin meaning “fear of water,” is characterized by spasms of inspiratory muscles, including the diaphragm, on attempts to drink [19]. This may become a conditioned reflex so that even the sight of water precipitates symptoms. It is thought that infection of brainstem neurons near nucleus ambiguus is responsible for this feature of the disease that is unique to rabies, and there is exaggeration of defensive reflexes that protect the respiratory tract [19,20]. Paralytic rabies is characterized by early motor weakness, often beginning in the bitten extremity, with progression to quadriplegia and often bilateral facial weakness. Sensory involvement is not usually prominent and sphincter involvement is common. Patients who have paralytic rabies usually survive longer than those who have encephalitic rabies. Patients who have both clinical forms of disease eventually progress to coma and, subsequently, often develop multiple organ failure, and cardiac and respiratory complications are quite common [21]. Patients survive longer with aggressive care in a critical care unit. Only six patients have survived rabies [4], and five of these patients received some rabies vaccine before the onset of their clinical disease (Table 1).

Diagnostic aspects

In most cases of rabies, there should be a strong clinical suspicion of the diagnosis based on the clinical presentation, and laboratory tests are important for diagnostic confirmation. MRI may be normal [22,23] or may show increased signals in gray matter areas [24,25]. Increased signals have been observed on T₂-weighted images in the medulla and pons [26]. Cerebrospinal fluid (CSF) analysis is often abnormal in human rabies. A CSF pleocytosis was found in 59% of cases in the first week of illness and in 87% after the first week [27]. The white cell count is usually less than 100 cells/ μ L, and the leukocytes are predominantly mononuclear cells. The CSF protein concentration may be mildly elevated, and glucose is usually in the normal range. The presence of neutralizing anti-rabies virus antibodies in serum is useful in unvaccinated patients, but antibodies may not appear until after the first week of clinical illness. Detection of rabies virus antigen, often using the fluorescent antibody technique, is a rapid diagnostic test that can be applied to punch skin biopsies, which are usually taken from the nape of the neck, because nerves adjacent to hair follicles may contain the viral antigen [13]. Brain tissue also contains viral antigen, but brain biopsies are not usually performed for rabies diagnosis. A recent advance in rabies diagnosis is detection of rabies virus RNA using reverse transcription–polymerase chain

Table 1
Cases of human rabies with recovery

Location	Year	Age of patient	Transmission	Immunization	Outcome	Reference
United States	1970	6	Bat bite	Duck embryo vaccine	Complete recovery	Baer et al [46]
Argentina	1972	45	Dog bites	Suckling mouse brain vaccine	Mild sequelae	Porras et al [47]
United States	1977	32	Laboratory (vaccine strain)	Pre-exposure vaccination	Sequelae	Tillotson et al [48]
Mexico	1992	9	Dog bites	Postexposure vaccination (combination)	Severe sequelae ^a	Alvarez et al [49]
India	2000	6	Dog bites	Postexposure vaccination (combination)	Severe sequelae ^b	Madhusudana et al [50]
United States	2004	15	Bat bite	none	Mild to moderate sequelae	Willoughby et al [39]

^a Patient died less than 4 years after developing rabies with marked neurologic sequelae (L. Alvarez, personal communication, 1997).

^b Patient died about 2 years after developing rabies with marked neurologic sequelae (S. Mahusudana, personal communication, 2005).

From Jackson AC. Human disease. In: Jackson AC, Wunner WH, editors. Rabies. San Diego: Academic Press; 2007; with permission.

reaction (RT-PCR) of saliva, tears, and skin biopsies [28–30], and this test is less useful for evaluation of CSF [30]. RT-PCR is fairly sensitive for rabies diagnosis; however, any diagnostic test, unless performed on multiple brain samples, does not completely exclude a diagnosis of rabies, and repeat testing may be necessary. Rabies virus variants from rabies cases can be characterized with RT-PCR and sequencing, which usually helps identify the origin of the variant (eg, rabies virus associated with silver-haired and eastern pipistrelle bats).

Transmission by transplantation

There have been eight well-documented cases of human rabies transmitted by corneal transplantation [4]. In 2004 transplantation was associated with the subsequent development of rabies in recipients of organs and a vascular conduit in the United States (four cases) [31,32] and in recipients of organs in Germany (three cases) [33]. The 20-year-old donor in Texas presented with fever, mental status changes, and throat pain [31,32], whereas the 26-year-old donor in Germany had traveled in India and newspapers reported that she had visited three hospitals with headache and aggressive and bizarre behavior before a cardiac arrest [34]. Rabies virus is present within small nerves of organs and arteries, and organ recipients are immunosuppressed to prevent organ rejection, compromising host defenses and creating a favorable environment for viral replication.

Laboratory screening for rabies has been recommended to prevent future transmissions by organ transplantation [35]; however, this premature recommendation was made without full consideration of many complex issues associated with organ transplantation. Clinical screening of organ donors should include a history of animal bites, evaluation for the presence of clinical features of rabies [4], and a travel history to rabies-endemic areas within a period of months. The physician responsible for the screening process must be knowledgeable about the diverse clinical features of rabies [4]. Laboratory screening of the donor would ideally be performed before organ transplantation. Rabies can only be reliably excluded on the basis of a laboratory evaluation performed on brain tissue. In the case of an organ donor, the best option would be to obtain the specimens immediately after harvesting the organs. The brain or brain tissues would need to be removed under the supervision of a pathologist and subsequently transported to a location where reliable rabies diagnostic laboratory testing could be performed. Experienced diagnostic laboratories probably have false-positive results on at least 1 per 500 cases on the initial evaluation, and false-positive results would be expected to be much higher for hospital laboratories performing infrequent testing. The organs and tissues would not be transplanted if a false-positive result is obtained. Because the demand for organs far outweighs the supply, many potential organ

recipients die each year while they are on a waiting list for procurement of suitable organs from donors. Hence, false-positive results could have very serious consequences that need to be weighed against a very low risk of rabies virus transmission. Less hurried laboratory evaluation of the donor after organ transplantation is another possibility, but the management options are more limited and include removal of the transplanted organ (eg, kidney) in some cases, and initiation of postexposure rabies prophylaxis in an immunosuppressed patient, which may be unsatisfactory. Pre-exposure rabies immunization (with three doses of rabies vaccine) of potential organ recipients while they are on the waiting list for transplantation is an alternative approach to help prevent transmission with organ transplantation. The costs of rabies immunization are high, however, and there is uncertainty about the protection provided by this approach. Hence, appropriate clinical screening of potential organ donors is of paramount importance in preventing reoccurrences of these tragic situations.

Prevention of rabies

Rabies is a preventable disease after a recognized rabies exposure. A decision to initiate rabies postexposure prophylaxis depends on the details of the exposure, the species and clinical status of the involved animal and whether the animal is available for observation (in case of dog, cat, or ferret) or laboratory testing, and the local epidemiologic situation. Wounds should be thoroughly cleansed. Both active immunization with a modern cell culture rabies vaccine and passive immunization with human rabies immune globulin should be given to a previously unimmunized individual [15,36,37]. Licensed vaccines in the United States and Canada include purified chick embryo cell vaccine and human diploid cell vaccine [36]. After a rabies exposure five doses are given intramuscularly in the deltoid muscle on days 0, 3, 7, 14, and 28. On day 0, human rabies immune globulin (HRIG) should be given at a dosage of 20 international units/kg body weight into and around the wounds, and any remaining volume should be given intramuscularly into the buttocks.

Therapy of human rabies

Unlike the situation for rabies prophylaxis, there is no known effective therapy for rabies. In 2003, a viewpoint article was published that summarized a consensus of physicians with expertise in rabies and basic scientists knowledgeable in rabies pathogenesis [38]. It was felt that aggressive therapy of rabies should be considered, particularly in young and healthy patients, in patients who have early clinical disease, and in patients who have received some rabies vaccine before the onset of the disease. Diagnostic tests may not be positive or the results not yet available at the time of initiation of therapy, but an improved outcome would be expected after initiation of

an effective therapy at an earlier time in the course of the disease. Rabies vaccine, human rabies immune globulin, ribavirin, interferon- α , and ketamine are all presently available therapeutic agents that could be considered for administration. It was felt that combination therapy might be more useful than a single agent, as shown for therapy of human immunodeficiency virus infection, chronic hepatitis C virus infection, and cancer.

In 2004 a 15-year-girl in Wisconsin developed rabies after a bat bite, with the early appearance of neutralizing anti-rabies virus antibodies [39]. This patient was treated in a critical care unit in Milwaukee with a therapeutic coma, intravenous ketamine, intravenous ribavirin, and amantadine by the enteric route. Benzodiazepines and supplemental barbiturates were given to deliberately maintain a burst-suppression pattern on her electroencephalogram. It is unclear whether the specific therapy she received played an important role in her survival [40,41]. The rationale for therapeutic coma is questionable. Subsequently, at least four similar approaches to therapy have been unsuccessful, including a detailed report of a case from Thailand [42]. Subsequent experimental studies performed in a mouse model and in primary neuronal cultures have cast doubt on the therapeutic efficacy of ketamine therapy [43], and more experimental work is needed on therapy with this drug. The bat virus variant, which was not isolated, that caused the infection of the Wisconsin girl may have been an attenuated rabies virus, and this may have been much more important in determining the outcome than the medical therapy she received [44]. The only previous human rabies case with an excellent outcome was a boy from Ohio who was also infected by a bat [45]. It is of concern that therapy used in Milwaukee, including therapeutic coma and ketamine, might be repeated countless times throughout the world, and the vast majority of this experience would go unpublished. This therapy may actually reduce the chance of a successful outcome in rabies, as well as consuming resources that could be much better used elsewhere, especially in developing countries with a large burden of human rabies [42]. For this reason, caution was recommended in using this therapy outside the context of a clinical trial with the usual safeguards [42]. Clearly, more basic research needs to be done to find effective therapeutic agents for rabies, including studies in cell culture and in animal models. The Wisconsin case establishes that survival from rabies is possible even without prior administration of rabies vaccine. The challenge is to find effective therapeutic agents for the management of rabies, but achieving this goal may require a better understanding of rabies pathogenesis.

References

- [1] Conomy JP, Leibovitz A, McCombs W, et al. Airborne rabies encephalitis: demonstration of rabies virus in the human central nervous system. *Neurology* 1977;27:67-9.
- [2] Constantine DG. Rabies transmission by air in bat caves. Atlanta (GA): National Communicable Disease Center, U.S. Government Printing Office, Washington, DC; 1967.

- [3] Gibbons RV. Cryptogenic rabies, bats, and the question of aerosol transmission. *Ann Emerg Med* 2002;39(5):528–36.
- [4] Jackson AC. Human disease. In: Jackson AC, Wunner WH, editors. *Rabies*. 2nd edition. Amsterdam: Elsevier Academic Press; 2007. p. 309–40.
- [5] Smith JS, Fishbein DB, Rupprecht CE, et al. Unexplained rabies in three immigrants in the United States: a virologic investigation. *N Engl J Med* 1991;324:205–11.
- [6] Lentz TL, Burrage TG, Smith AL, et al. Is the acetylcholine receptor a rabies virus receptor? *Science* 1982;215:182–4.
- [7] Baer GM, Shaddock JH, Quirion R, et al. Rabies susceptibility and acetylcholine receptor [Letter]. *Lancet* 1990;335:664–5.
- [8] Tsiang H. Evidence for an intraaxonal transport of fixed and street rabies virus. *J Neuropathol Exp Neurol* 1979;38:286–96.
- [9] Gillet JP, Derer P, Tsiang H. Axonal transport of rabies virus in the central nervous system of the rat. *J Neuropathol Exp Neurol* 1986;45:619–34.
- [10] Smart NL, Charlton KM. The distribution of challenge virus standard rabies virus versus skunk street rabies virus in the brains of experimentally infected rabid skunks. *Acta Neuropathol* 1992;84:501–8.
- [11] Jackson AC. Pathogenesis. In: Jackson AC, Wunner WH, editors. *Rabies*. 2nd edition. Amsterdam: Elsevier Academic Press; 2007. p. 341–81.
- [12] Fu ZF, Jackson AC. Neuronal dysfunction and death in rabies virus infection. *J Neurovirol* 2005;11(1):101–6.
- [13] Bryceson ADM, Greenwood BM, Warrell DA, et al. Demonstration during life of rabies antigen in humans. *J Infect Dis* 1975;131(1):71–4.
- [14] Jackson AC, Ye H, Phelan CC, et al. Extraneural organ involvement in human rabies. *Lab Invest* 1999;79(8):945–51.
- [15] World Health Organization. WHO expert consultation on rabies: first report. Geneva: WHO; 2005.
- [16] Coleman PG. Estimating the public health impact of rabies. *Emerg Infect Dis* 2004;10(1):140–2.
- [17] Blanton JD, Hanlon CA, Rupprecht CE. Rabies surveillance in the United States during 2006. *J Am Vet Med Assoc* 2007;231(4):540–56.
- [18] Silverstein MA, Salgado CD, Bassin S, et al. First human death associated with raccoon rabies—Virginia, 2003. *MMWR Morb Mortal Wkly Rep* 2003;52(45):1102–3.
- [19] Warrell DA. The clinical picture of rabies in man. *Trans R Soc Trop Med Hyg* 1976;70:188–95.
- [20] Warrell DA, Davidson NM, Pope HM, et al. Pathophysiologic studies in human rabies. *Am J Med* 1976;60(2):180–90.
- [21] Hattwick MAW. Human rabies. *Public Health Rev* 1974;3:229–74.
- [22] Mrak RE, Young L. Rabies encephalitis in a patient with no history of exposure. *Hum Pathol* 1993;24:109–10.
- [23] Sing TM, Soo MY. Imaging findings in rabies. *Australas Radiol* 1996;40(3):338–41.
- [24] Hantson P, Guerit JM, de Tourchaninoff M, et al. Rabies encephalitis mimicking the electrophysiological pattern of brain death. A case report. *Eur Neurol* 1993;33:212–7.
- [25] Awasthi M, Parmar H, Patankar T, et al. Imaging findings in rabies encephalitis. *AJNR Am J Neuroradiol* 2001;22(4):677–80.
- [26] Pleasure SJ, Fischbein NJ. Correlation of clinical and neuroimaging findings in a case of rabies encephalitis. *Arch Neurol* 2000;57(12):1765–9.
- [27] Anderson LJ, Nicholson KG, Tauxe RV, et al. Human rabies in the United States, 1960 to 1979: epidemiology, diagnosis, and prevention. *Ann Intern Med* 1984;100:728–35.
- [28] Noah DL, Drenzek CL, Smith JS, et al. Epidemiology of human rabies in the United States, 1980 to 1996. *Ann Intern Med* 1998;128(11):922–30.
- [29] Kamolvarin N, Tirawatnpong T, Rattanasiwamoke R, et al. Diagnosis of rabies by polymerase chain reaction with nested primers. *J Infect Dis* 1993;167:207–10.

- [30] Crepin P, Audry L, Rotivel Y, et al. Intravital diagnosis of human rabies by PCR using saliva and cerebrospinal fluid. *J Clin Microbiol* 1998;36(4):1117–21.
- [31] Srinivasan A, Burton EC, Kuehnert MJ, et al. Transmission of rabies virus from an organ donor to four transplant recipients. *N Engl J Med* 2005;352(11):1103–11.
- [32] Burton EC, Burns DK, Opatowsky MJ, et al. Rabies encephalomyelitis: clinical, neuroradiological, and pathological findings in 4 transplant recipients. *Arch Neurol* 2005;62(6):873–82.
- [33] Johnson N, Brookes SM, Fooks AR, et al. Review of human rabies cases in the UK and in Germany. *Vet Rec* 2005;157(22):715.
- [34] Brockmann S. Rabies, human, organ transplantation—Germany (04): rabies in transplant organ recipients: more information is needed about infectious diseases and organ transplantation. ProMED-mail 2005;20050221.0561. www.promedmail.org [accessed April 18, 2008].
- [35] Dietzschold B, Koprowski H. Rabies transmission from organ transplants in the USA. *Lancet* 2004;364(9435):648–9.
- [36] Centers for Disease Control and Prevention. Human rabies prevention—United States, 1999: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 1999;48(No. RR-1):1–21.
- [37] Jackson AC. Rabies. *Current Treatment Options in Infectious Diseases* 2003;5(1):35–40.
- [38] Jackson AC, Warrell MJ, Rupprecht CE, et al. Management of rabies in humans. *Clin Infect Dis* 2003;36(1):60–3.
- [39] Willoughby RE Jr, Tieves KS, Hoffman GM, et al. Survival after treatment of rabies with induction of coma. *N Engl J Med* 2005;352(24):2508–14.
- [40] Jackson AC. Rabies: new insights into pathogenesis and treatment. *Curr Opin Neurol* 2006;19(3):267–70.
- [41] Jackson AC. Recovery from rabies [editorial]. *N Engl J Med* 2005;352(24):2549–50.
- [42] Hemachudha T, Sunsaneewitayakul B, Desudchit T, et al. Failure of therapeutic coma and ketamine for therapy of human rabies. *J Neurovirol* 2006;12:407–9.
- [43] Weli SC, Scott CA, Ward CA, et al. Rabies virus infection of primary neuronal cultures and adult mice: failure to demonstrate evidence of excitotoxicity. *J Virol* 2006;80(20):10270–3.
- [44] Lafon M. Bat rabies—the Achilles heel of a viral killer? *Lancet* 2005;366(9489):876–7.
- [45] Hattwick MAW, Weis TT, Stechschulte CJ, et al. Recovery from rabies: a case report. *Ann Intern Med* 1972;76:931–42.
- [46] Baer GM, Shaddock JH, Houff SA, et al. Human rabies transmitted by corneal transplant. *Arch Neurol* 1982;39:103–7.
- [47] Porras C, Barboza JJ, Fuenzalida E, et al. Recovery from rabies in man. *Ann Intern Med* 1976;85:44–8.
- [48] Tillotson JR, Axelrod D, Lyman DO. Rabies in a laboratory worker—New York. *MMWR Morb Mortal Wkly Rep* 1977;26:183–4.
- [49] Alvarez L, Fajardo R, Lopez E, et al. Partial recovery from rabies in a nine-year-old boy. *Pediatr Infect Dis J* 1994;13:1154–5.
- [50] Madhusudana SN, Nagaraj D, Uday M, et al. Partial recovery from rabies in a six-year-old girl [letter]. *Int J Infect Dis* 2002;6(1):85–6.