

Rabies: new insights into pathogenesis and treatment

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Purpose of review

The occurrences of transmission of rabies virus by organ and vascular conduit transplantation, and recovery from rabies by a patient in Wisconsin, will be addressed. Perspectives will be given on the prevention of rabies by organ transplantation and on the management of patients with rabies.

Recent findings

In 2004 transplantation of organs and a vascular conduit was responsible for the transmission of rabies virus, resulting in seven fatal cases of rabies in the USA and Germany. Likely infectious rabies virus was present within nerves of the transplanted organs and arterial segment and productive infection developed in the immunosuppressed recipients. In 2004 a young patient, who did not receive postexposure rabies prophylaxis after a bat bite, survived rabies in Wisconsin. The importance of therapy she received on her favorable outcome remains unknown.

Summary

Recent transmissions of rabies virus from organ-transplantation donors highlight the importance of clinical recognition of rabies. Laboratory screening of potential donors for rabies prior to organ transplantation would be associated with logistical problems and serious consequences due to false-positive results. The survival of a patient with rabies has offered hope that effective therapy of rabies may become a reality in the future.

Keywords

pathogenesis, rabies, viral encephalitis

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Abbreviation

NMDA *N*-methyl-D-aspartate

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Introduction

Globally there are about 55 000 human cases of rabies each year, largely related to uncontrolled dog rabies in developing countries [1]. Rabies virus transmission is usually due to animal bites. In the USA and Canada most human cases are caused by bat rabies variants, and many of these are due to unrecognized bat exposures. In 2004 organs from patients with undiagnosed rabies were transplanted into recipients in Texas [2[•]] and in Germany [3], resulting in seven fatal iatrogenic cases. Also in 2004, a patient in Wisconsin survived rabies [4^{••}], which was the first case of survival without administration of rabies vaccine prior to the onset of clinical disease. Our understanding of rabies pathogenesis is gradually improving, but fundamental questions remain unanswered. Patients with rabies have faced a dismal outcome. Although we do not know why the patient recently survived rabies, this outcome offers hope that aggressive therapy may become much more successful in the future. An improved understanding of the pathogenesis of rabies may be helpful in the design of novel therapies for this ancient disease.

Pathogenesis

After a delay at or close to the site of inoculation during the incubation period of rabies, typically lasting weeks to months, rabies virus spreads to the central nervous system in peripheral nerves by retrograde fast axonal transport. Dissemination also occurs within the central nervous system in the same manner. The virus infects neurons in multiple brain regions and causes mild inflammatory changes, but under natural conditions rabies virus infection produces few degenerative neuronal changes and neuronal death is only infrequently observed histopathologically. The severe neurological disease associated with an absence of morphologic changes in most rabies virus-infected neurons has given rise to the idea that there is neuronal dysfunction in rabies, but the fundamental abnormality explaining this dysfunction has remained elusive despite many experimental studies [5^{••},6].

Human rabies transmitted by organ transplantation

In 2004 organs were inadvertently transplanted from undiagnosed donors who had rabies in Texas and Germany. The US donor was a 20-year-old male who presented with fever, mental status changes, and throat pain [2[•],7[•]]. A computed tomography head scan showed a small subarachnoid hemorrhage, which subsequently enlarged [7[•]]. The patient progressed to brain death and he became an organ and vascular conduit donor at

Baylor Medical Center in Dallas, Texas, USA. Both of the kidneys, the liver, and an iliac artery segment (for another liver transplant) were transplanted into four recipients. In addition, a lung recipient died of intraoperative complications. The recipients developed clinical rabies within 30 days and subsequently died. Post-mortem blood from the donor showed rabies virus neutralizing antibodies and a bat-associated rabies virus variant was identified from the transplant recipients. At autopsy, rabies virus antigen was detected within nerves of the transplanted organs [2*]. This was the expected anatomical site of viral localization responsible for transmission of the virus [8], despite speculation that the important site might be in macrophages [9]. Host defenses of transplant recipients are compromised since they are immunosuppressed to prevent organ rejection, so there is a favorable environment for viral replication.

Only preliminary information is available about the cases of rabies virus transmission by organ transplantation in Germany [3,10,11], which took place in late December 2004. The 26-year-old female donor had traveled in India in October 2004 and presumably there was transmission of rabies virus from a rabid dog. German newspapers reported that she visited at least three hospitals with headache and aggressive and bizarre behavior [12]. She had a cardiac arrest and six patients received organs or tissues from this donor. Patients receiving lung, kidney, and kidney/pancreas transplants developed rabies within 6 weeks and subsequently died. Recipients of the corneas and the liver did not develop rabies, although the liver recipient may have received a rabies vaccination in childhood [13].

Laboratory screening for rabies has been recommended to prevent future transmissions by organ transplantation [9]. 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, presence of clinical features of rabies [14], and a travel history to areas where rabies is endemic within a period of months. The physician responsible for the screening process must be knowledgeable about the diverse clinical features of rabies [14] and mindful of the possibility of not-yet-diagnosed rabies. Ideally, laboratory screening of the donor would be performed prior to 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 (normally under the supervision of a pathologist) and then transported to a location where reliable rabies diagnostic laboratory testing could be performed. In some states in the USA there is only one laboratory that

performs such testing and appropriate biohazard containment facilities are needed for positive control tissues. Reliable immunohistochemical testing could be developed for use on fixed tissues for testing in hospital laboratories that would not require biohazard containment facilities. However, even experienced diagnostic laboratories probably have false-positive results on at least one in 500 cases on the initial evaluation. 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. According to Organ Procurement and Transplantation Network data (www.optn.org) there were about 27 000 solid-organ transplantations in the USA in 2004; as of December 2005 there were over 90 000 candidates on the waiting list and this list is increasing. 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 would 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 (e.g. kidney) in some cases and initiation of postexposure rabies prophylaxis in an immunosuppressed patient, which may be unsatisfactory. Preexposure 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. However, the costs of rabies immunization are high and there would be uncertainty about the protection provided by this approach.

Recovery from rabies

In 2004 there was a first survivor from rabies who had not received rabies vaccine prior to the onset of clinical disease [4**,15]. This 15-year-old female was bitten by a bat on her left index finger while attending a church service. She subsequently released the bat. The wound was washed with peroxide, but she did not seek medical attention or receive any other treatment at that time. About 1 month after the bite she developed numbness and tingling of her left hand, and over the next 3 days she developed diplopia (associated with bilateral partial sixth-nerve palsies), unsteadiness, and nausea and vomiting. A magnetic resonance imaging brain scan was normal. On her fourth day of illness cerebrospinal fluid showed 23 white cells/ μl (93% lymphocytes) and mildly elevated protein at 50 mg/dl. She subsequently developed fever (38.8°C), nystagmus, left-arm tremor, and hypersalivation, and at about that time the history of the bat bite was obtained. The patient was transferred to a tertiary care hospital in Milwaukee, Wisconsin, 5 days

after the onset of neurologic symptoms. A repeat magnetic resonance imaging scan was normal and rabies virus antibodies were detected in serum and cerebrospinal fluid (initially 1:32). Nuchal skin biopsies were negative for rabies virus antigen, rabies virus RNA was not detected in the skin biopsies or in saliva by reverse transcriptase-PCR, and viral isolation on saliva was negative. The patient was intubated, and put into a drug-induced coma, which included the non-competitive *N*-methyl-D-aspartate (NMDA) antagonist ketamine at 48 mg/kg per day as a continuous infusion and intravenous midazolam for 7 days. There was a deliberate attempt to maintain a burst-suppression pattern on her electroencephalogram and supplemental phenobarbital was given. She also received antiviral therapy, including intravenous ribavirin and amantadine 200 mg/day administered enterally. She improved and was discharged from hospital with neurologic deficits and she has subsequently shown further progressive neurologic improvement.

This is the first documented survivor who did not receive rabies vaccine prior to onset of clinical rabies. As discussed in an accompanying editorial, it is unknown if therapy with one or more specific agents played an important role in the favorable outcome of this case [16^{••}]. Clearly, the efficacy of the drugs used in treating this patient need to be evaluated further. The induction of coma *per se* has not been shown to be useful in the management of infectious diseases of the nervous system, and to date there is no evidence supporting this approach in rabies or other viral encephalitides. Hence, therapeutic coma should not become routine for the management of rabies or other infectious diseases at this time. To date, there is no established experimental evidence supporting excitotoxicity in rabies, unlike some other viral infections of the nervous system, including Sindbis virus encephalomyelitis and HIV infection [17–20]. Unfortunately, multiple clinical trials have shown a lack of efficacy of neuroprotective agents in stroke, where there is strong experimental evidence of excitotoxicity in animal models [21]. Ketamine was used in the treatment of this patient; ketamine is a non-competitive NMDA antagonist that was recently recommended by a group of rabies experts [22] as a specific agent that might show efficacy in human rabies, based on previous studies *in vitro* and in a rat model in which antiviral effects were observed [23–25]. It is also possible that the patient's illness and favorable outcome may have been due to the fact that she was infected by an attenuated bat rabies virus, perhaps never previously isolated, rather than as a result of the therapeutic approach taken. The only previous survivor of rabies who had a good neurological recovery was also infected with a bat rabies virus [26]. Bat rabies viruses may be less neurovirulent than canine or other variants that are responsible for most human cases of rabies [27[•]].

Treatment

The ideal therapy for a patient with rabies is unknown. Young and previously healthy patients with an early clinical diagnosis of rabies (prior to laboratory confirmation) and prompt initiation of therapy should offer the best opportunity for a favorable outcome [22]. Recently, a group of physicians with expertise in rabies and rabies researchers published an article giving recommendations on therapies that could be considered for an aggressive approach [22]. These therapies include rabies vaccine, human rabies immune globulin, monoclonal antibodies (for the future), ribavirin, interferon- α , and ketamine. It was felt that combination of therapies might be useful where specific therapies had failed in the past. It remains unknown whether one or more of the drugs used to treat the rabies survivor from Wisconsin played an important role in her recovery. Skepticism has been expressed about the use of therapeutic coma in rabies [16^{••}], and the concern is greater outside of the context of a clinical trial, where most failed attempts of the therapy will probably go unpublished.

Conclusion

In 2004 rabies virus was transmitted to organ recipients and one vascular conduit recipient from two undiagnosed donors, resulting in seven fatalities. Better recognition of the manifestations of rabies by clinicians in developed countries would likely have prevented these transplantations and deaths. Laboratory screening for rabies in donors prior to transplantation would be associated with difficult logistical problems and false-positive results would have serious consequences. Hence, widespread laboratory screening for rabies should be not recommended prior to organ transplantation at the present time. A patient who did not receive rabies vaccine recovered from rabies in 2004. The favorable outcome of this case offers hope for future patients with rabies, and should motivate the medical community to determine the most effective available therapy for rabies and also to develop novel therapies based on an improved understanding of rabies pathogenesis, which will require further basic research studies.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 324).

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