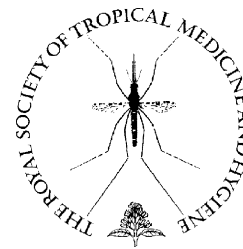




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REVIEW

Viewpoint: management of human rabies

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Summary Rabies remains a serious public health problem in many developing countries. A case in the West received media attention with the recovery of an American teenager who had not received rabies post-exposure prophylaxis. This case confirmed that rabies is not an invariably fatal disease. Review of the literature revealed only two survivors with good neurological status in nearly 40 years. Both had neutralizing antibodies in cerebrospinal fluid at or shortly after presentation, but the usual diagnostic tests for rabies were negative, a rather unique finding. It is highly probable that these two children managed to mount an unusually effective early immune response to the infection that contributed to, or was responsible for, recovery. Curative efforts for human rabies using critical care resources should especially target patients who show early neutralizing antibody. More basic research is needed to develop effective therapies for human rabies.

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1. Introduction

Human rabies is rarely seen in Europe, North America and Australia but is still a major and re-emerging problem in many developing countries of the world. Over 55 000 annual cases occur worldwide, and this number underestimates the human burden of disease due to misdiagnoses and under-reporting (Hemachudha et al., 2006a, 2006b; WHO, 2002). Virtually all patients in canine-rabies-endemic countries are diagnosed clinically without laboratory confirmation. Human rabies is an almost invariably fatal disease. Rare canines and other mammals recover from infection or develop sub-

clinical forms of disease (Aghomo and Rupprecht, 1990; Amengual et al., 2007; Fekadu et al., 1981; Follmann et al., 1994; Jackson, 2005, 2007b; Yasmuth et al., 1983). There have been five well-documented cases of survival from rabies in which post-exposure rabies prophylaxis failed. Doses of rabies vaccine were administered before the onset of clinical illness in each of these cases (Alvarez et al., 1994; Hattwick et al., 1972; Jackson, 2007a; Madhusudana et al., 2002; Porras et al., 1976; Tillotson et al., 1977). Such isolated reports generated hope that effective therapy for human rabies can be found.

2. Historical perspective

Curative efforts started with Celsius in about AD 30. He recognized the infectious nature of rabies and the fact that it

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is transmitted via canine saliva. He recommended cupping and cauterizing bite wounds to prevent death and suggested "placing the patient in a river or lake, head down until he can not avoid swallowing water." Being a good scientist, he must have tried this method and found that it did not work. Later he revoked this recommendation (McGrew, 1985). People in the Middle Ages turned to magic and prayer, usually to St Hubertus, the patron of hunters, fully recognizing that a horrible death was inevitable. Purging, bleeding, transfusing and a variety of then common local and systemic potions were tried. Traditional healers in India and Pakistan still apply red chillies to dog-bite wounds (Parviz et al., 1998). After Louis Pasteur developed what appeared to be an effective rabies vaccine for post-exposure prophylaxis in the 1880s, scientific efforts to heal patients with the disease began but were fruitless.

3. Management of rabies

Efforts in the latter half of the twentieth century became more focused and included administration of interferons, ribavirin, cytosine arabinoside and intravenous, intraventricular and intrathecal human and equine rabies immunoglobulin (Dutta and Dutta, 1994; Jackson, 2005, 2007a; Jackson et al., 2003; Kureishi et al., 1992; Warrell et al., 1989). High concentrations of ketamine have been shown to inhibit the replication of rabies virus in primary neuron cultures (Lockhart et al., 1992), although it is doubtful that such levels can be achieved in humans (Jackson et al., 2003). Furthermore, recent experimental studies have cast doubt on the efficacy of ketamine on rabies virus infection in primary neuron cultures and in a mouse model of experimental rabies (Weli et al., 2006).

Survival of rabies patients with severe neurological defects has been reported in four patients who received rabies vaccine before onset of symptoms. At least two of these patients subsequently died within a five-year period from complications related to severe neurological sequelae (Jackson, 2007a). Until recently, only one 6-year-old boy, who had a bat bite and developed rabies, made a complete recovery having received supportive care without antiviral drugs. He was found to have high serum and cerebrospinal

fluid (CSF) neutralizing antibody titres shortly after admission and efforts to isolate the virus failed (Hattwick et al., 1972).

Real hope was created when a 15-year-old girl, who had been bitten by a bat in Wisconsin and did not receive post-exposure prophylaxis, developed encephalitic rabies and was treated with therapeutic coma using benzodiazepines and supplemental barbiturates in order to produce a burst-suppression pattern on the electroencephalogram (Willoughby et al., 2005). This approach is used to manage status epilepticus. In addition, she received antiviral therapy with ribavirin and amantadine and also therapy with ketamine. She survived with mild-to-moderate neurological sequelae (Hu et al., 2007; Willoughby et al., 2005). This patient also had high rabies virus antibody titres in serum as well as CSF shortly after admission. Efforts to isolate the virus failed and viral antigen and RNA detection methods were negative. It remains unclear if her therapy, other than the good critical care, played a significant role in her recovery (Jackson, 2005). This therapeutic approach has been championed by Rodney Willoughby, although there is no evidence to date that any of the drugs administered played an important role in her survival.

There is no credible scientific basis for the use of therapeutic coma in rabies, and the risks of this therapy are substantial. Therapeutic coma and other components of Willoughby's therapy were used unsuccessfully at Chulalongkorn University Hospital in Bangkok, Thailand (Hemachudha et al., 2006b) and also by tertiary care centres in Germany, India, Brazil, Canada, The Netherlands and the USA (Table 1) (Bagchi, 2005; Drosten, 2007; Houston Chronicle, 2006; McDermid et al., 2008; Scotsman, 2005; van Thiel et al., 2008). Our Thai male patient with furious rabies was admitted still fully conscious and haemodynamically stable. No neutralizing anti-rabies virus antibodies were found in serum or CSF, and rabies virus was isolated from his brain and spinal cord at necropsy (Hemachudha et al., 2006b). He died of multisystem failure, similarly to all patients in our past experience, with over 200 rabies patients seen by two of the authors (HW and TH) in Bangkok during the past two decades. Among these, only about 25% had serum-neutralizing antibodies, but significant titres of CSF antibodies were not found.

Table 1 Cases of human rabies with treatment failures that included the main components of the Wisconsin/Milwaukee protocol promoted by Rodney Willoughby

| Case no. | Patient's age (years) | Virus source | Country | Reference |
|----------|-----------------------|-------------------|------------------|--------------------------|
| 1 | 46 | Transplant (dog) | Germany | Scotsman, 2005 |
| 2 | Unknown | Dog | India | Bagchi, 2005 |
| 3 | 33 | Dog | Thailand | Hemachudha et al., 2006b |
| 4 | 16 | Bat | USA (Texas) | Houston Chronicle, 2006 |
| 5 | 10 | Bat | USA (Indiana) | Christenson et al., 2007 |
| 6 | 11 | Dog (Philippines) | USA (California) | Christenson et al., 2007 |
| 7 | 73 | Bat | Canada (Alberta) | McDermid et al., 2008 |
| 8 | 55 | Dog (Morocco) | Germany | Drosten, 2007 |
| 9 | 34 | Bat (Kenya) | The Netherlands | van Thiel et al., 2008 |
| 10 | 7 | Vampire bat | Brazil | ^a |
| 11 | 20–30 | Vampire bat | Brazil | ^a |

^a Personal communication (to ACJ) from Dr Rita Medeiros, University of Para, Belem, Brazil.

The cost for caring for this patient by a multispecialist team at a university hospital in Thailand could have provided pre-exposure rabies vaccination, using the economical Thai Red Cross intradermal regimen for at least 16 000 slum-dwelling children in Bangkok. A recent database search evaluated the immune response in the rare rabies survivors. The authors concluded that survival appears to be related to early appearance of neutralizing antibodies in serum and CSF (Watson et al., 2007).

4. Conclusions and recommendations

What can be deduced from this information? Rabies is still a virtually invariably fatal illness and one that is associated with great suffering for patients and their loved ones. The clinical course is usually short-lived, unless it is prolonged by critical care interventions (Jackson, 2005, 2007a; Jackson et al., 2003). Two survivors without major neurological sequelae produced an early and effective endogenous immune response against rabies virus early after onset of symptoms that probably cleared the infection. It was documented by the presence of high CSF antibodies in both patients and the absence of detectable virus throughout the course of their illness.

What should be our approach to managing human rabies patients now? This issue was discussed at a conference at Toronto in 2001, before the publication of the Wisconsin case and the extensive publicity that followed (Jackson et al., 2003). Potential therapeutic agents were outlined and the use of combinations of agents was recommended when an aggressive approach is deemed desirable (Jackson et al., 2003). Our group in Thailand, working in a canine-rabies-endemic part of the world, has decided not to subject future patients with laboratory-proven furious or paralytic rabies to intensive therapeutic measures, including respiratory and cardiovascular support. Symptomatic and comfort care, including psychological support of the family, will be the primary goal for many patients. However, if our group did encounter a patient in the early stages of clinical rabies with neutralizing antibodies in CSF, we would consider initiating critical care measures, hoping that this patient would mount an antibody response that might lead to recovery. We would not use therapeutic coma because of a lack of scientific rationale for this therapy and an expanding record of multiple failed attempts from other major medical centres.

Aggressive care of rabies patients requires considerable resources, and, at the present time, we have decided to dedicate our resources to patients that have the greatest chance of having a good outcome. In developed countries with rare rabies cases and more resources, it may be reasonable to take an aggressive approach on a wider range of cases. Claims that therapeutic coma lengthens survival in rabies are probably due to the fact that an aggressive approach has been continued instead of switching to a palliative approach when the prognosis becomes very poor with an ongoing lack of neurological function. Our Thai patient, who received therapeutic coma, had brain liquefaction at necropsy, which meant that the destructive process in the brain had started earlier. A recent Canadian case treated with therapeutic coma was subsequently maintained for weeks with a poor neurological status and was found to have

marked loss of cortical neurons at autopsy (McDermid et al., 2008).

New approaches should be considered for managing human patients with rabies, rather than repeating an approach without a scientific rationale that has now failed for many patients. A better understanding of the pathogenesis of rabies may open the door to novel promising therapies in the future, and basic research must continue in this field. Eradication of rabies in the principal canine vector is feasible and should remain our primary goal.

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